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# Identification of core symptoms and symptom clusters in primary hepatocellular carcinoma during the intermittent period between transcatheter arterial chemoembolization treatments

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## Abstract

**Introduction:** Patients with liver cancer frequently receive multiple transcatheter arterial chemoembolization (TACE) treatments. While some studies have investigated the symptoms and symptom clusters that occur following TACE, there is limited understanding of the core symptoms and symptom clusters experienced during the intervals between TACE treatments.

**Objective:** This study aims to identify core symptoms and symptom clusters in patients with primary hepatocellular carcinoma (HCC) during the intermittent period of TACE, providing a reference for precise symptom management.

**Methods:** A convenience sample of 344 patients undergoing intermittent TACE was recruited. Symptom prevalence and severity were evaluated using the Chinese version of the MD Anderson symptom inventory and the HCC-specific symptom module. Principal component analysis was used to extract symptom clusters. A symptom network was constructed to illustrate inter-symptom relationships and to calculate centrality indices.

**Results:** Four symptom clusters were identified: upper gastrointestinal, feeling of illness, emotional-psychological, and liver function impairment. Lack of appetite demonstrated the highest strength ($rs$ = 1.10) and closeness ($rc$ = 0.0076) centrality in the symptom network. The strongest marginal association was found between distress and sadness ($r$ = 0.545).

**Conclusion:** Lack of appetite emerged as the core symptom, while the emotional–psychological cluster was the core symptom cluster. Nursing interventions should prioritize addressing appetite loss and managing emotional symptoms such as distress and sadness to enhance the effectiveness of symptom management during the intermittent period of TACE in patients with primary HCC.

***Keywords:*** Core symptom; Network analysis; Primary liver cancer; Symptom clusters; Transcatheter arterial chemoembolization

## 1. Introduction

In 2022, the National Cancer Center of China reported liver cancer as the second leading cause of cancer-related deaths and the fourth most commonly diagnosed malignancy in the country.[1] Notably, China accounts for more than half of the global burden of primary liver cancer. Globally, liver cancer poses a major public health concern, ranking among the top five causes of cancer-related deaths in 90 countries and regions.[2]

The number of new liver cancer cases is projected to rise by 55% annually from 2020 to 2040, with an estimated 1.4 million new diagnoses expected in 2040.[2] Early-stage hepatocellular carcinoma (HCC) can be treated with curative approaches such as surgical resection, ablation, and liver transplantation.[3] However, a significant challenge in liver cancer management is that most patients are diagnosed at an intermediate or advanced stage due to the subtle or non-specific nature of early symptoms.[4] Although recent advancements in HCC treatment have introduced immune checkpoint inhibitors and tyrosine kinase inhibitors,[5] transcatheter arterial chemoembolization (TACE) remains a critical first-line treatment for patients with intermediate-stage HCC.[6] This treatment has evolved significantly in recent years and is now a widely implemented intervention in clinical settings.

Cancer patients often experience a high symptom burden, frequently encountering multiple concurrent symptoms both during and after treatment. These symptoms tend to manifest in clusters —two or more interrelated symptoms – rather than in isolation, contributing to significant physical and psychosocial dysfunction.[7] In recent years, symptom-specific studies utilizing component and cluster analyses have increasingly focused on the intricate relationships among symptoms, identifying synergistic effects and symptom clusters.[8]

Among patients with HCC undergoing TACE, commonly reported symptoms such as pain, nausea, vomiting, and fever typically appear in clusters of three to six, leading to maladaptive outcomes and increasing the disease burden on both families and society.[9-12] However, the composition of symptom clusters can vary significantly depending on the symptom assessment tools used, the statistical methods applied, and the inclusion of different covariates.

Moreover, patients often require at least three to four, or even more, TACE treatments due to the extensive vascularization of HCC, the presence of multiple tumor foci, and a high recurrence rate. However, few studies have explored the relationships between symptom clusters and the individual symptoms within those clusters in HCC patients during the intermittent period between TACE treatments.

With recent advancements in clinical research methodologies and information technology, the concept of symptom networks has been increasingly utilized in chronic disease management. Network analysis enables the visualization and quantification of relationships among symptoms and symptom groups. By calculating node centrality, edge weights, and other network metrics, this method provides valuable insights into the underlying complexity of symptom clusters.[13,14]

This study aims to identify core symptoms and core symptom clusters in liver cancer patients during the intermittent period between TACE treatments by constructing a symptom network. The findings are expected to support the development of an integrated symptom management model to enable more accurate and effective clinical interventions.

## 2. Materials and methods

### 2.1. Participants

This study was approved by the Ethics Committee of Jiangnan University (Approval number: JNU20221201IRB39). All participants provided written informed consent prior to participation and were consecutively enrolled in accordance with the study protocol.

Inclusion criteria were as follows:

(i) Diagnosed with primary HCC based on the Chinese guidelines for diagnosis (2022 edition),[15]
(ii) Aged over 18 years,
(iii) Had clear consciousness, with adequate comprehension and expression abilities,
(iv) Completed at least one TACE treatment and were in the intermittent period between treatments.

Exclusion criteria included:

(i) Concurrent severe heart condition or brain disease,
(ii) Participation in other clinical trials that could interfere with the assessment of symptoms.

Based on the sample size estimation method for network analysis,[16] if there are $P$ nodes in the network, at least $P$ ($P$–1)/2 participants are required to ensure statistical power. In this study, $P$ represented 19 symptoms, indicating a minimum required sample size of 152. Ultimately, 344 patients were included in the analysis.

