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Original Article

Symptoms experienced after transcatheter arterial chemoembolization in patients with primary liver cancer: A network analysis

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ABSTRACT

Objective: This study aimed to establish a symptom network for patients with primary liver cancer post-transcatheter arterial chemoembolization (TACE), identifying core and bridge symptoms. The goal is to provide a foundation for precise and comprehensive nursing interventions.
Methods: A total of 1207 post-TACE patients were included using a consecutive sampling method. Data collection involved a general information questionnaire, the Anderson Symptom Assessment Scale, and a primary liver cancer–specific symptom module. The symptom network was constructed using the R language.
Results: In the overall network, distress exhibited the highest strength ($r_s = 1.31$) and betweenness ($r_b = 62$). Fatigue had the greatest closeness ($r_c = 0.0043$), while nausea and vomiting ($r = 0.76 \pm 0.02$) had the highest marginal weights. Nausea had the highest bridge strength ($r_{bs} = 5.263$). In the first-time TACE-treated symptom network, sadness ($r_{bs} = 5.673$) showed the highest bridge strength, whereas in the non-first-time symptom network, fever ($r_{bs} = 3.061$) had the highest bridge strength.
Conclusions: Distress serves as a core symptom, and nausea acts as a bridge symptom after TACE treatment in liver cancer patients. Interventions targeting bridge symptoms should be tailored based on the number of treatments, enhancing the quality of symptom management.

Introduction

In China, primary liver cancer is currently the second leading cause of cancer death and the fourth most frequent malignant tumour.[1] Infection, alcohol abuse, and aflatoxins significantly increase the risk of liver cancer in Asian populations.[2] Given the insidious nature of the early symptoms, patients are often diagnosed when the disease is in the middle or late stages. For patients with intermediate-stage liver cancer, transcatheter arterial chemoembolization (TACE) is a crucial first-line therapeutic option and an important step in the treatment of primary liver cancer.[3,4] This method is wellestablished and widely applied.

Patients often experience multiple symptoms simultaneously during and after cancer treatment, resulting in physical–psycho–social dysfunction owing to the consequences of the disease itself and the therapy.[5,6] Symptom-specific research is also increasingly focused on the complex relationships between symptoms, the discovery of synergistic effects between symptoms, and the identification of symptom clusters through component analysis and cluster analysis.[7,8] Previous preliminary studies investigating and analysing the symptoms of patients treated with TACE for liver cancer, including the prevalence of symptoms and symptom clusters, have shown that patients tend to experience a variety of symptoms—such as fever, pain, fatigue, nausea, and vomiting—and the existence of 3–6 symptom clusters, which lead to physiological, psychological, and social maladaptation and aggravate the burden on the family and society.[9–11] Owing to differences in the symptom survey scales chosen, statistical methods, and other covariates included in the analyses, the findings of these studies currently vary, and there is controversy regarding the relationship between symptoms within cluster.[12,13] Regarding interventions, the current literature focuses on the management of a particular symptom in patients with TACE for liver cancer. The existence of multiple symptoms requires the provision of the corresponding multiple sets of measures; however, currently constructed symptom management measures have low efficiency and accuracy. Nursing staff members need to know how to recognise the complex

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relationship between the symptoms of TACE patients with liver cancer, analyse the mechanism behind the symptoms to identify the core symptoms, and then conduct precise and effective interventions.

In recent years, with the development of information technology and changes in clinical research concepts, the concept of symptom networks has been gradually applied in chronic disease management. Network analysis provides a new approach to identifying core symptoms and gain insights into the complexity of symptom clusters by visualising and quantitatively explaining the relationships between various symptoms and symptom clusters.[14–16] More precise interventions are created by identifying node centrality, edge weights, and other network metrics.[16] The current study constructed a symptom network of multidimensional symptom experiences of patients with liver cancer following TACE treatment by means of network analysis to explore their core symptoms, bridge symptoms, and correlations among symptoms. This will provide a basis for the future construction of an integrative symptom management model that expands the core symptoms to different symptoms with potentially the same factors and develops from a single symptom management regime to one that has an integrative function.

Methods

Study design and settings

Patients with liver cancer who had received TACE at Zhongshan Hospital, Fudan University, between October 2022 and June 2023 were enrolled using a consecutive sampling technique. Zhongshan Hospital ranks among China's most prominent and experienced institutions for treating liver cancer, attracting patients from various provinces.

Participants

Patients who met the following criteria were included: (1) had been assessed to require TACE after receiving a clinical diagnosis of primary liver cancer; (2) aged 18 years or older; (3) able to perform the verbal and written communication required for this study; and (4) aware of their disease and agreed to participate. Patients with cognitive and mental impairments as well as other major comorbidities were excluded. Finally, 1207 patients were enrolled.

Measures

Data were collected in the ward on the day after patients with liver cancer underwent TACE. Questionnaires were used to collect information about self-reported symptoms and specific sociodemographic and clinical data. Patients who could independently complete the questionnaire while conscious were self-administered by the researcher after distributing a paper questionnaire, while patients with minor difficulties were questioned by the researcher on an item-by-item basis.

Self-reported symptoms

A multi-symptom self-assessment tool, the Anderson Symptom Assessment Scale, was used to assess the severity of 13 cancer-related symptoms: pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness or tingling in the past 24 h.[17] Each item is rated from '0' (no symptoms) to '10' (the most severe imaginable). The Cronbach's alpha coefficient was 0.87, indicating good internal consistency.

To identify the specific symptoms of patients with liver cancer, a symptom module specific to primary liver cancer (TSM-PLC) was used as it has good reliability (Cronbach's $\alpha = 0.835$) and content validity (content validity index = 0.910).[18] The TSM-PLC comprises six symptom entries—feeling bloated, diarrhoea, weight loss, jaundice, itching, and fever—rated on the same scale: from '0' (no symptoms) to '10' (the most severe imaginable).

