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Research

Cross-Lagged Panel Network Analysis of Symptoms in Patients with Gastric Cancer Undergoing Postoperative Chemotherapy

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ABSTRACT

Objectives: To develop temporal symptom networks at three postoperative chemotherapy time points and investigate the longitudinal relationships between 18 symptoms in patients with gastric cancer undergoing postoperative chemotherapy in China.
Methods: Symptom prevalence and severity were measured using the M. D. Anderson Symptom Inventory (MDASI) and Gastrointestinal Cancer Module of the MDASI (MDASI-GI) at T1, T2, and T3 on the day after the first, third, and sixth chemotherapy sessions, respectively. Cross-lagged panel network (CLPN) models were employed to examine the temporal dynamics of the 18 symptoms and their interrelationships.
Results: In total, 379 participants were included. Dry mouth had the highest out-prediction ($r = 0.101$) and out-strength ($r = 0.863$) values during T1→T2. The strongest direct effect was observed for the change in taste → lack of appetite ($\beta = 0.38$) during T2→T3. Feeling bloated had the highest values for out-strength ($r = 0.910$), out-prediction ($r = 0.215$), and bridge strength ($r = 1.010$) during the T2→T3 period. The two CLPNs showed medium to high stability based on the centrality stability coefficients of out-strength and in-strength.
Conclusions: Lack of appetite can be improved during chemotherapy by managing vomiting and taste changes. Attention should be paid to the dry mouth and feeling bloated, as they are the strongest predictors in the early and middle stages of treatment.
Implications for Nursing: Understanding the relationship between symptoms during chemotherapy in patients with postoperative gastric cancer can help clinicians identify targets for intervention at different times.

According to GLOBOCAN 2022, there have been approximately 968,000 newly diagnosed cases of gastric cancer globally, resulting in approximately 660,000 deaths. Notably, 37% of these cases and 39.4% of the deaths were reported in China.[1] Surgery is the preferred treatment for resectable gastric cancer, and postoperative adjuvant chemotherapy can eliminate residual lesions, consolidate surgical outcomes, and improve survival rates.[2] Although postoperative adjuvant chemotherapy for gastric cancer can improve the survival rate of patients, it also causes patients to experience a series of side effects such as pain, vomiting, nausea, fatigue, insomnia, constipation, diarrhea, and loss of appetite during chemotherapy.[3] These symptoms do not exist in isolation, but several symptoms occur simultaneously and influence each other, creating a cluster phenomenon in the form of "symptom clusters."[4] The concept of symptom clusters was introduced by Dodd et al[4] and further refined by Kim et al,[5] who postulated that symptom clusters should consist of at least two stable and interrelated symptoms that are relatively independent of other symptom clusters. The most commonly used method for identifying symptom clusters, a variable-centered analytic approach in oncology research, is exploratory factor analysis (EFA), followed by hierarchical cluster analysis (HCA).[6] In our previous research, we applied EFA to cluster the symptoms of patients with gastric cancer during chemotherapy after surgery and identified five relatively stable symptom clusters.[7] The symptoms within these clusters interact and reinforce each other synergistically, resulting in a more pronounced negative impact on patient prognosis. Understanding the patterns of occurrence and interactions of symptoms within these clusters and recognizing and intervening in key symptoms, such as sentinel symptoms, can alleviate the severity of other symptoms within the cluster.[8] In addition, bridge symptoms are associated with the symptom cluster structure and are correlated with different symptoms.[9]

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Layperson Summary

What we investigated and why

Patients with gastric cancer undergoing postoperative chemotherapy experience a range of symptoms, often manifesting as symptom clusters. However, as the chemotherapy cycles progress, the stability of these symptom clusters tends to decline. Network analysis can identify core and bridge symptoms within the symptom network, allowing these symptoms to be targeted for interventions aimed at alleviating the overall symptom burden. It is important to note that the core and bridge symptoms may vary across different chemotherapy cycles, making it crucial to understand the temporal interactions of these symptoms for effective monitoring and intervention throughout the chemotherapy process. Therefore, we employed cross-lagged network analysis to explore the predictive relationships among symptoms in patients with gastric cancer postoperative during chemotherapy, providing a basis for precision interventions.

How we did our research

We collected symptom data from 379 patients with gastric cancer undergoing postoperative chemotherapy at three distinct time points: early, mid, and late stages of treatment, using the M. D. Anderson Symptom Inventory (MDASI) and the Gastrointestinal Cancer Module of the MDASI (MDASI-GI). We established two cross-lagged networks to identify the longitudinal relationships and predictive effects among the symptoms.

What we have found

Our study reveals a complex longitudinal relationship among 18 symptoms in patients with gastric cancer undergoing postoperative chemotherapy. We highlighted that lack of appetite serves as a distinct target for intervention at different time points; it can be mitigated in the early stages by addressing vomiting and in the late stages by managing taste changes. The two strongest predictors identified were dry mouth and feeling bloated.

What it means

Understanding the temporal interactions of symptoms indicates that intervening in symptoms at one-time point can reduce the severity of other symptoms at subsequent time points. Additionally, targeting bridging symptoms can diminish the connections between symptom clusters.

