Preferences for oral nutritional supplement therapy among postoperative patients with gastric cancer: a discrete choice experiment

Qiuchen Wang1 · Hua Yuan1 · Zhiming Chen1 · Jia Wang1 · Jiannan Yao1 · Mingyue Zhu1 · Hui Xue2 · Xiuying Zhang1

Received: 27 January 2022 / Accepted: 13 May 2022 / Published online: 27 May 2022
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Abstract

Purposes Patients after gastrectomy have poor compliance with oral nutritional supplement (ONS) therapy. Incorporating patient preferences into treatment decisions allows possible product improvements or treatment focus adjustments. The purpose of this research was to investigate the preferences for ONS therapy among postoperative patients with gastric cancer, and to provide person-centered oral nutrition management strategies.

Methods A discrete choice experiment was designed and implemented within a Chinese cancer population. The survey was administered via paper-based questionnaires during face-to-face interviews with assistance from health professionals. A mixed logit model was used to estimate respondents’ preferences for different levels of nutrition therapy attributes.

Results One hundred ninety respondents valued “Adverse reactions-almost none” ($\beta$ 3.43 [SE, 0.28]) the most, followed by “Flavor-good taste” ($\beta$ 0.68 [SE, 0.13]) and “Follow-up frequency-once every 2 weeks” ($\beta$ 0.52 [SE, 0.13]), and were willing to pay more for these attribute levels. Respondents would be 93.73% more likely to accept a nutrition therapy program if there were almost no adverse reactions compared to the frequent adverse reactions.

Conclusions Health professionals should pay attention to the management and prevention of adverse reactions when prescribing nutritional products, and provide diversified ONS products when necessary to meet patient preferences. When formulating intervention strategies, health professionals should also consider the different characteristics of patients, acknowledge the importance of the role of nurse specialists in a novel model of multidisciplinary nutritional care, standardize ONS information, follow up regularly, and encourage patients’ families to participate in daily nutrition care.

Keywords Discrete choice experiment · Gastric cancer · Oral nutritional supplement · Preferences · Patient compliance · Willingness to pay

Introduction

Gastric cancer was responsible for over one million new cases in 2020 and an estimated 769,000 deaths, ranking fifth for incidence and fourth for mortality globally, of which more than 50% were in East Asia [1]. Currently, radical gastrectomy is still the main method of gastric cancer treatment [2]. However, resection of the stomach will reduce reservoir function and bring problems from the reconstruction of the structure of the digestive tract [3]. Moreover, some tumor-derived cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, can cause anorexia by affecting hormone secretion. Among all types of cancer, malnutrition in patients with gastric cancer ranks first, reaching 65 to 85% [4].
The European Society for Clinical Nutrition and Metabolism (ESPEN) recommended that oral nutritional supplements (ONS) be given priority in nutritional treatment for patients suffering from malnutrition [5], as they are non-invasive, and more closely resemble the patient’s natural feeding process [6]. ONS can improve the nutritional status and immune function [7], and reduce the incidence of complications [8], thus shortening the length of hospital stay [9]. However, the efficacy of ONS varies due to the patient’s compliance behavior. Previous studies have shown that patients in the high-compliance group have significantly improved nutritional status compared with those in the low-compliance group [10, 11]. ONS compliance is sometimes not satisfactory, and the compliance of patients with ONS after gastrectomy was even only 26.20–58.00% [10, 12, 13]. A recent longitudinal study in China found that the average compliance of patients after gastrectomy at 12 weeks was as low as 30.59%, and did not find a clear advantage of ONS in reducing the incidence of complications in patients, which affected the prognosis of patients [13].

The patient’s compliance is affected by many factors [14–16]. Previous studies have shown that the main reason for the discontinuation of ONS was gastrointestinal intolerance [15]. A longitudinal study found that adverse reactions to ONS, the identity of the main caregivers, and the patient’s financial ability were independent factors that affected patient compliance in China [13]. Support from patients’ family members and peers will also influence patient compliance. Health professionals are increasingly encouraged to involve patients’ preferences in treatment decisions to improve compliance [17]. However, there is little knowledge about patients’ priorities and needs about ONS therapy, and practical concerns include the extra time needed and the difficulties in eliciting patient preferences, which pose challenges for clinical staff.