### 2.2. Measures

#### *2.2.1. Demographic and clinical characteristics*

Demographic and clinical data were collected using a self-administered questionnaire. Demographic information

included age, gender, educational background, and marital status. Clinical data comprised the patient's Child-Pugh classification and the number of TACE treatments received.

#### *2.2.2. MD Anderson Symptom Inventory (MDASI-C) and primary liver cancer-specific symptom module (TSM-PLC)*

Symptom prevalence and severity were assessed using the Chinese version of the MDASI-C[17,18] and the TSM-PLC.[9] The MDASI-C is a self-report instrument that evaluates 13 common cancer-related symptoms and their impact on daily functioning and emotional well-being. It has demonstrated high reliability, with a Cronbach's α coefficient ranging from 0.82 to 0.94. The TSM-PLC, developed by Wang *et al.*,[9] is a validated and reliable symptom module designed to capture liver cancer-specific symptoms. The scale has shown good internal consistency (Cronbach's α coefficient = 0.835) and strong content validity (content validity index = 0.91). All items were rated on a numerical scale ranging from "0" (no symptom) to "10" (worst imaginable).

### 2.3. Data collection

In this study, data were collected using a structured questionnaire. Before data collection, three investigators underwent standardized training to ensure consistency. Patients were thoroughly informed about the study's objectives, significance, and procedures for completing the scales. Eligible participants had received at least one TACE treatment and were hospitalized while awaiting the next scheduled treatment. All participants provided written informed consent after fully understanding the study and were then asked to complete the MDASI-C and TSM-PLC assessments.

A total of 352 questionnaires were distributed. Of these, three participants were excluded due to deterioration in health that prevented further participation, and five declined to complete the survey due to lack of interest. Ultimately, 344 valid questionnaires were collected, resulting in an effective response rate of 97.72% (344/352).

### 2.4. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics (version 26.0, IBM Corp, Armonk, USA) and R software (version 4.2.3, R Core Team, 2023; https://www.r-project.org/; Austria). Descriptive statistics, including means, standard deviations, frequency distribution, and component proportions, were employed to summarize demographic characteristics, symptom prevalence, and symptom severity.

The associations between covariates and overall symptom severity were evaluated using stratified linear regression analysis. Variables that reached statistical significance ($p<0.001$) after adjusting for potential confounders were subsequently included in the network analysis to enhance the accuracy of symptom relationship identification.

Exploratory factor analysis was employed to identify symptom clusters using the principal component method with maximum variance rotation. Symptoms with an incidence rate of <20% were excluded to ensure the stability of the resulting clusters and symptom networks.[19] The internal consistency of each symptom cluster was assessed using Cronbach's α coefficient.

The following criteria were used to evaluate the symptom clusters:

(i) Factor eigenvalue ≥1,
(ii) Factor loading ≥0.4 (in cases of cross-loading, the item was assigned based on the highest loading),
(iii) At least two symptoms per factor,
(iv) Cronbach's α coefficient >0.7.

The qgraph package in the R statistical environment was utilized to construct sparse and interpretable network models for analyzing clinical symptom severity. These networks were estimated using a regularized approach that combines the augmented Bayesian information criterion with L1-penalized regression modeling.[16] Bidirectional interaction graphs were generated using spring-embedder visualization and Fruchterman-Reingold graph layout algorithms.[20]

Node centrality is a critical indicator for identifying core symptoms from a mechanistic perspective. Centrality analysis was conducted using three indices: strength, betweenness, and closeness. Among these, strength is considered the most reliable indicator, with higher values reflecting greater symptom centrality within the network based on underlying mechanisms.[21]

The R package bootnet was employed to assess the accuracy and stability of the estimated network. Precision was evaluated by calculating 95% confidence intervals (CI) for each edge weight using 1,000 bootstrap samples. Stability was assessed by computing the correlation stability (CS) coefficient with 1,000 bootstrap samples, with a target CS coefficient of more than 0.5 and a minimum acceptable threshold of 0.25.[22]

## 3. Results

### 3.1. Demographic and clinical characteristics

This study involved HCC patients who underwent TACE treatment between June 2022 and December 2023 at the Affiliated Hospital of Jiangnan University and were awaiting their subsequent TACE treatment. Data from 344 participants aged between 34 and 84 years were analyzed

(Figure 1). The majority of participants are male (85.47%) and either unemployed or retired (77.91%). A significant proportion of participants reported substantial financial pressure (77.91%) and had a Child-Pugh class A liver function status (78.78%). Detailed participant characteristics are presented in Table 1.

### 3.2. Occurrence of symptoms and symptom clusters

The frequency and severity of each symptom and the results of the factor analysis are shown in Table 2. Symptoms with an incidence rate of <20% during the TACE interval – such as shortness of breath (9.6%), amnesia (12.79%), nausea (17.44%), vomiting (9.01%), numbness (4.36%), diarrhea (15.12%), and fever (15.14%) – were excluded from the factor analysis to reduce the influence of low-incidence symptoms on the results.[4]

The most prevalent symptoms are fatigue (86.00%), distress (81.40%), and sadness (73.54%). Among these, the most severe symptoms are fatigue (3.05 ± 1.60), distress (2.75 ± 1.63), and sleep difficulty (2.60 ± 2.14). Exploratory factor analysis of the 12 symptoms (Table 2) yields a Kaiser-Meyer-Olkin statistic of 0.795 and a Chi-square value of approximately 1,499.17 (Bartlett's sphericity test, $p<0.001$).