Symptom clustering provides only a general understanding of which cancer-related symptoms occur together and does not reflect the strength of the relationships between these symptoms, leading to a lack of focus on interventions targeting symptom clusters, ultimately affecting the effectiveness of interventions.[10,11] Furthermore, the stability of symptom clusters tends to decrease over time. Rha and Lee[12] analyzed longitudinal data from 249 patients with cancer. They discovered that the number of symptoms within the gastrointestinal symptom cluster evolved during the chemotherapy cycles following the initiation of treatment. Therefore, network analysis has established itself as a new research paradigm for symptom management. Network analysis, which originates from psychopathology, enables the exploration of connections between symptoms.[13] This method constructs an undirected network model of the internal features of a system using nodes and edges, providing a visual representation to analyze in-depth the intricate relationships between different variables. Network analysis can identify critical intervention targets, ranging from local (core and bridge symptoms) to global (network structure). This can improve the precision and efficiency of symptom interventions while reducing the incidence of symptom clusters in clinical care.[14,15]

Fatigue is a core symptom that serves as a bridge between the somatic and psychological domains.[16] However, core symptoms evolve as the disease progresses. For example, fatigue is the most central symptom in the network of patients with lung cancer 1 to 2 days after the operation. At the same time, shortness of breath, weakness, and cough are the most common symptoms in the network 5 to 6 days postoperatively.[17] In addition, symptoms such as restlessness, weight loss, and chest tightness are identified as core symptoms at three different stages after CT-guided microwave ablation of lung tumors.[18] A contemporaneous network based on cross-sectional data cannot capture time-series relationships between symptoms or show how one symptom affects another over time.[19] Given the dynamic nature of core symptoms during tumor chemotherapy, it is not sufficient to rely on network analysis alone to explore the causal relationships between symptoms. It is important to investigate which symptoms can predict the occurrence or severity of other symptoms and visualize the interactions between them. The cross-lagged panel network (CLPN) model combines cross-lagged modeling and network analysis to investigate lagged predictability and influence effects between network nodes using longitudinal data. Compared with traditional cross-sectional network analysis, CLPN considers the autoregressive effects of variables and estimates the influence of individual items at an earlier time point on all items at a later time point. Some researchers have investigated predictive relationships between risk and protective factors for suicidality in adolescents at two time-points by constructing symptom networks using CLPN analysis.[20] Shang et al[21] utilized CLPN analysis to construct temporal networks for patients with colorectal cancer at three perioperative time points. They discovered that sleep disturbances exhibited the highest outgoing expected influence at T1, which could predict bloating, fatigue, distress, and pain 2 to 3 days postoperatively.

In this study, we used longitudinal data to construct CLPNs in patients with gastric cancer undergoing postoperative chemotherapy at the beginning (the day after the first chemotherapy), middle (the day after the third chemotherapy), and end (the day after the sixth chemotherapy) of postoperative chemotherapy. Therefore, the aims of this study were as follows: (1) to construct temporal symptom networks using the CLPN model, (2) to determine how symptoms at one-time point may predict symptom severity at another, and (3) to determine how symptoms interact over time.

Methods

Sample

In this prospective study, we recruited postoperative chemotherapy patients with gastric cancer from four hospitals in 12 wards of Jiangsu Province, China, from July 2021 to February 2024. Data were collected via questionnaires at three-time points: T1, T2, and T3—the days after the first, third, and sixth chemotherapy sessions, respectively. Of the 465 enrolled patients, 86 were excluded owing to incomplete data. Therefore, a total of 379 patients were included in the CLPN analysis.

The inclusion criteria were diagnosis of primary gastric cancer, age $\geq$18 years, experience with gastric cancer resection, and six cycles of chemotherapy. The exclusion criteria included other concurrent malignancies, hearing or speech impairment, or participation in other clinical trials.

Procedure

A data collection and quality control team was formed, with a designated lead at each center and a liaison at each of the three sub-centers. Each ward appointed a leader and two research assistants. Prior to the study, the relevant staff members were trained. Written informed consent was obtained from all patients. Each patient was assigned a unique identifier upon enrollment in the study. The patients completed the questionnaires independently, and the collected data were kept confidential. Questionnaires were distributed one day after the initiation of chemotherapy. Team leaders and heads of the 12 wards reviewed case data that were collected weekly by team members. In addition, the liaisons of the three sub-centers conducted monthly spot-checks of the case data collected by their respective center members, reviewing 4 to 6 cases each time and matching them with the actual cases to verify the authenticity of the data collection while overseeing and guiding the questionnaire survey. If the patient withdrew midway, the request was honored. This study adhered to the principles of the 1975 Declaration of Helsinki and was approved by the Jiangsu Province Hospital of the Chinese Medicine Institutional Review Board (IRB approval no. 2021NL-089-03).

Measurements

Demographics and Disease-Related Information

The demographic data collected in this study included age, sex, education, marital status, residence, monthly income, and smoking and alcohol history. Disease-related information included the cancer stage, comorbidities, surgery type, and chemotherapy regimen. Patients provided demographic information, and disease-related information was extracted from the hospital's electronic medical record system.

M. D. Anderson Symptom Inventory (MDASI) and the Gastrointestinal Cancer Module of the MDASI (MDASI-GI)

Our previous research used the MDASI and MDASI-GI to assess the symptoms experienced by patients with gastric cancer undergoing postoperative chemotherapy, identifying five symptom clusters through EFA.[7] In our current study as well, we employed the MDASI and MDASI-GI to evaluate the symptoms and their severity at three time-points for patients with gastric cancer, marking five symptom clusters by distinct colors based on the findings of our previous research. The sickness symptom cluster (A1 Pain, A2 Fatigue, and A3 Disturbed sleep) is marked in orange, and the emotional symptom cluster (B1 Distress, B2 Shortness of breath, B3 Difficulty remembering, and B4 Sadness) is shown in blue. We depict the gastrointestinal symptom cluster (C1 Nausea, C2 Vomiting, C3 Lack of appetite, and C4 Dry mouth) in green, the neurologic symptom cluster (D1 Drowsiness and D2 Numbness) in yellow, and five gastrointestinal cancer-specific symptoms (E1 Constipation, E2 Diarrhea, E3 Difficulty swallowing, E4 Change in taste, and E5 Feeling bloated) in purple. The corresponding Cronbach's coefficients of the MDASI-GI at the three-time points were 0.800, 0.815, and 0.768, respectively.