In our sample, we utilized both the Anderson Symptom Assessment Scale and the TSM-PLC to assess symptoms (Cronbach's alpha = 0.890). The overall symptom severity score is calculated as the sum of all individual symptom severities.

Sociodemographic and clinical data

We collected sociodemographic information from participants using a self-designed general information questionnaire. The sociodemographic variables included age (continuous), gender (male = 1; female = 2), education attainment (primary school or below = 1; otherwise = 0), marital status (married = 1; single or divorced = 0), current residence (urban = 1; rural = 2), family history of tumours (yes = 1; otherwise = 0), and employment status (yes = 1; otherwise = 0). Disease and treatment-related variables included duration of cancer survivorship (continuous), presence of comorbid chronic viral hepatitis (yes = 1; no = 0), history of tumour removal surgery (yes = 1; no = 0), cirrhosis of the liver (yes = 1; no = 0), number of previous TACE treatments (continuous), chronic comorbidities (hypertension = 1; diabetes = 2; cardiovascular disease = 3; otherwise = 4), Child–Pugh grade ('A' = 1; 'B' = 2; 'C' = 3), and Eastern Cooperative Oncology Group (ECOG) score ('0' = 1; '1' = 2; '2' = 3; '3' = 4).

Data analysis

To statistically analyse the data for this investigation, R4.1.3 software was employed. Means, standard deviations, frequencies, and component ratios were used to describe the general information and the incidence and severity of symptoms in the study population. The statistical significance between covariates and overall symptom severity was tested using stratified linear regression analysis. After controlling for confounders, the most significant factors in the regression analyses ($P < 0.001$) were included in the network analyses, thereby more accurately determining the relationship between symptoms. Symptoms with factor loadings > 0.4 were retained to form symptom clusters using exploratory factor analysis combined with maximum variance orthogonal rotation.

The *Qgraph* module in the R software was used to construct sparse complex networks based on symptom severity using the extended Bayesian criterion in conjunction with least absolute shrinkage and selection operator regression analysis.[19,20] Undirected association networks were constructed using the spring layout and Fruchterman–Reingold approaches.[21]

Utilising the R package *bootnet*, we used bootstrapping techniques to evaluate the network's accuracy and stability.[22] To evaluate the precision of the estimation network, which was developed using nonparametric bootstrapping, we calculated 95% confidence intervals (CIs) for each edge weight value using 1000 bootstrap samples. Additionally, the stability of the estimated network was assessed by calculating the correlation stability coefficient (CS-coefficient) with 1000 bootstrap samples. This assessment was guided by a subset of case sets, aiming for a CS-coefficient of preferably 0.5 or higher, but considering a minimum threshold of 0.25.[19,23]

We used strength (the sum of the absolute values of the edge weights between a node and all the nodes it is directly connected to), closeness (the inverse of the average distance between a node and the nodes it is connected to), and betweenness (the number of times a node appears in all the shortest paths in the network) to describe the central role of nodes within a network.[19] Among these indicators, strength is regarded as the most reliable indicator of centrality. A higher value indicates that a symptom is more central within the network regarding its underlying mechanisms.[21]

Additionally, the *mgm* package was used to identify the predictability of each code.[24] Symptom nodes with high predictability could potentially be managed by intervening in the surrounding nodes.[25,26]

Table 1
Characteristics of participants ($N = 1207$)

Characteristics	*n* (%), Mean ± SD (IQR)
Age (years)	56.77 ± 10.03 (22–83)
18–44	146 (12.1)
45–59	543 (45.0)
60–74	490 (40.6)
≥ 75	28 (2.3)
Duration of cancer survivorship (months)	23.34 ± 35.76 (0.5–324)
≤ 1	98 (8.1)
> 1, ≤ 3	290 (24.0)
> 3, ≤ 6	147 (12.2)
> 6, ≤ 12	145 (12.0)
> 12	527 (43.7)
Number of previous TACE treatments	2.29 ± 2.61 (0–15)
0	358 (29.7)
1–2	435 (36.0)
3–5	273 (22.6)
6–10	118 (9.8)
> 10	23 (1.9)
Gender	
Male	1105 (91.5)
Female	102 (8.5)
Marital status	
Married	1177 (97.5)
Single or divorced	30 (2.5)
Education attainment	
Primary school or below	639 (52.9)
Otherwise	568 (47.1)
Employment	
Yes	472 (39.1)
Otherwise	735 (60.9)
Current residence	
Cities	782 (64.8)
Countryside	425 (35.2)
Self-perceived economic burden	
None	303 (25.1)
Mild	650 (53.9)
Moderate	233 (19.3)
Sever	21 (1.7)
Family history of tumours	
Yes	117 (9.7)
No	1090 (90.3)
Comorbidities	
Hypertension	418 (34.6)
Diabetes	208 (17.2)
Cardiovascular disease	63 (5.2)
Otherwise	81 (6.7)
History of hepatitis B virus	
Yes	1114 (92.3)
No	93 (7.7)
History of HCC removal surgery	
Yes	584 (48.4)
No	623 (51.6)
Cirrhosis of the liver	
Yes	994 (82.4)
No	213 (17.6)
Other treatments have been previously received	
Targeted therapies	691 (57.2)
Immunotherapy	538 (44.6)
Other topical treatments	190 (15.7)
ECOG PS score	
0	659 (54.6)
1	544 (45.1)
2	4 (0.3)
Child–Pugh grade	
A	1054 (87.3)
B	153 (12.7)
Whether laboratory indicators are normal	
Alpha-fetoprotein (AFP)	564 (46.7)
Carcinoembryonic antigen (CEA)	1200 (99.4)
Glycan antigen CA19-9	935 (77.5)
Abnormal prothrombin	331 (27.4)
Number of tumours	
Solitary tumour	388 (32.1)
Multiple tumour	758 (62.8)
Unambiguous	61 (5.1)

Child-Pugh, The Child-Pugh (CP) classification is the standard to assess liver function and is determined by five factors: serum bilirubin and albumin levels, prothrombin time, ascites, and encephalopathy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; IQR, inter quartile range; TACE, transcatheter arterial chemoembolization.