The discrete choice experiment (DCE) is one innovative approach to overcoming this limitation, which the aim is to elicit and quantify preferences [18]. In recent years, Oliveira et al. [19, 20] have used a DCE to elicit and compare preferences in terms of the attributes of home enteral nutrition among patients and physicians. However, available measures were designed for tube feeding therapy for patients with chronic diseases other than cancer. In addition, these DCEs neglected the impact of health guidance and follow-up strategies other than nutritional products on the patient. Therefore, this study aims to investigate the preferences for ONS therapy among postoperative patients with gastric cancer, and to provide distinctive references for the development of ONS management strategies in the future.

Methods

Attribute and level identification

We used a mixed-method approach to develop attributes and levels for the DCE. First, we reviewed the relevant literature by searching the electronic databases of Embase, PubMed, Web of Science, Chinese National Knowledge Infrastructure, and Wanfang database using key terms such as “tumors,” “oral nutritional supplements,” “patient compliance,” and “patient preferences.” Researchers then developed the initial attributes and levels [15, 21–24]. Subsequently, we conducted semi-structured interviews with 15 patients after gastrectomy who had the experience of taking ONS to validate and refine our selection of attributes and levels [25]. The topics in the interviews included (1) feelings and views of patients taking ONS; (2) related factors that affect patients’ adherence to ONS; (3) sources of help to promote patients’ adherence to ONS; and (4) acceptability and availability of health services, including health guidance and out-of-hospital follow-up. Then, four focus groups, each of which consisted of 4–5 patients, were invited to discuss the wording of the attributes and levels and reduced the number of attributes to manageable numbers through voting ranking methods [26, 27]. Finally, the expert team, consisting of two gastric oncologists, two dietitians, two nutrition specialist nurses, and two researchers, discussed and determined the range of the levels, and took their clinical plausibility into account [28]. The final experimental design included eight attributes with two to three levels each (see Table 1).

Choice sets and questionnaire design

We constructed the choice sets using an unlabeled design to avoid reducing the attention that respondents gave to the targeting attributes [29]. One “opt-out” option was included in the DCE to determine whether it was possible to participate in ONS therapy [30]. A D-efficient Bayesian design was developed in Ngene software. Ngene allowed the researcher to force the design to maintain orthogonality while optimizing efficiency [31]. Based on our qualitative interviews, assumptions were made about the direction of ONS therapy preferences for some of the attributes [32]. To reduce the cognitive burden of respondents, 36 pairs of choice sets were generated by using a fractional factorial design in Ngene software, and the survey was randomly divided into 3 blocks, each with 12 choice sets [33].

To test the consistency of the respondents’ choices, the third scenario of each block was repeated as the thirteenth scenario, but with treatments A and B switched [34]. Therefore, in one block of the DCE questionnaire, respondents were presented with 13 choice sets. An example from one of the scenarios is presented in Appendix A. The final survey also included several sociodemographic characteristics to support the investigation of how preferences might differ according to respondents’ characteristics such as their education level or caregivers’ influence.
The draft survey was pilot-tested with 30 respondents recruited from the oncology department of a tertiary hospital to refine the language, test the construction, validate the content, and confirm the direction of the prior assumptions for the attributes.

### Setting and sample

A convenience sampling approach was used to recruit patients from the gastrointestinal surgery and oncology department of a tertiary hospital in Changchun from February 2021 to August 2021. Eligibility criteria were as follows: (1) age ≥ 18 years old; (2) patients were diagnosed by pathology as stage I, II, III, or IV gastric cancer; (3) had distal or total gastrectomy; (4) currently receiving ONS therapy or had received it during the previous year. If the patient had other malignant tumors, or had impaired consciousness and could not communicate normally, they would be excluded.

### Data collection

Surveys were administered by research assistants specifically trained by the research team. We collected explicit and informed consent from potential respondents after providing them with a detailed explanation of how their data would be used. The survey was administered via paper-based questionnaires during face-to-face interviews with assistance from health professionals. Surveys took place during respondents’ hospital stay at a time and location mutually convenient and before hospital discharge. To ensure the quality of the research, the investigator explained in detail the precautions of the questionnaire before the start of the survey and answered the questions that the respondent encountered during the answering process on the spot.

### Data analysis

All analyses were conducted using Stata version 16.0. Respondents’ sociodemographic and clinical characteristics were summarized as mean ± standard deviation (SD) for continuous variables and in frequencies (percentage) for categorical variables.

The mixed logit model was used for the choice data analysis to estimate respondents’ preferences on each attribute. The model allowed for unobserved heterogeneity of preferences. It also allowed for multiple observations from each respondent.