Statistical Analysis

Descriptive analyses and reliability tests were performed using SPSS version 26.0. The packages glmnet, qgraph, and bootnet were used to estimate the CLPN in R v4.1.2. These networks captured the transitions of symptom severity from T1 to T2 and from T2 to T3 and revealed predictive pathways within the symptom networks. Our analysis included five key components: operating CLPN models, visualization of CLPNs, computing and visualizing predictability of centralized indicators, their analysis, and assessing the stability and accuracy of the network parameters.[22] We used the glmnet package for LASSO regression to run the CLPN model and the qgraph function to create dynamic networks that include and remove autoregressive models. The autoregressive effect is typically the strongest pathway within a network; however, this was not the focus of this study. In addition, autoregressive effects can diminish the visual impact of other pathways within the network. Therefore, we have excluded the autoregressive pathway from the figures presented in the main text. The network comprised 18 nodes, each symbolizing a distinct symptom, with arrows denoting cross-lagged effects. The thickness of the arrows signifies the magnitude of these effects (thicker arrows indicate more robust relationships), whereas the color indicates the direction of the effect (blue arrows signify positive relationships).

Out-prediction is the extent to which each variable predicts other variables in the network. In contrast, in-prediction refers to the degree to which other variables within the network predict each variable.[22] These metrics are derived from the estimated CLPN model. In-prediction was defined as the proportion of variance in each variable at T2 that was explained by the complete set of variables at T1, yielding values ranging from 0−1. Out-prediction is calculated as the sum of squared outgoing standardized regression coefficients of the target variable at T1, which predicts each variable at T2.[22] Out-strength and in-strength are two commonly used centrality metrics in CLPN analysis that can identify the most central symptoms among the 18 symptoms. The out-strength quantifies the sum of all outgoing edges from a node, indicating the extent to which a node predicts other nodes within the network. Conversely, in-strength measures the total sum of all incoming edges to a node, reflecting the degree to which other nodes in the network predict a node. We identified bridge symptoms among the five clusters by calculating bridge strength, which is the sum of the absolute bridge out-strength and in-strength.[23]

Network stability was estimated using bootnet. First, we estimated the accuracy of the edges using 95% confidence intervals (CIs) derived from bootstrapped samples (bootstrapped samples = 1,000). Second, we assessed the stability of node centrality estimates by implementing a subsetting bootstrap procedure, which involves removing a certain proportion of samples and re-estimating the network.[24] If the centrality ranking of the new network remains highly correlated with that of the original network after the majority of samples are excluded, we can conclude that the centrality estimates are relatively stable. Additionally, we calculated the centrality stability coefficient (CS coefficient) as a reference metric, where a coefficient value $\geq$ 0.25 signifies acceptable stability.[24] Finally, we employed centrality difference tests to evaluate the difference between out-strength and in-strength across symptoms.[24]

Results

General Characteristics

Supplementary Table 1 summarizes the demographic data of the 379 patients with gastric cancer, of whom 69.13% were male and 30.87% were female, with a mean age of 62.13 (Standard Deviation = 10.69) years. Most participants were married (96.31%) and had an educational level of junior high school or lower (67.80%). Additionally, 58.78% reported monthly income between CNY4000−5999. Furthermore, 32.19% of the patients had one or more chronic diseases, and 23.75% had a history of smoking, alcohol consumption, or both. Notably, more than half of the patients were diagnosed with stage III gastric cancer (56.20%). Of these, 324 (85.49%) received chemotherapy regimens containing oxaliplatin. Regarding the surgical procedures, most participants received total gastrectomy (124; 32.71%), followed by radical distal gastrectomy (117; 30.87%). Laparoscopic surgery was the most frequently performed surgery among the patients, followed by open (182; 48.02%) and robotic (11; 2.90%) surgery. Further details are provided in Supplementary Table 1.

TABLE
Prevalence (%) and Severity (Mean ± SD) of Symptoms in Gastric Cancer Patients Undergoing Postoperative Chemotherapy