The network difference test is conducted to assess differences in network properties between groups, using the R package *NetworkTools*.[27] A *P*-value < 0.05 indicates a significant difference.

Results

Participants' general characteristics

Participants' ($n = 1207$) mean age was 56.77 ± 10.03 years. Most were men ($n = 1105$, 91.5%), were married ($n = 1177$, 97.5%), had a secondary school level of education or less ($n = 639$, 52.9%), and were unemployed or retired ($n = 735$, 60.9%). Regarding disease and treatment-related information, most had a history of prior hepatitis B virus infection ($n = 1114$, 92.3%), as well as the presence of cirrhosis ($n = 994$, 82.4%). A total of 435 (36.0%) had received one to two TACE treatments prior to the investigation, of which nearly half ($n = 584$, 48.4%) had previously undergone liver tumour resection. Most had a liver function status rating of Child–Pugh class A ($n = 1,054$, 87.3%) and an ECOG PS score of 1–2 ($n = 548$, 45.4%). Most had multiple tumours ($n = 758$, 62.8%), and nearly half had abnormalities in the alpha-fetoprotein index ($n = 564$, 46.7%) or the abnormal prothrombin index ($n = 331$, 27.4%). Detailed information on general information is given in Table 1.

Occurrence of symptoms and symptom clusters

Table 2 displays the frequency and intensity of each symptom as well as the findings of the factor analysis. Fatigue ($n = 754$, 62.5%), pain ($n = 685$, 56.8%), and disturbed sleep ($n = 606$, 50.2%) were the most prevalent symptoms after TACE. Regarding symptom severity, pain (1.76 ± 1.94), disturbed sleep (1.68 ± 1.88), and fatigue (1.62 ± 1.48) were the most severe symptoms. Owing to the low incidence of difficulty remembering (< 1%), this factor was removed from the factor analysis after discussion with the research team. Exploratory factor analysis of the 18 symptoms showed a Kaiser–Meyer–Olkin statistic of 0.904, a chi-square value of around 9878.471 (according to the Bartlett's sphericity test; $P < 0.001$), and a cumulative contribution to the variance of 57.071%, yielding the following clusters: mood- and treatment-related general symptoms, upper gastrointestinal symptoms, sensory abnormalities, and nutrition-related symptoms (for more details, see Table 2).

Factors associated with overall symptom severity

The stratified regression analysis of overall symptom severity showed that age ($\beta = -0.146$, $P < 0.001$), employment ($\beta = -0.077$, $P = 0.019$), ECOG score ($\beta = 0.124$, $P < 0.001$), abnormal prothrombin value at normal level ($\beta = -0.086$, $P = 0.008$), normal glycan antigen CA19-9 ($\beta = -0.070$, $P = 0.015$), and surgical history ($\beta = -0.062$, $P = 0.046$) were associated with overall symptom severity. In the subsequent network analysis, these factors were included as covariates.

Characterisation of symptom network and its interconnectedness

After controlling for covariates (ECOG PS score: $\beta = 0.124$, $P < 0.001$; age: $\beta = -0.146$, $P < 0.001$), Fig. 1A shows the symptom network. The results with covariate adjustments are shown in the Supplementary materials for reference.

Table 2
Symptom prevalence, severity and cluster analysis ($N = 1207$)

	n (%)	Mean ± SD	F1	F2	F3	F4	Variable commonality
Mood- and treatment-related general symptoms							
Pain	685 (56.8)	1.76 ± 1.94	0.697	–	–	–	0.661
Fatigue	754 (62.5)	1.62 ± 1.48	0.753	–	–	–	0.732
Disturbed sleep	606 (50.2)	1.68 ± 1.88	0.684	–	–	–	0.651
Distress	508 (42.1)	0.86 ± 1.15	0.784	–	–	–	0.713
Shortness of breath	222 (18.4)	0.34 ± 0.82	0.647	–	–	–	0.425
Lack of appetite	527 (43.7)	1.14 ± 1.46	0.714	–	–	–	0.657
Drowsiness	255 (21.1)	0.39 ± 0.81	0.670	–	–	–	0.496
Dry mouth	519 (43.0)	0.94 ± 1.22	0.517	–	–	–	0.410
Sadness	237 (19.6)	0.35 ± 0.79	0.686	–	–	–	0.542
Feeling bloated	565 (46.8)	1.11 ± 1.37	0.562	–	–	–	0.437
Fever	149 (12.3)	0.30 ± 0.90	0.553	–	–	–	0.374
Upper gastrointestinal symptoms			–	–	–	–	
Nausea	381 (31.6)	0.88 ± 1.49	–	0.828	–	–	0.839
Vomiting	240 (19.9)	0.56 ± 1.28	–	0.854	–	–	0.828
Sensory abnormalities			–	–	–	–	
Numbness or tingling	81 (6.7)	0.12 ± 0.48	–	–	0.421	–	0.252
Jaundice	74 (6.1)	0.11 ± 0.01	–	–	0.516	–	0.502
Itching	129 (10.7)	0.21 ± 0.69	–	–	0.803	–	0.646
Nutrition-related symptoms			–	–	–	–	
Diarrhoea	25 (2.1)	0.04 ± 0.33	–	–	–	0.762	0.585
Weight loss	22 (1.8)	0.02 ± 0.20	–	–	–	0.662	0.522
Removal of symptoms							
Difficulty remembering	9 (0.7)	0.01 ± 0.14	–	–	–	–	–
Cumulative variance contribution ratio (%)			28.828	41.753	49.765	57.071	
Total score of symptom severity		12.44 ± 12.34					

The bootstrapped CIs were minimal, indicating good accuracy of the network according to the results of the edge weights bootstrap (Fig. 2A). The bootstrap subset (Fig. 2B) shows that the network maintains good stability. The correlation stability coefficient for the subset bootstrap was 0.75 for the expected influence and 0.75 for strength.