Four symptom clusters with eigenvalues >1 are extracted, accounting for a cumulative contribution of 69.66% to the total variance:

(i) Upper gastrointestinal symptom cluster: Weight loss, lack of appetite, pain, bloating, and dry mouth.
(ii) The feeling of illness symptom cluster: Sleep difficulty, drowsiness, and fatigue.

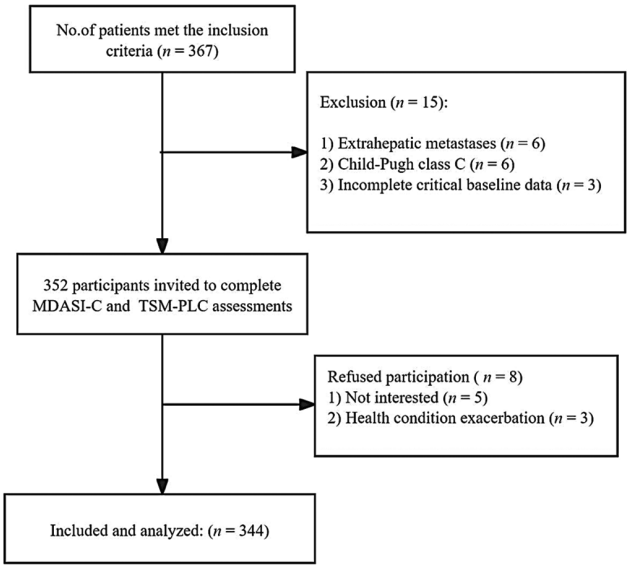


**Figure 1.** Flow diagram of the recruitment process
Abbreviations: MDASI-C: MD Anderson Symptom Inventory; TSM-PLC: Primary liver cancer-specific symptom module.

(iii) Emotional and psychological symptom cluster: Distress and sadness.
(iv) Liver function impairment symptom cluster: Jaundice and itching.

The Cronbach's α coefficients for these clusters are 0.791, 0.778, 0.826, and 0.745, respectively.

### 3.3. Associated factors with the overall symptom severity

This study utilized multivariate linear modeling to evaluate composite symptom profiles, with the composite symptom severity score as the primary outcome measure. To develop multiple linear regression models, the analytical framework included 11 predictors—such as age, gender, educational attainment, Child-Pugh status, Barcelona clinic liver cancer (BCLC) stage, employment status, number of prior TACE treatments, and financial pressure.

Table 3 presents the linear regression models for overall symptom severity. The BCLC stage (β = 0.390, $p<0.0001$), Child-Pugh status (β = 0.151, $p=0.002$), number of previous TACE treatments (β = 0.123, $p=0.018$), and financial pressure (β = 0.248, $p<0.0001$) are significantly associated with higher overall symptom severity scores. These factors are subsequently included in the network analysis and controlled as potential confounding variables.

### 3.4. Network analysis of symptoms and accuracy of the edge weight

The symptom network demonstrates a strong correlation between distress and sadness ($r = 0.545$), as well as between itching and jaundice ($r = 0.534$) (Figure 2). Notably, lack of appetite (strength = 1.10) and sadness (strength = 0.93) exhibit the highest strength values. Additionally, lack of appetite demonstrates the highest closeness centrality (closeness = 0.0076) and the highest betweenness centrality (betweenness = 52) (Figure 3).

After incorporating clinical covariates into the network, the weight of each connection decreases; however, the overall connection pattern between symptoms remains largely unchanged. Centrality analyses further reveal that, based on strength, lack of appetite ($rs = 1.10$ vs. $rs = 1.13$) is the most central symptom, and the distress–sadness pair ($r = 0.545$ vs. $r = 0.527$) remains the most central symptom cluster in both adjusted and unadjusted networks.

In this study, a nonparametric bootstrap sampling method was employed to estimate 95% CIs for all edge weights, thereby assessing their precision. The narrow bootstrap CIs indicate that the network estimation is highly accurate (Figures 4 and 5).

**Table 1. Characteristics of participants (*n*=344)**

| Characteristics | Number of participants (*n*) | Percentage |
|---|---|---|
| Age (years) | | |
| 18 – 44 | 15 | 4.36 |
| 45–59 | 148 | 43.02 |
| ≥60 | 181 | 52.62 |
| Gender | | |
| Male | 294 | 85.47 |
| Female | 50 | 14.53 |
| Education attainment | | |
| Primary school or below | 64 | 18.60 |
| Junior and senior school | 266 | 77.33 |
| College or university | 14 | 4.07 |
| Employment | | |
| Yes | 42 | 12.21 |
| Otherwise | 302 | 87.79 |
| Child–Pugh score | | |
| A | 271 | 78.78 |
| B | 73 | 21.22 |
| Comorbidities | | |
| Diabetes | 84 | 24.42 |
| Hypertension | 130 | 37.79 |
| Number of previous TACE treatments | | |
| 1 – 2 | 168 | 48.84 |
| 3 – 4 | 108 | 31.39 |
| ≥5 | 68 | 19.77 |
| Marital status | | |
| Married | 333 | 96.80 |
| Single or divorced | 11 | 3.20 |
| Financial pressure | | |
| Not at all | 16 | 4.65 |
| A little bit | 60 | 17.44 |
| Somewhat | 208 | 60.47 |
| Very much | 60 | 17.44 |
| Duration of cancer survivorship (months) | | |
| <6 | 116 | 33.72 |
| 6 – 12 | 69 | 20.06 |
| >12 | 159 | 46.22 |
| BCLC stage | | |
| A | 24 | 6.98 |
| B | 202 | 58.72 |
| C | 118 | 34.30 |

Abbreviations: BCLC: Barcelona clinic liver cancer; TACE: Transcatheter arterial chemoembolization.