Symptoms	(T1)		(T2)		(T3)	
	Prevalence	severity	Prevalence	severity	Prevalence	severity
Pain	313 (82.59)	3.71 ± 2.39	318 (83.91)	2.03 ± 1.55	276 (72.82)	1.88 ± 1.76
Disturbed sleep	319 (84.17)	2.97 ± 2.23	315 (83.11)	3.38 ± 2.43	337 (88.92)	5.26 ± 2.27
Sadness	313 (82.59)	3.03 ± 2.06	348 (91.82)	4.06 ± 1.86	356 (93.93)	3.66 ± 2.44
Constipation	307 (81.00)	3.34 ± 2.07	126 (33.25)	1.63 ± 2.48	226 (59.63)	3.19 ± 1.96
Change in taste	304 (80.21)	2.22 ± 1.86	300 (79.16)	1.93 ± 1.58	338 (89.18)	4.23 ± 2.03
Distress	292 (77.04)	3.06 ± 2.05	319 (84.17)	2.99 ± 2.19	303 (79.75)	3.14 ± 2.12
Feeling bloated	291 (76.78)	3.30 ± 2.14	311 (82.06)	2.49 ± 1.79	298 (78.63)	1.84 ± 1.49
Fatigue	278 (73.35)	1.61 ± 1.34	358 (94.46)	5.17 ± 2.20	328 (86.54)	2.51 ± 1.33
Nausea	276 (72.82)	2.54 ± 2.19	340 (89.71)	3.83 ± 2.00	327 (86.27)	2.67 ± 2.78
Vomiting	269 (70.98)	2.42 ± 2.19	306 (80.74)	3.77 ± 2.40	210 (55.41)	3.76 ± 2.18
Drowsiness	261 (68.87)	2.85 ± 2.35	300 (79.16)	4.00 ± 2.39	297 (78.36)	2.57 ± 1.78
Numbness	260 (68.60)	2.44 ± 2.30	337 (88.91)	4.60 ± 2.51	294 (77.57)	1.61 ± 1.86
Lack of appetite	259 (68.34)	2.20 ± 1.98	290 (76.52)	2.38 ± 2.15	325 (85.75)	3.07 ± 2.01
Difficulty swallowing	232 (61.21)	2.29 ± 2.39	208 (54.88)	1.01 ± 1.20	91 (24.01)	0.58 ± 1.07
Difficulty remembering	222 (58.58)	2.20 ± 2.39	329 (86.81)	3.16 ± 1.82	346 (91.29)	4.58 ± 2.04
Diarrhoea	191 (50.39)	1.27 ± 1.49	141 (37.20)	0.90 ± 1.35	208 (54.88)	0.91 ± 1.30
Shortness of breath	134 (35.36)	1.32 ± 2.13	143 (37.73)	0.75 ± 1.35	109 (28.76)	0.83 ± 1.63
Dry mouth	98 (25.86)	1.31 ± 2.37	309 (81.53)	4.07 ± 2.39	325 (85.75)	3.19 ± 1.96

Symptom Prevalence and Severity

Table displays the prevalence and severity of the symptoms at the three time-points. At T1, disturbed sleep (319; 84.17%) was the most prevalent symptom, followed by pain (313; 82.59%) and sadness (313; 82.59%). In terms of symptom severity, pain was identified as the most severe symptom (3.71 ± 2.39), followed by constipation (3.34 ± 2.07), and feeling bloated (3.30 ± 2.14). At T2, fatigue (358; 94.46%), sadness (348; 91.82%), and numbness (337; 89.91%) had the highest prevalence. The three most severe symptoms were fatigue (5.17 ± 2.20), numbness (4.60 ± 2.51), and dry mouth (4.07 ± 2.39). T3 had the highest prevalence of sadness (356; 93.93%), followed by difficulty in remembering (346; 91.29%), and changes in taste (338; 89.18%). Disturbed sleep (5.26 ± 2.27), difficulty remembering (4.58 ± 2.04), and change in taste (4.23 ± 2.03) were the three most severe symptoms.

CLPN Analysis

Fig. 1 illustrates the CLPNs for T1→T2 and T2→T3 in patients with gastric cancer after autoregression removal. The CLPNs with autoregression are shown in Supplementary Fig. 1. Fig. 2 shows the in-strength, out-strength, and bridge strength of the 18 nodes in CLPNs for T1 → T2 and T2 → T3. During T1→T2, the strongest direct positive effect was "Vomiting (C2) → Lack of appetite (C3)" ($\beta = 0.31$), followed by "Fatigue (A2) → Distress (B1)" ($\beta = 0.26$). The most influential item was dry mouth (C4; out-strength: $r = 0.863$), which mainly predicted changes in taste (C4→E4; $\beta = 0.18$) and sleep disturbances (C4→A3; $\beta = .15$). Dry mouth was associated with the highest bridge strength (C4; $r = 0.718$) in the gastrointestinal symptom cluster. The in-strength for distress (B1; $r = 0.845$) was the greatest during T1→T2. A higher severity of fatigue at T1 was prospectively associated with a higher distress severity (A2→B1; $\beta = 0.26$) at T2. In addition, distress (B1; out-strength: $r = 0.004$) had a limited influence on other nodes but was strongly influenced by them.

In periods T2→T3, feeling bloated had the highest out-strength (E5; $r = 0.910$) in the CLPN, with its effects affecting other variables through direct or indirect effects. For example, it predicts nausea (E5→C1, $\beta = 0.33$), dry mouth (E5→C4; $\beta = 0.22$), distress (E5→B1; $\beta = 0.19$), and pain (E5→A1; $\beta = 0.14$). The change in taste ranked second (E4; out-strength: $r = 0.661$) and primarily predicted a lack of