The edge weight data from bootstrapped difference tests (Fig. 3A) show that nausea and vomiting ($r = 0.76 \pm 0.02$), distress and sadness ($r = 0.48 \pm 0.03$), and fatigue and pain ($r = 0.31 \pm 0.02$) were significantly different from the other edge weights, implying a stronger relationship between these symptoms. The bootstrapped node difference test findings (Fig. 3B) show that distress was significantly different from the other nodes ($DTs = 1.40$).

Node centrality and predictability

Fig. 1B shows the three centrality indices of the network nodes. In the network, distress ($r_{strength} = 1.31$), fatigue ($r_{strength} = 1.29$), and nausea ($r_{strength} = 1.08$) had the largest values for strength; fatigue ($r_{closeness} = 0.0043$), distress ($r_{closeness} = 0.0042$), and lack of appetite ($r_{closeness} = 0.0042$) had the largest values for closeness; and distress ($r_{betweenness} = 62$), lack of appetite ($r_{betweenness} = 60$), disturbed sleep ($r_{betweenness} = 44$), and drowsiness ($r_{betweenness} = 44$) had the greatest betweenness centrality. The predictability surrounding each node is represented by the circles around them in Fig. 1A, which range from 45.0% to 97.7% for the 18 nodes of the network, with the most predictable symptoms being diarrhea, jaundice, and numbness at 97.7%, 95.6%, and 95.2%, respectively.

Network node bridge centrality

The bridge centrality of the nodes in the overall network is depicted in Fig. 1C. Of all the symptoms, nausea had the highest bridge centrality ($r_{bs} = 5.263$), followed by vomiting ($r_{bs} = 4.713$). Moreover, among the mood- and treatment-related general symptom clusters, fatigue ($r_{bs} = 1.845$) had the highest bridge centrality, followed by distress ($r_{bs} = 1.764$) and lack of appetite ($r_{bs} = 1.753$).

Comparison of first-time and nonfirst-time posttranscatheter arterial chemoembolization network

After subjecting the overall data to propensity score matching, this study made subgroup comparisons about whether it was the first time they had been treated with TACE. Based on the network invariance test ($P > 0.5$) and the global intensity invariance test ($P > 0.5$), there was no significant difference between the symptom networks of first-time TACE-treated ($n = 221$) and nonfirst-time TACE-treated ($n = 466$) symptom networks. However, marginal tests in both networks showed a moderate association between fatigue and dry mouth in first-time TACE-treated patients ($r = 0.24$) and between diarrhoea and weight loss in nonfirst-time TACE-treated patients ($r = 0.29$). Nausea and vomiting ($r = 0.57$ vs. $r = 0.75$), distress and sadness ($r = 0.52$ vs. $r = 0.42$), fatigue and pain ($r = 0.30$ vs. $r = 0.28$), and pain and feeling bloated ($r = 0.29$ vs. $r = 0.24$) showed strong associations in both networks. Further, combined node centrality analyses showed that at the strength centrality level, distress ($r_s = 1.44$ vs. $r_s = 1.24$), fatigue ($r_s = 1.21$ vs. $r_s = 1.22$), nausea ($r_s = 0.97$ vs. $r_s = 1.10$), lack of appetite ($r_s = 1.06$ vs. $r_s = 1.09$), and pain ($r_s = 1.11$ vs. $r_s = 1.08$) were the most central symptoms in both networks. For both subgroups of bridge symptoms, this study also tested the bridge centrality in both subnetworks (Fig. 4). In the network of first-time post-TACE symptoms, sadness ($r_{bs} = 5.673$) showed the highest bridge strength, followed by nausea ($r_{bs} = 3.823$); however, in the network of nonfirst-time treatments, fever ($r_{bs} = 3.061$) had the highest bridge strength, followed by weight loss ($r_{bs} = 2.706$).

Discussion

Patients with liver cancer experienced a wide range of concomitant symptoms following TACE, with pain, fatigue, sleep disturbance, distress, dry mouth, and abdominal distension being the most prevalent and severe. Age and ECOG scores were significant influences on symptom severity. The older the patient, the lower the self-perceived symptom severity because older patients have a reduced sensitivity to symptoms and traditionally express their discomfort in a covert manner.[28,29] Most older patients had previously received TACE treatment, had improved tolerance to the treatment, and had experience with the symptoms that