All attribute variables were specified as having a random component except for cost, which was specified as fixed in all models. The statistical significance of coefficients ($\beta$) indicated whether levels of attributes influenced choices, while

| Table 1 | List of final attributes and levels |
|---------|-----------------------------------|
| Attributes | Levels | Description of the attributes |
| Information provider | Dietitian  | Professionals who provide health guidance on the effects of oral nutritional supplements, how to take them, coping strategies for adverse reactions, nutritional monitoring, and follow-up when patients need to take oral nutritional supplements when they suffer from malnutrition |
| Health guidance approach | Attending physician | One-to-one refers to the targeted individual guidance of individual patient when professionals provide health guidance; Group education refers to the targeted and focused education of patients with similar needs when professionals provide health guidance |
| Health guidance approach | Nurse specialist | |
| Health guidance approach | One-to-one | |
| Health guidance approach | Group education | |
| Adverse reactions | Almost none | The degree of gastrointestinal intolerance such as fullness, bloating, nausea, vomiting, and abdominal pain when taking oral nutritional supplements |
| Adverse reactions | Occasionally | |
| Adverse reactions | Often | |
| Flavor | Good taste | The taste experience when taking oral nutritional supplements may be related to the formula, appearance, smell, texture, etc. of the food itself |
| Flavor | Bad taste | |
| Follow-up method | Via outpatient | Tools used by professionals to follow up with patients during the period of taking oral nutritional supplements |
| Follow-up method | Via telephone | |
| Follow-up method | Via WeChat | |
| Follow-up method | Once a week | The number of follow-up visits per unit time by professionals during the period of taking oral nutritional supplements |
| Follow-up method | Once every 2 weeks | |
| Follow-up method | Once every 4 weeks | |
| Psychological support | Yes | During the period of taking oral nutritional supplements, whether professionals provide additional guidance such as emotional support and psychological counseling |
| Psychological support | No | |
| Cost (RMB/week) | 200 | The average weekly cost of purchasing nutritional supplements for patients taking oral nutritional supplements |
| Cost (RMB/week) | 400 | |
| Cost (RMB/week) | 600 | |

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the size of the coefficient indicated the relative importance of one attribute level to another. Willingness to pay (WTP) was calculated by assessing the ratio of the preference of other attributes to the preference of cost. All attribute variables were coded as dummy variables except for cost, which was specified as continuous in all models. All model coefficients were assumed to be normally distributed. The \texttt{nlcom} command was used to simulate the uptake rate, which was when the levels of one or more attributes changed compared with the baseline ONS therapy program, changes in the probability of a respondent receiving an ONS therapy program. Finally, models were stratified by demographic variables to explore differences, in the preferences of respondents with different demographic characteristics. For all calculations, statistical significance was determined at the $p < 0.05$ level.

## Results

### Respondent characteristics

Of the 300 patients surveyed, 232 responses were received, reflecting a 77.33% response rate. Of the 232 responses, 18 respondents did not complete the questionnaire and were excluded; of the remaining 214 eligible respondents, 190 completed the consistency test of the DCE questionnaire and were included in the analysis. The average age of the respondents was $58.05 \pm 11.38$ years old, and there were more men than women, accounting for about 73.16% and 26.84%, respectively. Summary statistics of the study sample ($n = 190$) are given in Table 2.

### Preferences

Table 3 reports the results of the regression model. The results confirmed that all attributes were important to respondents when considering ONS therapy choice, with significant coefficients for almost all levels of each attribute, and the direction of the regression coefficients was consistent with expectations. Good taste, almost no adverse reactions, nurse specialist, one-to-one, telephone follow-up, follow-up once every 2 weeks, psychological support, and lower costs were preferred by respondents compared with the respective reference categories. Compared to other attributes, “Adverse reactions-almost none” had a relatively higher weight ($\beta = 3.43$ [standard error (SE), 0.28]), followed by “Flavor-good taste” ($\beta = 0.68$ [SE, 0.13]) and “Follow-up frequency-once every 2 weeks” ($\beta = 0.52$ [SE, 0.13]), while the impact of “Psychological support” on decision-making was the weakest ($\beta = 0.27$ [SE, 0.10]). Furthermore, significant SD was found across all attribute levels except that “Follow-up frequency,” suggesting preference heterogeneity among the respondents.