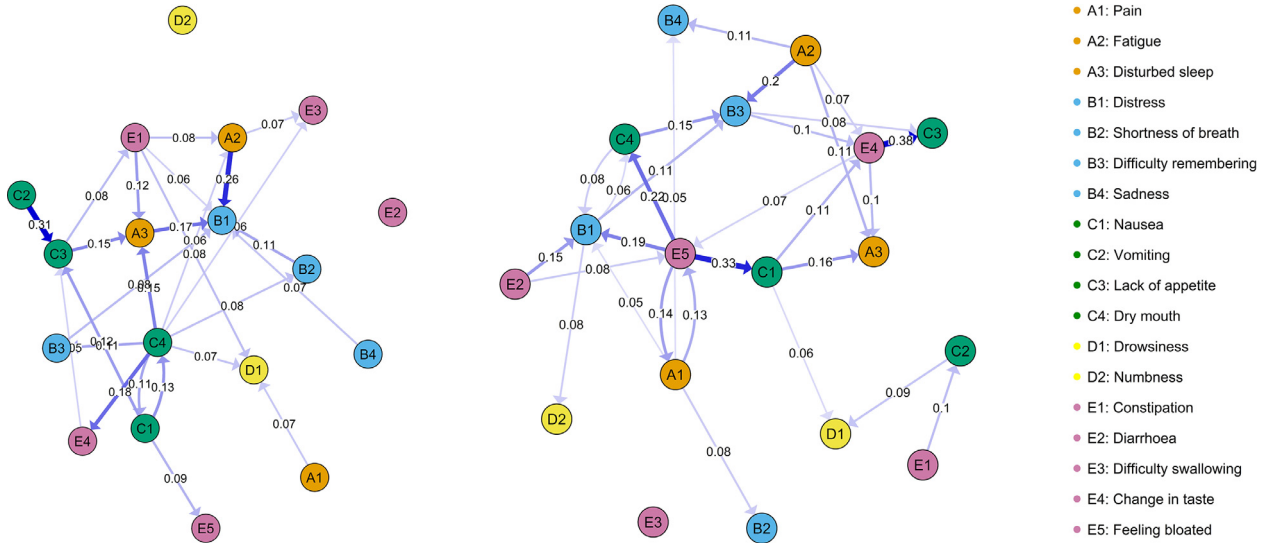

FIG 1. CLPNs with autoregressive paths removed for T1 → T2 (left) and T2 → T3 (right).

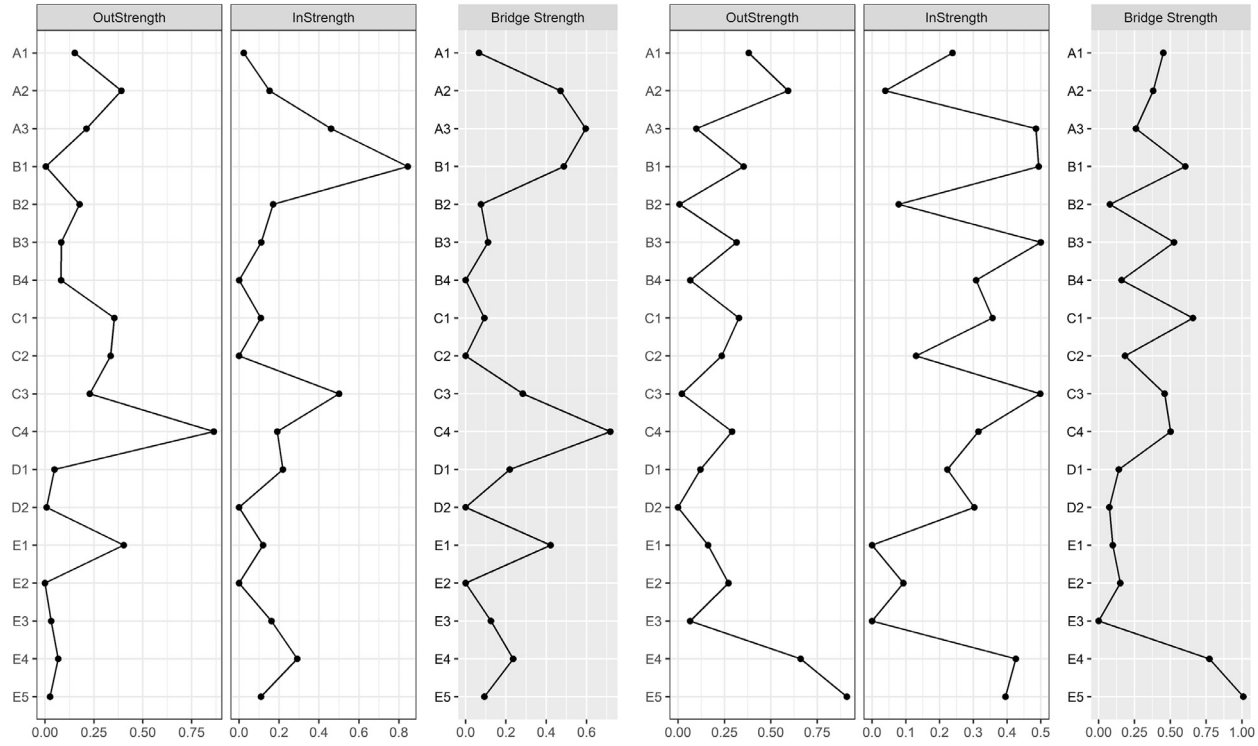

FIG 2. Centrality, and bridge centrality in CLPNs for T1 → T2 and T2 → T3.

appetite (E4→C3; $\beta = 0.38$) and disturbed sleep (E4→A3; $\beta = 0.10$) at T3. Among gastrointestinal cancer-specific symptoms, feeling bloated was the bridge symptom with the highest bridge strength (E5, r =1.010). All the centrality index values are listed in Supplementary Tables 2 and 3.

Fig. 3 illustrates the out-prediction and in-prediction of CLPN symptoms. Distress (in-prediction: $r = 0.124$), lack of appetite (in-prediction: $r = 0.094$), and disturbed sleep (in-prediction: $r = 0.060$) had limited predictive power for the other nodes. However, it was significantly affected by the number of connected nodes during T1→T2. The most predictive items were feeling bloated (out-prediction: $r = 0.215$), followed by a change in taste (out-prediction: $r = 0.167$) in the network during T2→T3, which were susceptible to other nodes rather than influencing other nodes. Additional details are provided in Supplementary Tables 2 and 3.