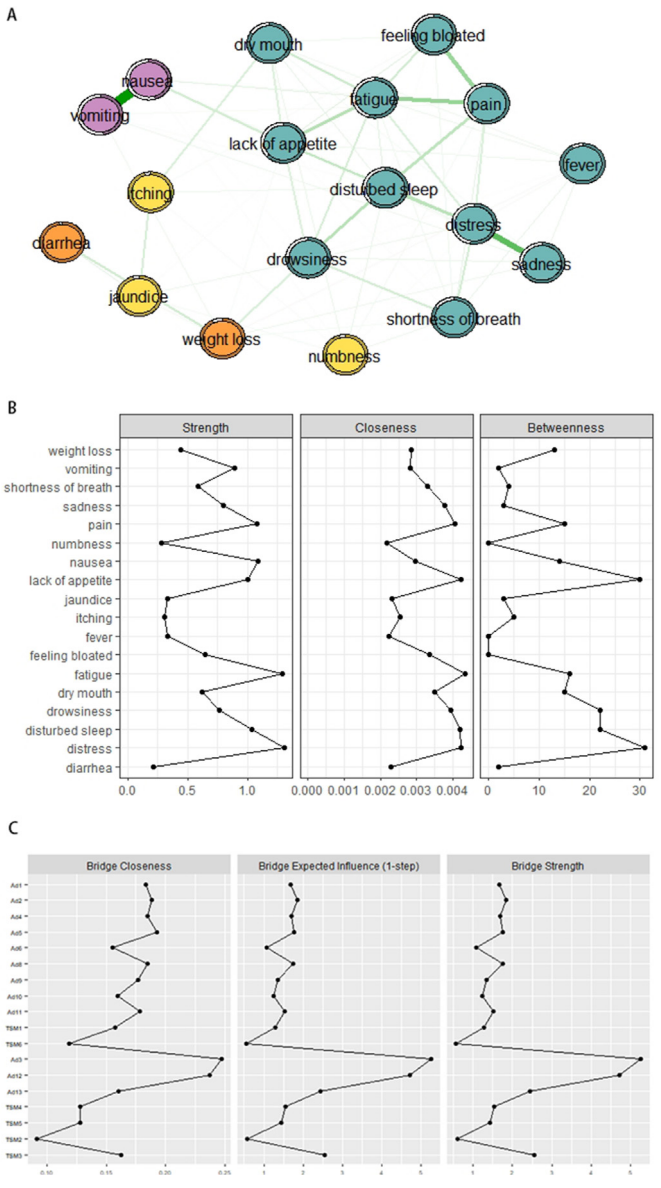

Fig. 1. Symptom networks and centrality measures in the full sample networks (N=1207). (A) Symptom networks and predictability of 18 symptoms; (B) strength, betweenness, and closeness of 18 symptoms; (C) Bridge centrality index of 18 symptoms.

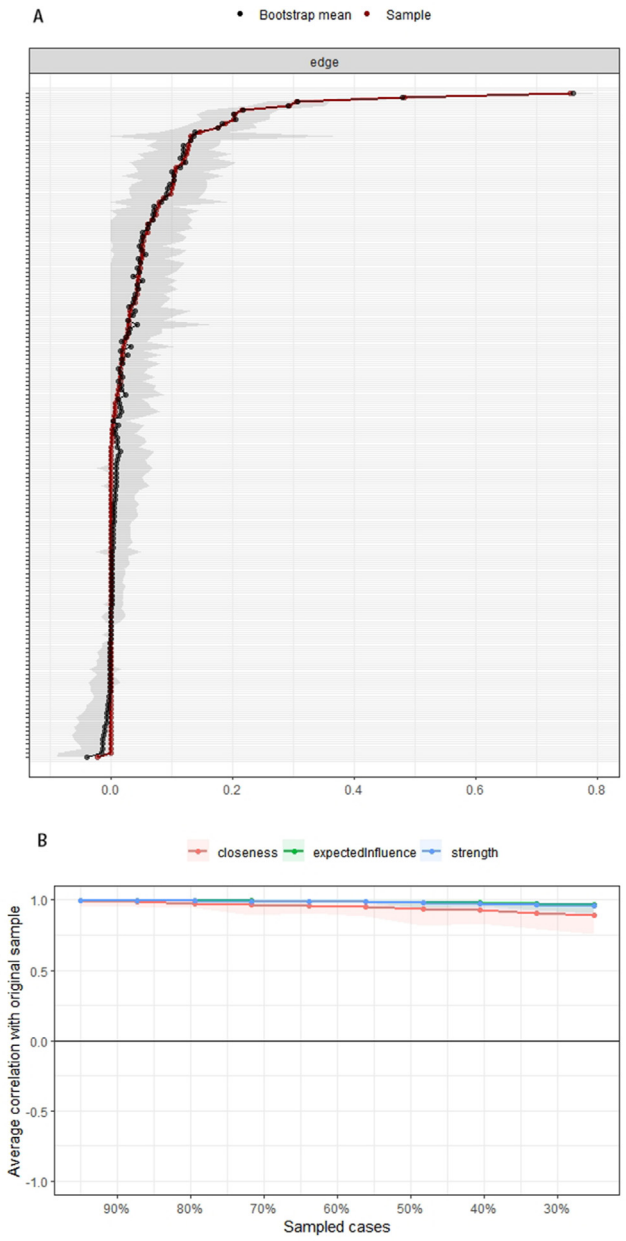

Fig. 2. Accuracy and stability of the symptom networks. (A) Bootstrap analysis results of the edge weights; (B) correlation stability coefficient for strength, closeness, and expected influence.

might occur after treatment. Additionally, when patients had a higher ECOG PS score, they might have poorer physical activity status and be more likely to experience a range of uncomfortable symptoms while also experiencing more psychological burden.[30]

Overall network analysis showed that distress and fatigue had the highest node centrality and were the core symptoms in the network. The results of the subgroup analyses demonstrated that there were no significant variations in the two symptomatic networks between the first-time and nonfirst-time TACE groups in terms of network structure or overall strength. The core symptoms after TACE treatment in patients with liver cancer remained distress and fatigue, independent of whether it was the first treatment or not.