### Willingness to pay

Table 4 reports the results of the WTP calculations, which measure how much money an individual would be willing to spend to improve ONS therapy attributes, or would need to be compensated for undesired ONS therapy attributes. The results confirmed that patients showed significant willingness to pay...
for most of the ONS treatment attributes. Respondents were willing to pay 1150.60 RMB (95% confidence interval (CI): 883.08–1418.11) for “Almost no adverse reactions” and 228.22 RMB (95% CI: 144.62–311.83) for “Good taste flavor.” Comparatively speaking, WTP for “Provided psychological support” was the lowest, which was 89.19 RMB (95% CI: 24.18–154.19). There was little difference in the WTP for nurse specialists and attending physicians, which were 135.75 RMB (95% CI: 55.17–216.33) and 106.50 RMB (95% CI: 16.17–196.82) respectively. Respondents’ WTP for “One-to-one approach” and “Telephone follow-up” was roughly the same, about 113 RMB.

**Predicted choice probabilities**

Probabilities of acceptance of a baseline ONS therapy program after a change in the level of one or more of the attributes were simulated, with the most significant findings reported in Fig. 1. With all other baseline attributes held constant, respondents would be 93.73% more likely to accept an ONS therapy program if there were almost no adverse reactions compared to the frequent adverse reactions; when multiple attribute levels changed at the same time, the optimal ONS therapy program increased the probability of receiving ONS therapy by 99.08%. The optimal program needs to meet the following points at the same time: (1) when the respondent took ONS, there were almost no adverse reactions; (2) the provided ONS tasted good; (3) health guidance information was provided by nurse specialists; (4) one-to-one health guidance; (5) followed up via telephone; (6) followed up once every 2 weeks; (7) provided psychological support; and (8) the cost per week was about 200 RMB. If adverse reactions occurred occasionally and...
health guidance information was provided by nurse specialists and followed up once every 2 weeks, respondents would be approximately 94.78% more likely to accept an ONS therapy program, which was close to the optimal program.

Table 4 Regression results with willingness to pay estimates (n = 190)

| Attributes and levels                              | WTPa (RMB) | 95% CIb   |
|---------------------------------------------------|-------------|-----------|
| **Flavor (relative to bad taste)**                |             |           |
| Good taste                                        | 228.22**    | 144.62–311.83 |
| **Adverse reactions (relative to often)**         |             |           |
| Almost none                                       | 1150.60**   | 883.08–1418.11 |
| Occasionally                                      | 791.25**    | 578.51–1003.99 |
| **Information provider (relative to dietitian)**  |             |           |
| Nurse specialist                                  | 135.75**    | 55.17–216.33 |
| Attending physician                               | 106.50*     | 16.17–196.82 |
| **Health guidance approach (relative to group education)** |         |           |
| One-to-one                                        | 113.25**    | 43.59–182.90 |
| **Follow-up method (relative to via outpatient)** |             |           |
| Via telephone                                     | 113.76*     | 18.46–209.06 |
| Via WeChat                                        | 47.08       | −27.81–121.96 |
| **Follow-up frequency (relative to once a week)** |             |           |
| Once every 2 weeks                                | 173.27**    | 80.95–265.59 |
| Once every 4 weeks                                | 57.41       | −12.59–127.40 |
| **Psychological support (relative to no)**        |             |           |
| Yes                                               | 89.19**     | 24.18–154.19 |

aWillingness to pay  
bConfidence interval  
p < 0.05; ** p < 0.01

Fig. 1 Simulated preferences with changes in ONS therapy program characteristics. The baseline ONS therapy program was defined as follows: (1) when the participant took ONS, adverse reactions often occurred; (2) the provided ONS tasted bad; (3) health guidance information was provided by a dietitian; (4) group education health guidance; (5) followed up via outpatient; (6) followed up once a week; (7) not provided psychological support; and (8) the cost per week was about 600 RMB.
Subgroup analysis

Subgroup analysis (see Appendix B) indicated that the observed heterogeneity in the DCE was (at least in part) explained by caregivers, per capita monthly income, education level, adverse reactions, and duration of taking ONS.

The caregivers of patients after gastrectomy were mainly their spouse and children, which were labeled as the children group and the spouse group respectively. In general, the impact of “One-to-one health guidance” on the children group (β: 0.87, p < 0.01) was much stronger than that on the spouse group (β: 0.26, p < 0.05), and they were willing to pay over five times more than the spouse group (416 versus 75 RMB). The lower-income group (β: 0.61, p < 0.01) was more concerned about “Follow-up frequency.” The higher-income group (β: 0.69, p < 0.01) was more concerned about “One-to-one health guidance.” The patients after gastrectomy who took ONS for less than 1 month paid more attention to “Psychological support” (β: 0.40, p < 0.01).