### 3.5. Stability of centrality indicators

In terms of the subset bootstrap, the CS coefficient of node strength is 0.52 for the network without clinical covariates and 0.59 for the network with clinical covariates (Figure 6). These results indicate that strength centrality rankings exhibit higher stability compared to closeness and betweenness.

## 4. Discussion

To the best of available knowledge, this is the first study in China to explore symptom clusters and conduct symptom network analysis in primary HCC patients during the intermittent period between TACE treatments. This study identifies four symptom clusters – upper gastrointestinal, feeling of illness, emotional and psychological, and liver function impairment – during this interval. The number and composition of these clusters differ slightly from those reported in previous studies.[11,23,24] Network analysis reveals that lack of appetite is the core symptom, while distress and sadness exhibit the strongest correlation. Furthermore, fatigue emerges as the most prevalent and severe symptom experienced by HCC patients during this treatment interval.

Additionally, the study demonstrates that the BCLC stage, financial pressure, Child-Pugh stage, and the number of prior TACE treatments significantly influence symptom severity. Patients with advanced BCLC stages often exhibit reduced physical activity levels, making them more susceptible to a variety of distressing symptoms. Those experiencing significant financial burdens tend to report higher levels of distress, likely due to limited access to social support systems. Patients undergoing multiple TACE sessions often face prolonged treatment and recovery periods, during which adverse effects progressively accumulate and intensify.

Previous study indicates that prolonged cancer treatment cycles can increase the incidence of adverse effects, potentially leading patients to lose hope.[25] In addition, patients classified as Child-Pugh grade B are more likely to experience severe symptoms due to impaired liver function following interventional therapy.

Lack of appetite emerges as the core symptom, demonstrating the highest values for strength, betweenness, and closeness in the network analysis. Nausea – commonly occurring after TACE treatment – often causes significant discomfort, making it difficult for patients to eat, which in turn leads to altered taste perception and subsequent appetite loss.[26] In patients with HCC, contributing factors such as cirrhosis, portal hypertension, portal hypertensive gastropathy, and hepatic insufficiency may further exacerbate appetite loss.[27] Furthermore, negative emotional