Network centrality can be used as an indicator to identify important symptoms in addition to severity and incidence. Distress did not have the highest prevalence or severity of all 18 symptoms, but it showed the highest strength centrality in the overall network and formed moderate associations with symptoms such as sadness, lack of appetite, disturbed sleep, and fatigue. Distress is particularly common in patients with cancer, leading to maladjustment, relationship problems, and demoralisation, and can be considered a clinical symptom with overlapping domains with anxiety and depression.[31] Five defining characteristics of psychological distress in patients with cancer were found through a conceptual analysis: anxiety, depression, death anxiety, demoralisation, and inability to cope effectively. The complexity of treatment, inadequate assessment of the disease, unmet demands for care, and unpleasant symptoms were identified as significant influences on the development of psychological distress.[32] Psychological symptoms are an important and stable part of the symptom network in patients with cancer, with sadness and distress being the most prominent symptoms.[21] Distinguishing distress from sadness, feelings of sadness are central to depressive symptoms and predict clinical depression.[33] However, psychological distress is primarily characterised by anxiety and worry, rather than depression, which is primarily characterised by sadness.[34] The centrality of distress and sadness in the network could change over time; distress

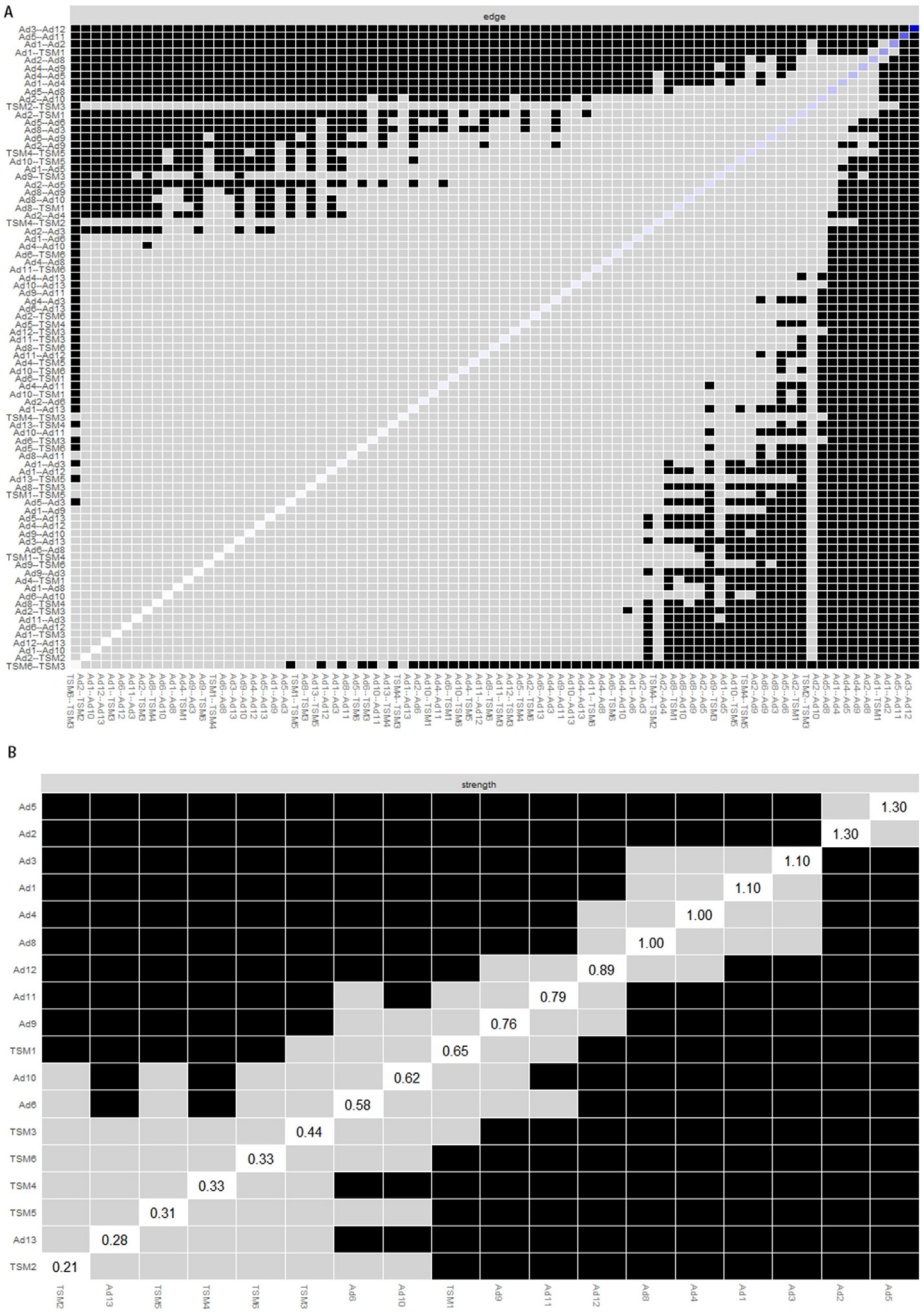

Fig. 3. Results of different tests. (A) Bootstrapped different test for edges; (B) bootstrapped difference test for nodes. Ad1: pain; Ad2: fatigue; Ad3: nausea; Ad4: disturbed sleep; Ad5: distress; Ad6: shortness of breath; Ad8: lack of appetite; Ad9: drowsiness; Ad10: dry mouth; Ad11: sadness; Ad12: vomiting; Ad13: numbness or tingling; TSM1: feeling bloated; TSM2: diarrhea; TSM3: weight loss; TSM4: jaundice (yellowing in eyes or skin); TSM5: itching; TSM6: fever.

and anxiety could represent the more direct emotional impact of a cancer diagnosis owing to concerns about its course, and sadness and depression could be the result of realising the impact of the disease on one's life.[35]

Consequently, it can be assumed that patients admitted to the hospital for TACE treatment usually need to undergo several repeated TACE treatments to control tumour progression and that the long treatment cycle, the burden of treatment costs, and the fear of recurrence, progression, and death can elicit distressing emotions. Moreover, physical symptoms such as nausea, pain, lack of appetite, sleep disturbance, and the feeling of powerlessness in coping with the symptoms can aggravate patients' distress after receiving treatment.[36,37] However, in clinical practice, interventions for symptom management after TACE usually focus on acute physical symptoms such as nausea, vomiting, abdominal pain, and fever, which are included in post-TACE embolic syndrome, and they tend to neglect the management of acute psychological symptoms that occur after the operation, with some studies showing that only 10% of patients are identified as psychologically distressed and receive psychological interventions.[38–40] For patients with cancer, alleviating negative emotions such as distress and sadness and receiving positive psychological interventions are key components of effective symptom control.[21]