Discussion

Given the poor adherence to ONS therapy among patients after gastrectomy, this study provided an in-depth exploration of the crucial factors that could affect patients’ preferences, allowing either possible product improvements or therapeutic focused adjustments. To our knowledge, this was the first study to quantify patients’ preferences for ONS therapy; our outcomes could be helpful to provide person-centered oral nutrition management strategies.

We found that adverse reactions were the most concerning characteristic for patients after gastrectomy, and they were willing to pay a higher cost to experience ONS treatment with fewer adverse reactions. The main problems patients encountered postoperatively were early satiety, anorexia, dysphagia, reflux, and postprandial dumping syndrome. Especially the incidence of early dumping syndrome was more than 60%, which affected the eating process [35]. Compared with other cancer patients, gastric cancer patients seemed to be more sensitive to gastrointestinal discomfort. In our study, 33.16% of postoperative patients had experienced symptoms of gastrointestinal discomfort during ONS treatment. Diarrhea may be related to the rapid passage of high osmotic pressure nutrient solution through the intestine due to the patient eating too fast [13]. ONS should begin with a low concentration and low volume to minimize diarrhea. Polymeric ONS could prevent related diarrhea because the osmotic pressure was close to isotonic [36]. However, compared with peptide-based ONS, it was more likely to cause abdominal distension. This may be because the polymeric ONS was rich in dietary fiber. When the patient’s intestinal flora was imbalanced, the nutrient residues would decompose and ferment to produce a large amount of gas, which would swell the intestinal tube and increase the tension of the intestinal wall [37]. Therefore, health professionals should pay attention to the management and prevention of adverse reactions when prescribing ONS, choose the appropriate dosage form according to the patient’s gastrointestinal function, and give detailed instructions on the use of the preparation such as the correct temperature, concentration, and dosage.

In our research, the flavor was identified as the second most important attribute. The components of ONS could affect the flavor experience of patients. For example, omega-3 fatty acid, an active ingredient in immune nutrition, had a fishy smell that made patients unwilling to continue taking ONS [14]. Flavor was an important driving force for nutritional intake. Compared with poor-tasting foods, after giving better-tasting foods, research subjects would be willing to consume 44% more energy [38]. It’s worth noting that repeated intake of the same ONS over time may contribute to monotony [39]. At present, the development of ONS on the market in terms of taste was relatively comprehensive in Western countries, and all the different flavors could meet the needs of all kinds of people. While the Chinese market was relatively early in the development stage and the flavors were monotonous [40]. Our results provided a basis for the necessity of the introduction and development of ONS in the Chinese market. Although the cost of ONS was an important factor that affected patients’ treatment choices, it had the least impact compared to other attributes. This may be because our respondents had taken ONS for a short period and the expenses incurred were within the affordable range. However, when the payment was reduced from 600 to 200 RMB per week, the probability of patients receiving ONS treatment would increase by more than 50%. As China’s medical insurance system limited the scope of payment for nutritional supplements or ONS, patients still bore high costs outside of medical insurance, and long-term use will increase the economic burden [41]. Therefore, it is necessary for medical policymakers to consider expanding the reimbursement ratio of medical insurance or reducing the production cost and price of ONS.

We found that patients after gastrectomy showed a preference for health guidance. Studies have shown that providing detailed information on the nutritional needs of patients by medical staff can increase the compliance of hospitalized patients by 41 to 67% [42]. The preference in our sample for a nurse specialist over an attending physician may be because the information given by the nurse specialist was considered by some patients to be easier to understand than that given by the physician [43]. Another study showed that the cooperation of dietitians, nurses, and physicians could promote patient acceptance of nutritional
care [44]. However, patients’ exposure to many sources of information from physicians, dietitians, or nursing assistants may result in unclear information on ONS and its nutritional status [45]. Therefore, in the process of exploring a novel model of multidisciplinary nutritional care, we should attach importance to the role of specialist nurses and standardize the information about ONS to improve compliance.