Stability and Accuracy of CLPNs

We compared the stability of the CLPNs using the CS coefficients of bridge strength, edges, in-strength, and out-strength. The CS coefficients of bridge strength reached 0.749 in the periods T1→T2 and T2→T3, indicating moderate to strong stability. Bootstrapping revealed that the CLPNs were stable in terms of out-strength (CS coefficient = 0.517), in-strength (CS coefficient = 0.517), and edges (CS

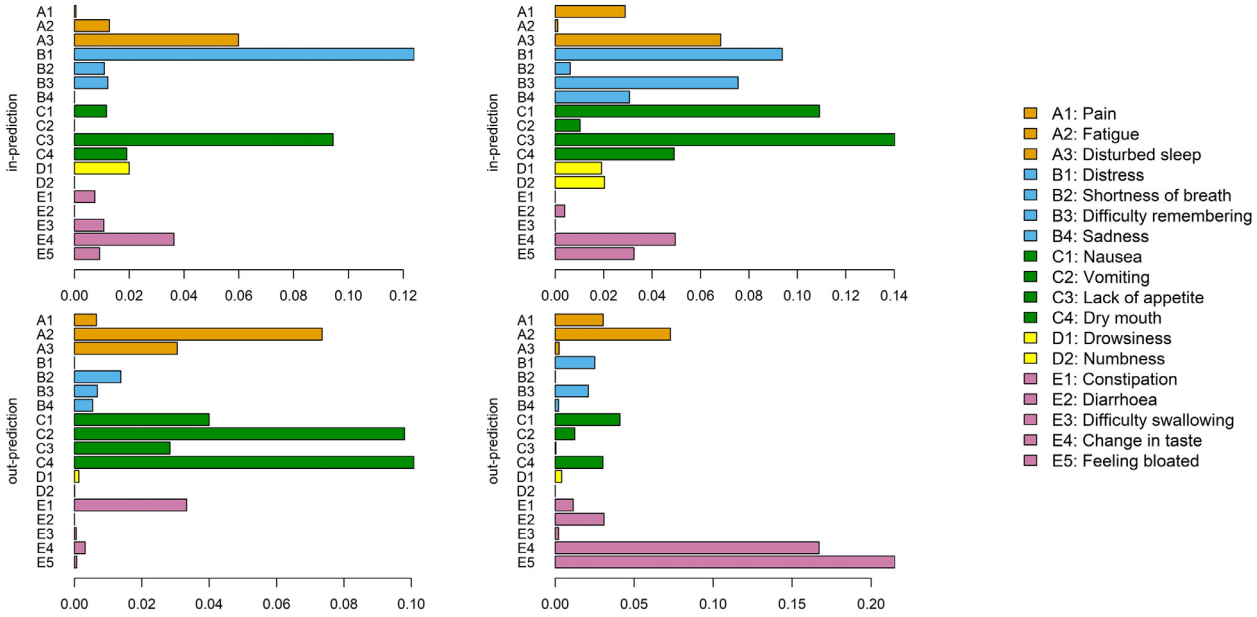

FIG 3. Prediction in CLPNs for T1 → T2 and T2 → T3.

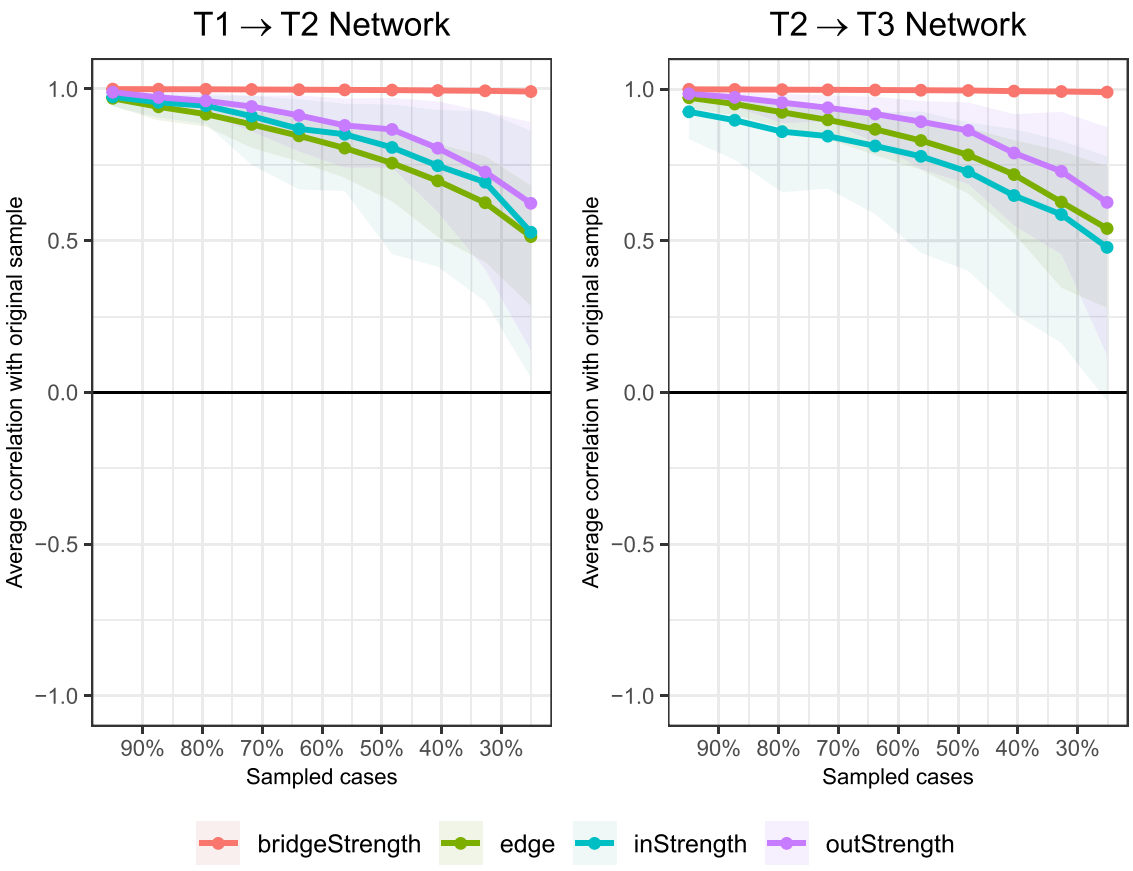

FIG 4. Network stability for T1→T2 (left) and T2→T3 (right). This figure aims to evaluate the stability of centrality estimates, specifically the correlation between the remaining samples and the original samples after removing a certain proportion of data.

coefficient = 0.438) in periods T1→T2 and T2→T3. Further details are presented in Fig. 4. The results of the bootstrap edge-weighting program are presented in Supplementary Fig. 2. The estimates of the edges of the two cross-lagged networks are relatively accurate, with the strongest edges showing no overlap with the confidence intervals, indicating that the results are reliable. We also compared out-strength and in-strength using centrality difference testing (Supplemental Fig. 3), which revealed significant differences for most of the nodes.