Given that distress is a core symptom of acute symptoms in patients with liver cancer after TACE treatment and has a strong correlation with other symptoms, alleviating distress could be the most influential target for intervention at this stage. Health care professionals can develop an integrated symptom management strategy, focusing on 'distress' to

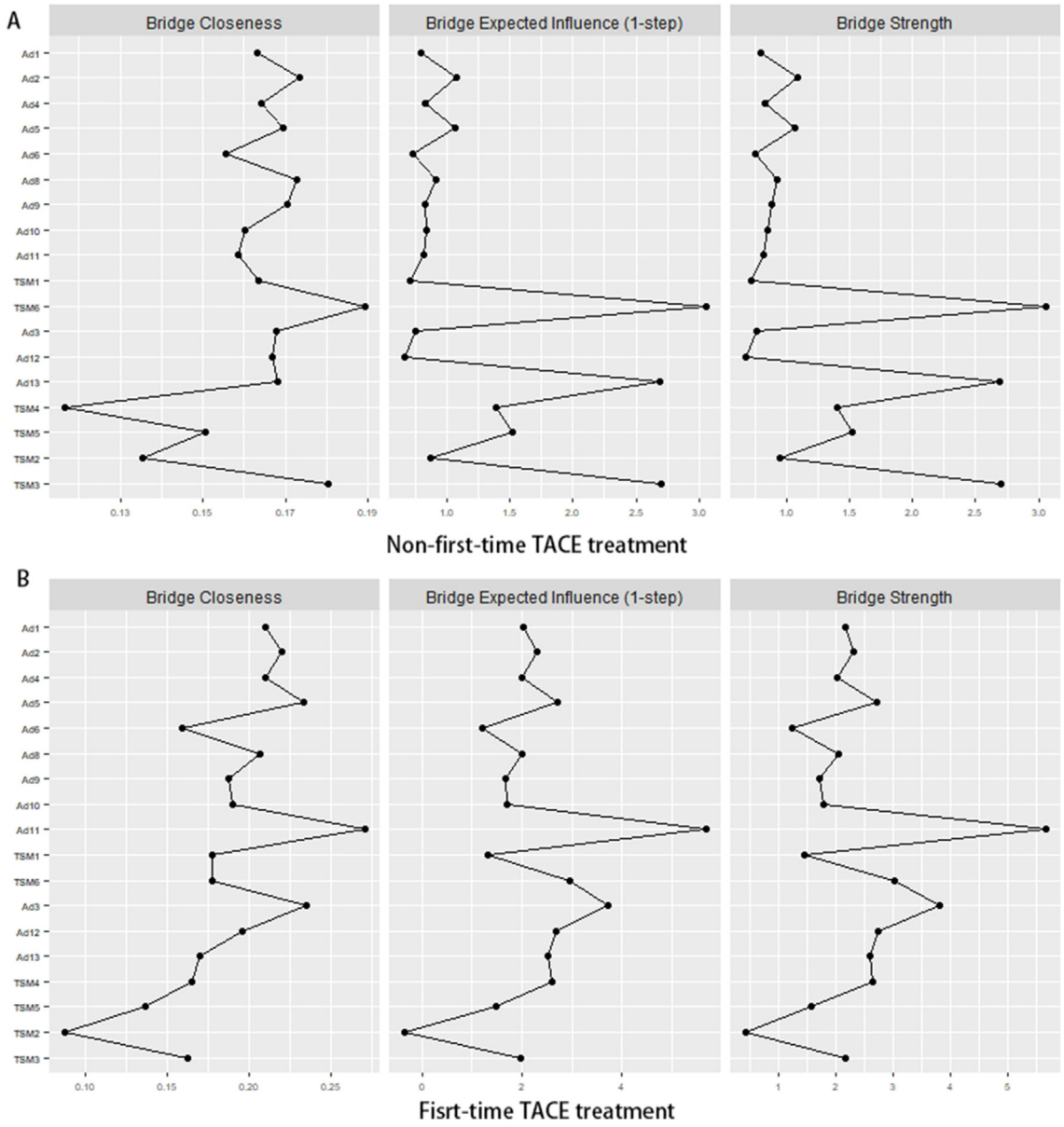

Fig. 4. Bridge node centrality of subgroup networks. (A) Bridge centrality index of the network in non-first-time TACE treatment; (B) Bridge centrality index of the network in first-time TACE treatment. Ad1: pain; Ad2: fatigue; Ad3: nausea; Ad4: disturbed sleep; Ad5: distress; Ad6: shortness of breath; Ad8: lack of appetite; Ad9: drowsiness; Ad10: dry mouth; Ad11: sadness; Ad12: vomiting; Ad13: numbness or tingling; TSM1: feeling bloated; TSM2: diarrhea; TSM3: weight loss; TSM4: jaundice (yellowing in eyes or skin); TSM5: itching; TSM6: fever.

address the negative emotions and additional symptoms experienced by patients with liver cancer after TACE. Specifically, positive psychological interventions and cognitive interventions such as positive stress reduction and cognitive-behavioural interventions for patients who report distress are integral to promoting their recovery.