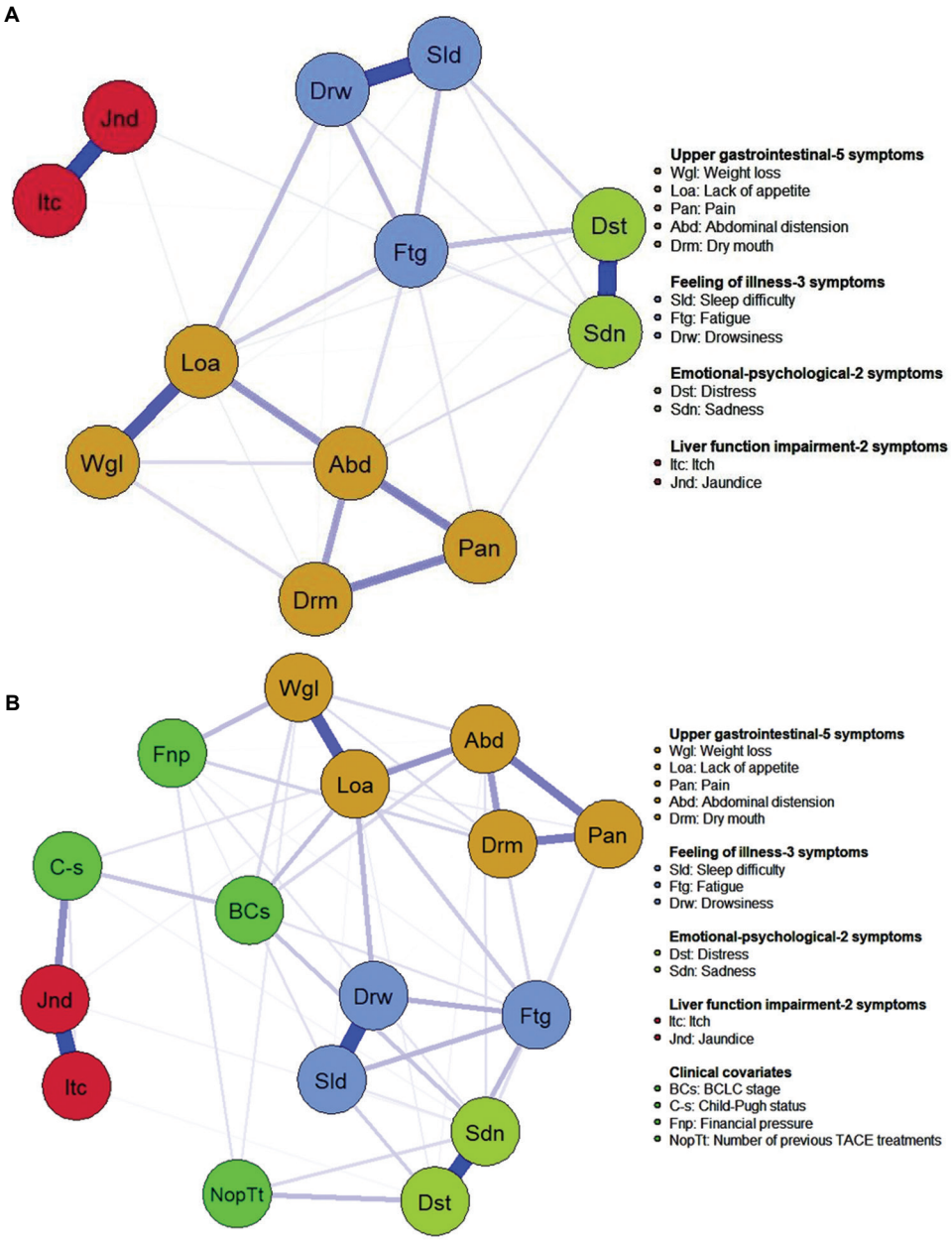


**Figure 2.** Symptom networks of the total sample ($n$ = 344): (A) without clinical covariates and (B) with clinical covariates. Node colors represent different symptom clusters: Red for liver function impairment, gray for upper gastrointestinal symptoms, light green for emotional-psychological symptoms, blue for the feeling of illness, and dark green for clinical covariates.
Abbreviations: Abd: Abdominal distension; BCs: Barcelona clinic liver cancer; C-s: Child-Pugh status; Drm: Dry mouth; Drw: Drowsiness; Dst: Distress; Ftg: Fatigue; Gnd: Barcelona clinic liver cancer stage; Itc: Itch; Jnd: Jaundice; Loa: Lack of appetite; Nop Tt: Number of previous transcatheter arterial chemoembolization treatments; Pan: Pain; Sdn; Sadness; Sld: Sleep difficulty; Wgl: Weight loss; Fnp: Financial pressure; TACE: Transcatheter arterial chemoembolization.

states can impair both appetite and gastrointestinal function, affecting digestion and nutrient absorption.[28]

Network theory suggests that targeting central symptoms in interventions may help mitigate the broader symptom network, thereby enhancing the precision and effectiveness of treatment strategies.[29] Healthcare professionals should encourage patients to promptly report changes in appetite and implement integrated symptom management strategies aimed at improving nutritional intake. Patients may benefit from consuming

**Table 2. Symptom prevalence, severity, and cluster analysis (*n*=344)**

| Symptom cluster | *n* (%) | Mean±SD | F1 | F2 | F3 | F4 | Variable commonality |
|---|---|---|---|---|---|---|---|
| Upper gastrointestinal | | | | | | | |
| Weight loss | 19 (56.70) | 1.61±1.59 | 0.632 | 0.389 | −0.225 | 0.086 | 0.609 |
| Lack of appetite | 227 (66.00) | 2.22±1.75 | 0.624 | 0.491 | 0.057 | 0.108 | 0.645 |
| Pain | 150 (43.60) | 1.48±1.89 | 0.749 | −0.029 | 0.267 | −0.042 | 0.635 |
| Abdominal distension | 231 (67.20) | 2.07±1.60 | 0.762 | 0.131 | 0.234 | −0.003 | 0.652 |
| Dry mouth | 143 (41.69) | 1.13±1.43 | 0.735 | 0.107 | 0.102 | 0.000 | 0.563 |
| Feeling of illness | | | | | | | |
| Sleep difficulty | 241 (71.10) | 2.60±2.14 | 0.088 | 0.827 | 0.242 | 0.012 | 0.751 |
| Drowsiness | 225 (65.40) | 1.97±1.55 | 0.133 | 0.832 | 0.181 | 0.018 | 0.743 |
| Fatigue | 296 (86.00) | 3.05±1.60 | 0.270 | 0.591 | 0.352 | 0.056 | 0.549 |
| Emotional-psychological | | | | | | | |
| Distress | 280 (81.40) | 2.75±1.63 | 0.135 | 0.306 | 0.821 | −0.036 | 0.788 |
| Sadness | 253 (73.54) | 2.19±1.52 | 0.212 | 0.251 | 0.836 | 0.075 | 0.812 |
| Liver function impairment | | | | | | | |
| Itching | 69 (20.10) | 0.60±1.31 | −0.012 | 0.071 | −0.071 | 0.887 | 0.796 |
| Jaundice | 71 (20.60) | 0.56±1.17 | 0.045 | −0.002 | 0.106 | 0.896 | 0.895 |
| Cumulative variance contribution ratio (%) | - | - | 21.96 | 41.20 | 56.16 | 69.66 | - |
| Cronbach's α | - | - | 0.791 | 0.778 | 0.826 | 0.745 | - |

Abbreviation: SD: Standard deviation.