Discussion

In our study, CLPN analysis jointly considered network pathways and predictive indices, which helped investigate the dynamic evolution of and complex interactions between symptoms in patients with gastric cancer after chemotherapy. We found that "Change in taste→ Lack of appetite" had the strongest direct effect during T2→T3. Vomiting, dry mouth, change in taste, and feeling bloated were the most important nodes in the CLPN during T1→T2 and T2→T3. Capturing the predictive patterns and relationships among the symptoms in this study could provide empirical support for formulating effective and targeted interventions.

The influence of symptoms extends beyond the confines of symptom clusters. This study revealed that several bridge symptoms can affect symptoms in other symptom clusters. Bridge symptoms are considered key symptoms that contribute to the emergence and maintenance of clusters.[25] During the period T1→T2, dry mouth within the gastrointestinal symptom cluster can predict the worsening of symptoms in four other symptom clusters, including disturbed sleep, change in taste, drowsiness, and difficulty remembering. However, these symptoms had no reciprocal effect on dry mouth. In the period T2→T3, feeling bloated within the gastric cancer-specific symptom cluster primarily predicted the symptoms within the gastrointestinal cluster. Wang et al[7] also indicated that symptoms within the gastrointestinal and gastric cancer-specific symptom clusters often co-occur. A cross-lagged network analysis conducted by Zhu et al[26] identified "feeling fear" as the most critical bridge symptom between negative symptom and positive emotional clusters, which could serve as a breakthrough point for reducing network density. In the future, bridge symptoms such as dry mouth and feeling bloated could be targeted for interventions to interrupt the bridge across different clusters, assessing their effectiveness in controlling the occurrence or worsening of other symptom clusters.[15]

In the period T1→T2, the strongest direct positive effect was "Vomiting → Lack of appetite." Chemotherapy-induced vomiting can cause distress and anxiety in patients, which can affect their enjoyment of food, leading to a significant loss of appetite and weight during chemotherapy.[27] Antiemetics are often used clinically to prevent the occurrence of vomiting or reduce its severity.[28] They affect areas of the brain associated with nausea, vomiting, and eating behavior that overlap with the taste pathways.[29] Therefore, it is possible that both the direct and indirect effects of these antiemetics may play a role in appetite alterations during chemotherapy.[30] A study conducted by Taguchi et al[31] found that patients receiving multiple doses of antiemetics were more likely to report a loss of appetite. It is necessary to choose antiemetics that relieve acute vomiting and show efficacy in delayed lack of appetite.[32] Interventions such as acupressure and music therapy can be used to reduce the severity and frequency of vomiting.[33,34] In addition, clinicians can use peppermint oil to reduce both vomiting and loss of appetite in patients with cancer undergoing chemotherapy.[35]

Distress had the highest in-prediction, with the most pointed arrows during T1→T2, making it susceptible to other symptoms at T1. Among these symptoms, fatigue and disturbed sleep had the greatest impact on distress. Several researchers have confirmed fatigue as a core symptom of cancer, which can leave individuals feeling like their body is not functioning as it should, contributing to challenging emotional responses. Sleep problems were also the most common problems associated with higher levels of distress.[36,37] Consistent with the findings of Syrowatka et al,[38] fatigue and disturbed sleep were predictors of distress in patients with breast cancer. It is unclear whether fatigue and disturbed sleep are causal indicators of distress; a reduction in fatigue and disturbed sleep does not always lead to a reduction in distress. However, fatigue and disturbed sleep may serve as indicators for identifying patients with high distress.[39] Therefore, early detection of fatigue and sleep problems in patients with cancer assists the clinical staff in taking appropriate action to manage and resolve these patient issues. In our study, the role of fatigue in predicting distress disappeared in the T2→T3 period, possibly because the strength of fatigue decreased during the fourth chemotherapy session.[40]

Dry mouth had the highest predictive power, especially in predicting changes in taste, nausea, etc., during T1→T2. Dry mouth is caused by low salivary flow from the salivary glands. Salivary glands with an accelerated cell cycle are sufficiently susceptible to targeting by chemotherapeutic agents that act specifically on the short cell cycle of tumor cells based on a selective toxicity design. Kaizu et al[41] emphasize that insufficient salivary secretion limits the ability to dissolve food particles, which may reduce the intensity of taste sensation and the number of molecules reaching the taste receptors. Therefore, quantitative and qualitative changes in saliva have a direct impact on taste sensitivity and taste cell integrity, affecting the nutritional status of patients receiving chemotherapy.[42,43] Several researchers have also confirmed that saliva supplementation can improve taste function in patients with cancer undergoing chemotherapy or radiotherapy.[44] Singh et al[45] also found that patients suffering from severe nausea have a high rate of dry mouth. Compared to other symptoms that trouble patients with cancer, dry mouth is considered a normal physiological phenomenon and is often ignored by patients because it is prevalent in daily life. Given the findings of this study that dry mouth predicts the development of other symptoms, clinicians should emphasize the recognition and assessment of dry mouth and take appropriate actions. Many simple and inexpensive methods, such as anti-xerostomia medications and oral care, can mitigate the effects of dry mouth on altered taste.[46]