Bridge symptoms are broadly defined as symptoms that connect different symptom clusters of different mental disorders (diseases) or different symptom subgroups of the same mental disorder (disease).[41] Researchers identify bridge symptoms by generating network data related to bridge strength, betweenness, closeness, and expected impacts.[42] In the overall network of this study, nausea showed the highest bridge centrality (including bridge strength, expected impact, and closeness) and a strong correlation with vomiting. The early appearance of nausea after TACE treatment often makes patients feel uncomfortable or even unable to eat, leading to changes in patients' sense of taste or lack of appetite and increasing fatigue;[43] Concurrently, intense nausea and vomiting and insufficient intake will lead to electrolyte imbalance, and patients will experience muscle weakness, soreness of the hands and feet, and even weight loss in a short period.[44] Consequently, it can be assumed that nausea links the mood- and treatment-related general symptom cluster, in which fatigue is located, and the nutrition-related symptom cluster, in which weight loss is located, to the treatment-related upper gastrointestinal symptom cluster. Further, treatment-induced nausea and vomiting can significantly reduce patients' treatment adherence and affect their treatment regimen, significantly affecting their overall quality of life.[45,46] As suggested in previous studies, bridge symptoms are a target for deactivating symptom cluster interactions in clinical interventions and treatments, and interventions targeting bridges could be more effective than overall interventions.[42,47] Thus, clinical staff should promptly identify the high-risk group of nausea and vomiting after TACE, administer the preoperative prophylactic antiemetic and postoperative use of medication management, and guide patients to take certain

measures to reduce the incidence and severity of nausea, thus reducing the transmission of symptoms between groups.[48]

However, the symptoms with high bridge centrality differed between the two subgroup networks when bridge centrality was tested separately for each network. For the symptom network of first-time TACE-treated patients, sadness showed the highest bridge strength. Notably, patients receiving TACE for the first time had a shorter duration of illness and could have experienced negative emotions such as fear, distress, and sadness owing to uncertainty about the disease and treatment, intolerance, and fear of death and treatment. Further, sadness, as a highly self-focused negative emotion, can mediate physiological symptoms such as fatigue, sleep disorders, and pain.[49,50] Previous longitudinal studies have confirmed that sadness has the strongest centrality and is a strong predictor of symptoms at follow-up and that anxiety manifestations such as worry and tension are predicted by feelings of sadness, which predict depression, and that it is also highly transmissible at the level of psychological symptoms.[31] Consequently, sadness is used as a bridge in the network to exacerbate other psychological or physical symptoms. Based on the constructed symptom network, distress and sadness had the strongest edge weights, with distress at the core of the network and sadness bridging it, implying that psychological symptom identification and management could be more important for patients receiving TACE for the first time. The bridge strength for fever was highest for patients who were not first-time TACE recipients. Although fever after TACE is usually mild and self-limiting, it can still significantly prolong a patient's hospital stay, interfere with subsequent treatment, or reduce the patient's confidence in repeating the treatment. Patients with fever after liquefaction necrosis in the centre of the tumour are more prone to a range of postoperative reactions.[51] Thus, follow-up studies should examine patients with different numbers of treatments to identify potential targets for patients at different stages of treatment.

In summary, core and bridge symptoms provide two distinct intervention ideas for symptom management after TACE, and future research needs to explore whether core symptom interventions targeting distress can maximise improvements in other symptoms and whether bridge symptom interventions targeting nausea can break the link between symptom clusters. In addition, especially for hepatocellular carcinoma patients receiving TACE for the first time, psychological care such as positive stress reduction is critical.

Implications for nursing practice and research

This study utilised a network analysis approach to investigate the core symptoms, bridging symptoms, and associations among symptoms in liver cancer patients post TACE. The identification of distress as the core symptom with the highest strength underscores the need for nursing interventions focused on psychological support and distress management. Furthermore, nursing practices should incorporate methods to assess and mitigate nausea as its management can significantly impact the overall symptom burden of the patient. The variation in bridge symptoms between first-time and nonfirst-time TACE-treated patients (sadness and fever, respectively) indicates the necessity for personalised care plans. Nursing interventions should be tailored according to the patient's treatment history, recognising that different symptoms may become more prominent or burdensome depending on the number of TACE treatments received. Lastly, these findings open new avenues for nursing research. Future studies could explore the development of specific intervention strategies targeting these identified symptoms, particularly focusing on how these strategies can be adapted for patients at different stages of their treatment journey. Research could also investigate the underlying mechanisms of these symptoms in liver cancer patients post TACE, providing deeper insights that could further refine nursing care practices.

Limitations

First, this study employed a cross-sectional design, which allowed us to identify correlations between symptoms but not explain the temporal dynamics of symptom relationships. Second, participants were recruited from one hospital that admits patients from various provinces and cities, providing a certain degree of representativeness. However, there could still be some biases that could limit the generalizability of our findings to other clinical settings. Subsequent studies should strive to validate these results across a broader range of settings. Finally, participants who could not complete self-assessment scales owing to severe comorbidities and/or cognitive impairments were excluded, potentially leading to an underestimation of the severity and centrality of symptoms.

Conclusions

We constructed a network model of symptom experience in patients with liver cancer who received TACE for postoperative treatment and found that distress was the core symptom of the network. Nausea had the highest bridge centrality and was an important bridge symptom. The bridge symptoms of the two networks differed between first-time TACE recipients and nonfirst timers, suggesting that we can target the core and bridge symptoms mentioned above for intervention and tap into potential intervention targets for patients at different treatment stages.

CRediT author statement

Wei Xu: conceptualisation, data curation, formal analysis, writing – original draft. **Zheng Zhu:** supervision, writing – review and editing. **Huijuan Lu:** supervision, writing-review and editing, funding acquisition. **Jingxian Yu:** data curation, ethical review. **Juan Li:** writing – review and editing. All authors were granted complete access to all the data in the study, with the corresponding author bearing the final responsibility for the decision to submit for publication. The corresponding author affirms that all listed authors fulfill the authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

The authors declare no conflict of interest.

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Ethics statement

The study obtained the approval of the Ethics Committee of Zhongshan Hospital, Fudan University (IRB No. FNF220202/B2023-125R). All participants provided written informed consent.

Data availability statement

The datasets created and analysed for this work are not publicly accessible owing to medical institutions' protection of patient data on those with liver cancer; however, they are available from the corresponding author upon justifiable request.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI or AI aids were used in the writing process.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2023.100361.

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