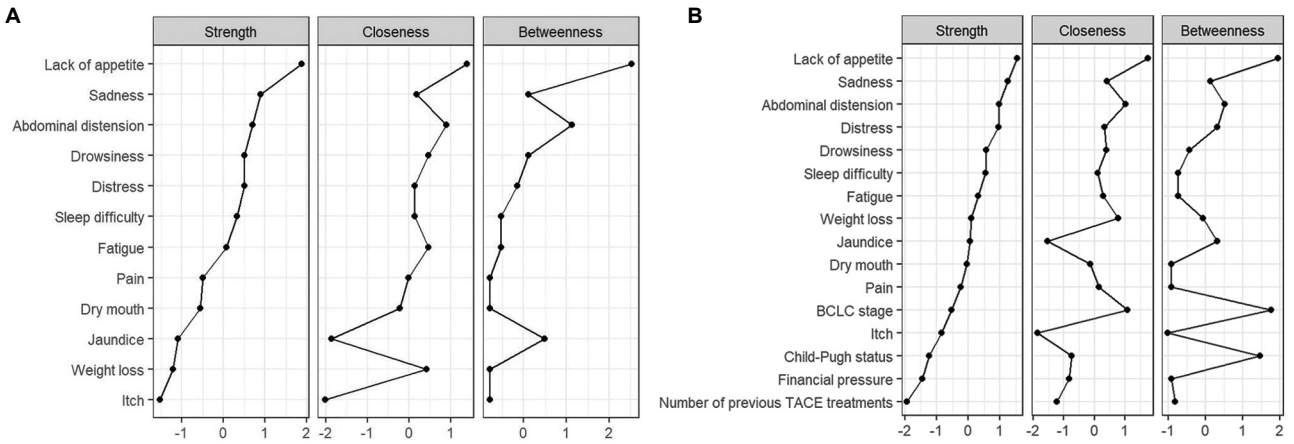


**Figure 3.** Centrality indices of symptoms network nodes: (A) without clinical covariates and (B) with clinical covariates.
Abbreviations: BCLC: Barcelona clinic liver cancer; TACE: Transcatheter arterial chemoembolization.

smaller, more frequent meals throughout the day. Due to liver dysfunction, protein intake should be carefully regulated, with an emphasis on plant-based sources. Diets should also include essential minerals such as iron, calcium, magnesium, and zinc, as well as adequate vitamins. In addition, healthcare providers should offer dietary guidance by recommending suitable recipes and providing food exchange charts tailored specifically for patients undergoing TACE for primary liver cancer. Further research into the central role of appetite loss and its underlying mechanisms is essential for refining symptom management and improving patient outcomes.

Distress and sadness emerge as prominent symptoms with the strongest associations within the overall symptom network. The emotional–psychological symptom cluster constitutes a significant and consistent component of the symptom network in individuals with cancer.[20] Distress is highly prevalent among cancer patients and is frequently associated with maladjustment, relational difficulties,