To our knowledge, there was currently no standardized nutritional follow-up strategy, which may be related to limited medical resources and cost-effectiveness [46]. To a certain extent, our research results provide a perspective for formulating effective follow-up strategies. A systematic review showed that ONS compliance in surveys was significantly lower than in clinical studies, possibly because patients received more follow-up and encouragement from healthcare professionals [47]. More frequent follow-up visits were inconvenient for many patients who did not live near their primary health care facilities, and longer follow-up intervals were not conducive to the timely understanding of the patient’s condition. The preference in our sample for telephone follow-up over other forms might be explained by it being convenient compared to outpatient follow-up, and more traditional compared to WeChat (currently the most popular smartphone application in China for message). Given the limited number of hospital outpatient visits in the wake of the COVID-19 pandemic, electronic follow-up was increasingly favored by patients. Although WeChat was common in daily life in China, considering that our sample was mostly middle-aged and elderly, they were not very familiar with the WeChat function; this may be the reason why WeChat follow-up preference was not significant. Psychological support had the weakest influence on decision-making. This may be because most patients after gastric cancer lived with their families and children, and family support alleviated patients’ anxiety and insecurity [48]. Therefore, when health professionals implement follow-up strategies, encouraging family members of patients to participate in daily diet care might improve compliance.

The results of subgroup analysis showed that patients with different demographic or clinical characteristics had specific preferences. When the main caregiver of gastric cancer patients was their children, and the family’s per capita monthly income was more than 3000 RMB, more emphasis was placed on one-to-one health guidance, expressing the need for personalized health guidance. Patients who took ONS for a short time desired psychological support, which may be related to the burden of the disease. Therefore, individual characteristics should be taken into consideration when formulating intervention strategies and avoid adopting unchanging policies and methods for people with different preferences.

**Strengths and limitations**

There were several strengths in this study. First, in this study, the attributes and levels were developed using a mixed-method approach. The three methods have pros and cons, and they complement each other. Second, to improve the comprehension of the DCE and the precision of the parameters in this study, paper-based questionnaire–assisted face-to-face surveys were conducted and an explanation on how to complete the choice tasks was provided. In total, 88.79% of respondents passed the consistency test, which indicates that the true preferences of the respondents are reflected in this DCE.

Our study also has several limitations. First, as discussed in other stated preference surveys, the true preferences were not revealed because the decisions made were merely hypothetical [49]. Second, due to the inherent limitations of the DCE, we only included the eight attributes considered by the respondents as the most important, and could not reflect the influence of other attributes on the treatment preference of ONS. Finally, this study only included patients from the Department of Oncology and Gastrointestinal Surgery of a hospital in Northeast China, which may not be representative of other patients in China. In future studies, it is necessary to further confirm the information on the preference of Chinese patients after gastrectomy on ONS. International comparisons may also help identify similarities and differences in the ONS therapy preferences.

**Conclusions**

Among the potential strategies for improving ONS compliance, patients show varying degrees of preference for attributes related to ONS therapy. Health professionals should pay attention to the management and prevention of adverse reactions when prescribing nutritional products, and provide diversified ONS products when necessary to meet patients’ preferences. When formulating intervention strategies, health professionals should also consider the different characteristics of patients, emphasize the importance of the role of nurse specialists in a novel model of multidisciplinary nutritional care, standardize ONS information, follow up regularly, and encourage patients’ families to participate in daily nutrition care.

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1007/s00520-022-07154-8.

**Acknowledgements** We would like to thank the medical workers and all the researchers involved in the study.

**Author contribution** QCW: conceptualization; methodology; software; data curation; investigation; writing—original draft; writing—reviewing and editing. HY: conceptualization, methodology, supervision. ZMC: data curation, supervision, validation. JW: data curation, investigation, visualization. JNY: software, validation. MYZ: visualization, validation. HX: conceptualization; methodology; supervision;
writing—reviewing and editing. XYZ: conceptualization; methodology; supervision; writing—reviewing and editing.

**Funding** This work was supported by the funds of the National Natural Science Foundation of China [31800895]; the Undergraduates’ Teaching Reform Project of Jilin University [ALK201946, SK202083, 2020szjpk58].

**Availability of data and material** The data used to support the findings of this study are included within the article, and all data included in this study are available upon request by contact with the corresponding authors.

**Code availability** Not applicable.

**Declarations**

**Ethics approval** The study was approved by the Ethics Committee of the Nursing School of the University of Jilin, China (No. 2020082803), and completed registration in the Chinese clinical trial registry (registration number; ChiCTR2000041047).

**Consent to participate** Informed consent was obtained from all individual respondents included in the study.

**Consent for publication** The manuscript contains any individual person’s data in any form (including individual details, images, or videos); consent for publication was obtained from that person.

**Competing interests** The authors declare no competing interests.

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