In the period T2→T3, the lack of appetite at T3 was mainly predicted by the change in taste. In terms of prevalence, changes in taste at T3 were ranked among the top three. It has been reported that > 80% of patients cancer develop changes in taste from the first days of chemotherapy and persist for up to 6 months after treatment.[47,48] Anthracyclines, paclitaxel, carboplatin, and docetaxel, the active ingredients in chemotherapy, have been shown to cause changes in taste.[46,49] The renewal of taste cells tends to be disrupted by cytotoxic chemotherapeutic agents because of the short lifespan of taste receptor cells. At least one taste is impaired after the start of chemotherapy. A change in sweet taste is the most common taste change in patients with cancer.[50,51] Owing to increased taste recognition thresholds for sweetness, diets with normal taste ratios do not satisfy the taste needs of chemotherapy patients and do not stimulate their appetite; therefore, patients show a lack of interest in eating.[41,52] Taste changes were significantly correlated with lower taste sensitivity, changes in perceived taste of food, macronutrient preferences, and nutritional status, suggesting that patients' sensitivity to taste stimuli likely plays a role in modulating eating behavior during chemotherapy. Although taste function usually returns to normal after the completion of chemotherapy, it is important to emphasize the major impact of chemosensory changes on a patient's appetite and nutritional status during the disease. Therefore, better characterization of taste changes before the start of chemotherapy is important for better understanding and management of patients' dietary behavior during treatment. Therefore, we recommend self-observation and ear acupuncture to address chemotherapy-induced taste changes.[53,54]

As the node with the highest out-prediction, the presence of bloatedness at T2 could predict many symptoms, such as nausea, dry mouth, and distress. Among these, "Feeling bloated→ Nausea" was the best predictive pathway. Although the prevalence of vomiting (55.41%) decreased with increasing duration of chemotherapy, 86.27% of the patients still reported nausea after five cycles of chemotherapy. Singh et al[45] used latent class analysis to identify subgroups of patients with chemotherapy-related nausea. The subgroup with severe nausea had a higher incidence of gastrointestinal symptoms such as dry mouth and bloating. Molassiotis et al[55] reported that feeling bloated was one of the most predictive variables for nausea using random forest modeling. The participants in this study were patients who underwent chemotherapy after gastric cancer surgery. Gastroparesis is a common complication of radical gastrectomy for gastric cancer, with obstructions in gastric emptying as the main symptom. Food accumulated in the residual stomach leads to damage to the gastric mucosa and thus to gastric insufficiency, which in turn triggers the symptoms of bloating and nausea. Notably, our study demonstrated a reciprocal relationship between nausea and bloating. Nausea at T1 predicted feeling bloated at T2, while feeling bloated at T2 predicted nausea at T3. Treatment of nausea at T1 may alleviate the feeling of fullness at T2 and attenuate nausea and other gastrointestinal symptoms at T3. Therefore, we suggest that patients undergoing postoperative chemotherapy for gastric cancer eat fewer foods and more frequently to reduce bloating and nausea. Meals can be divided into 5−6 meals per day, thereby reducing the amount of food consumed each time.

In our study, symptom networks and cross-lagged models were used to obtain information on the predictability and directionality of nodes, as well as the stability of the network beyond symptom frequency and severity. We also identified important symptoms that could serve as intervention targets for improving the efficiency and precision of symptom management.

Limitations

Although longitudinal relationships between symptoms have been successfully identified in Chinese patients with gastric cancer, some limitations of this study deserve attention. First, we collected data from multiple study centers using different investigators to collect symptom information from the patients, which may introduce bias despite strict quality control. Second, chemotherapy regimens often incorporate immunotherapy or targeted therapy, and we did not consider the effects of these treatment plans on patient symptoms. Third, some patients may have proactively used antiemetic medications or other management strategies that could have influenced symptom predictability. Finally, we evaluated only 18 symptoms using a single symptom dimension, neglecting other important symptoms that may contribute to symptom experience. Therefore, subgroup analyses based on covariates that differ notably at baseline should be conducted in the future to obtain more precise interactions between symptoms.

Conclusion

Our study demonstrated a complex longitudinal relationship between the 18 symptoms in patients with gastric cancer who were treated with postoperative chemotherapy. We emphasize that loss of appetite represents different target symptoms for intervention at different time points, which can be halted in the early stages by relieving vomiting and in the late stages by intervening in taste changes.

Dry mouth and bloating were the strongest predictors for both periods. We recommend further research to investigate the effectiveness of these interventions in clinical practice to improve symptom management and the overall quality of life for patients undergoing postoperative chemotherapy.

Ethics statement

This study is in accordance with the Declaration of Helsinki and was approved by Jiangsu Province Hospital of Chinese Medicine Institutional Review Board (IRB No. 2021NL-089-03).

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Declaration of competing interest

The authors declare that the study was conducted without any commercial or financial relationships. The absence of any commercial or financial relationship can be considered as a potential conflict of interest.

CRediT authorship contribution statement

Siyu Li: Writing – review & editing, Writing – original draft, Software, Project administration, Conceptualization. **Kaili Zhu:** Writing – original draft, Data curation, Conceptualization. **Chao Xia:** Methodology, Investigation, Writing – review & editing. **ling Yang:** Writing – review & editing, Writing – original draft, Software, Project administration, Conceptualization. **Peibei Duan:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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

No AI tools/services were used during the preparation of this work.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.soncn.2024.151805.

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