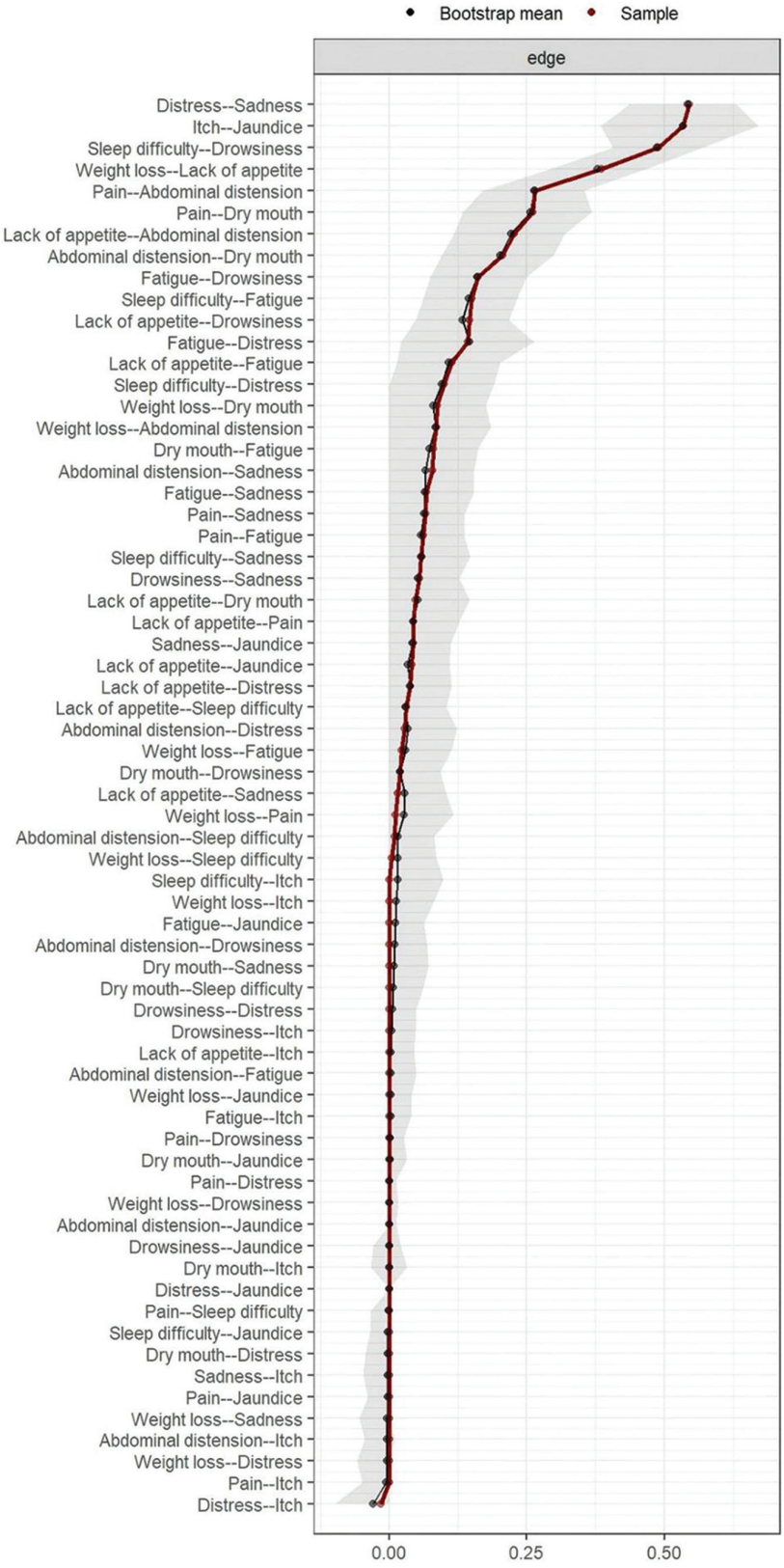


**Figure 4.** Bootstrap analysis results of the edge weights without clinical covariates

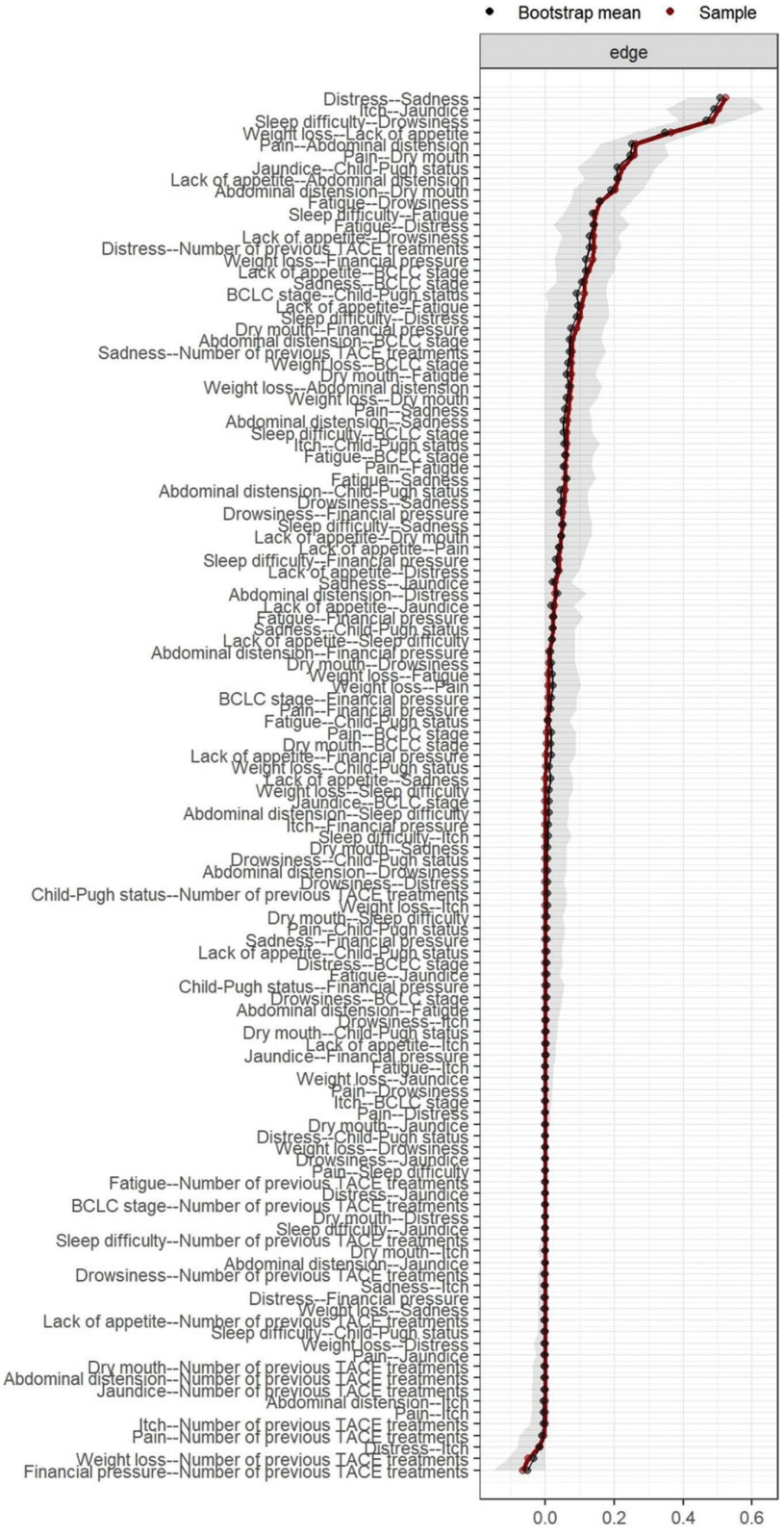


**Figure 5.** Bootstrap analysis of edge weights with clinical covariates
Abbreviations: BCLC: Barcelona clinic liver cancer; TACE: Transcatheter arterial chemoembolization.

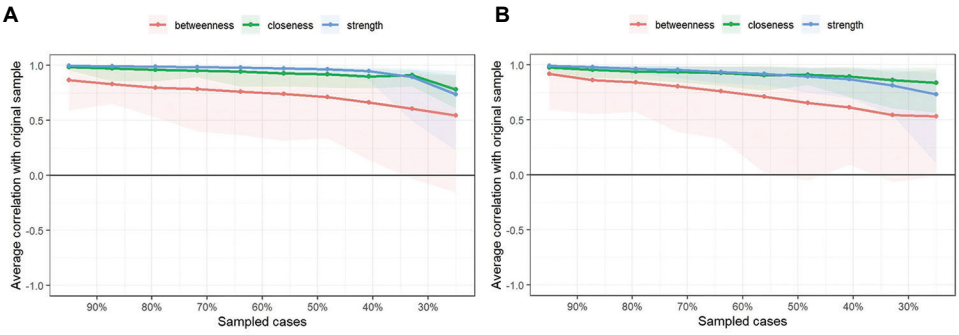


**Figure 6.** Correlation stability coefficient for strength, expected influence, and closeness: (A) without clinical covariates and (B) with clinical covariates

**Table 3. Results of the linear regression model examining overall symptom severity**

| Characteristics | *β* | *p* |
|---|---|---|
| Gender | 0.073 | 0.116 |
| BCLC stage | 0.389 | <0.0001 |
| Age | −0.057 | 0.238 |
| Education attainment | −0.024 | 0.612 |
| Employment | −0.049 | 0.291 |
| Child-Pugh status | 0.148 | 0.002 |
| Comorbidities | 0.020 | 0.657 |
| Number of previous TACE treatments | 0.124 | 0.017 |
| Marital status | 0.045 | 0.332 |
| Financial pressure | 0.248 | <0.0001 |
| Duration of cancer survivorship | −0.060 | 0.253 |

Abbreviations: BCLC: Barcelona clinic liver cancer; TACE: Transcatheter arterial chemoembolization.

and demoralization.[30] A study by Hongqi *et al.*[24] in China reported that perioperative affective and neurological symptoms tend to persist in patients with primary liver cancer. Psychological distress in these patients is influenced by factors such as the complexity of treatment, inadequate assessment of their condition, unmet care needs, and the presence of distressing physical symptoms. Patients undergoing TACE often require multiple treatment cycles, which may exacerbate emotional distress due to prolonged recovery periods, financial burden, and concerns about disease recurrence, progression, and mortality.[31] In clinical practice, post-TACE symptom management typically prioritizes physical symptoms such as nausea, vomiting, abdominal pain, and fever, while psychological symptoms are frequently overlooked. Evidence suggests that only about 10% of patients experiencing psychological distress are identified and receive appropriate psychological support.[32,33]

A network analysis study of gastric cancer patients highlights that addressing psychological distress and promoting emotional well-being are critical strategies for improving outcomes across the entire cancer trajectory.[34] Consequently, early identification and psychological adjustment to reduce emotional distress should be integral components of long-term symptom management. Healthcare providers should educate patients on treatment expectations prior to TACE, guide them in assessing symptom severity following the procedure, and emphasize the importance of recognizing their individual needs and circumstances. Psychological interventions – such as stress reduction techniques, mindfulness-based therapies, meaning-centered interventions, dignity therapy, life review, and spiritually oriented meditation – should be tailored to meet the specific psychological and emotional needs of each patient.[35]

Fatigue is the most prevalent and severe symptom reported among cancer patients. It is characterized as a persistent sense of weariness that is subjectively experienced and not necessarily related to physical activity. With an incidence rate ranging from 14% to 100%, fatigue has consistently been identified as the most prevalent symptom among cancer survivors in various studies.[36] This symptom can significantly diminish hope and negatively impact quality of life. It impairs functional capacity, disrupts daily routines, limits social interaction, and may ultimately reduce life expectancy.[37] Regular assessment of fatigue and patient education on effective management strategies are essential for improving quality of life. Interventions such as massage therapy and aerobic exercise have shown potential in alleviating fatigue-related symptoms.[38]

## 5. Limitations

Several limitations should be considered in interpreting the findings of this study. First, potential bias may have been introduced by the exclusion of symptoms with low

incidence rates (<20%). Second, the study was conducted at a single center with a relatively small sample size, which may limit the generalizability of the results. Future research should involve multicenter studies with larger sample sizes to improve the generalizability of the data. Third, the cross-sectional design of this study does not allow for the determination of causal relationships between the symptoms. Longitudinal studies are needed to examine the dynamic trajectories of symptom networks and centrality indices over time. This approach would help clarify symptom causality and guide the identification of effective intervention targets for more precise and efficient clinical symptom management.

## 6. Conclusion

This study explored the multidimensional symptoms experienced by HCC patients during the interval between TACE treatments using a cross-sectional survey. Four symptom clusters were identified: upper gastrointestinal, feeling of illness, emotional-psychological, and liver function impairment. Network analysis revealed a lack of appetite as the core symptom during the TACE treatment interval, whereas the emotional-psychological symptom cluster emerged as the core symptom cluster. Future research should focus on identifying these core symptoms and symptom clusters to develop targeted interventions that improve clinical outcomes and patient care.

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## Conflict of interest

The authors declare that they have no conflict of interest.

## Author contributions

*Conceptualization*: Jianfeng Zhang
*Formal analysis*: Xia Shen
*Investigation*: Jianfeng Zhang, Hongyan Duan, Jie Zhang
*Methodology*: Mengchen Ji
*Writing–original draft*: Jianfeng Zhang
*Writing–review & editing*: Yueqin Ni

## Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of Jiangnan University (Approval number: JNU20221201IRB39). Written informed consent was obtained from all participants prior to their enrollment.

## Consent for publication

Written informed consent for publication was obtained from all participants before their enrollment.

## Availability of data

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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