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Original Article

Home-based symptom management for patients with malignant lymphoma undergoing intermittent chemotherapy: A prospective observational study using network analysis

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ABSTRACT

Objective: This study aimed to explore the symptom burden of patients with malignant lymphoma at home during the intermittent periods of chemotherapy and identify core symptoms using network analysis.
Methods: A prospective observational study was conducted, recruiting 208 patients from December 2019 to December 2020. Symptom burden was assessed using the MD Anderson Symptom Inventory-Chinese version (MDASI-C) at three time points during the first to third chemotherapy cycles (T1–T3). Symptom networks were constructed for each time point, and centrality indices were analyzed to identify core and bridge symptoms. Network comparison tests (NCT) were used to examine changes in symptom interconnectivity over time.
Results: A total of 208 participants were included in the data analysis. Fatigue and vomiting were the most prevalent and severe symptoms reported at all time points, respectively. In the presented symptom network, lack of appetite ($r_s = 1.13$), sadness ($r_s = 1.20$), and nausea ($r_s = 1.13$) were the core symptoms of T1, T2, and T3, respectively. Lack of appetite ($r_b = 21$, $r_c = 0.01$), distress ($r_b = 25$, $r_c = 0.01$), and dry mouth ($r_b = 11$, $r_c = 0.01$) were identified as bridge symptoms at T1, T2, and T3, respectively. NCT results indicated no statistical differences in the global symptom network strength and overall edge weight among the three time points, while sadness exhibited higher betweenness and closeness in the network of T2 (T1 vs. T2, $P_c = 0.03$, $P_b = 0.03$; T2 vs. T3, $P_c = 0.01$, $P_b = 0.03$)
Conclusions: The findings highlight lack of appetite, sadness, and nausea as critical targets for symptom management in patients with malignant lymphoma undergoing intermittent chemotherapy. Caregivers and healthcare providers should focus on these symptoms to improve home-based symptom management and enhance patient well-being.

Introduction

Although combination chemotherapy has improved the prognosis for patients with malignant lymphoma, the majority experience long-term symptom disorders from the toxic effects of its treatment, which contribute to poor quality of life.[1,2] In China, the rapid turnover of hospital beds aims to conserve medical resources and reduce the economic burden on patients. However, this practice also results in shorter hospital stays and extended recovery periods at home during chemotherapy. Moreover, lymphoma patients are primarily in charge of their health management at home. The adverse symptoms experienced at home with insufficient access to effective health guidance during the intermittent periods of chemotherapy will significantly affect chemotherapy compliance and treatment confidence. This situation may lead to an increased rate of unplanned hospitalizations and treatment interruptions,[3] ultimately hindering patients' recovery. Therefore, optimizing the strategies of symptom management at home is pressing to facilitate a safe transition between the hospital and the home and to improve the quality of life of the patients. As demonstrated in dementia care, a review identified nonpharmacological interventions for

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managing dementia symptoms in home-based settings.[4] Additionally, a previous randomized study demonstrated the effectiveness of home-based multimodal symptom management in alleviating symptom experiences in adolescents undergoing chemotherapy.[5] While studies have explored symptom management in various populations, little is known regarding the home-based symptom management of lymphoma patients during intermittent chemotherapy.

Recent research in symptom management has shifted focus from single symptoms to the co-occurrence of symptoms. Patients undergoing chemotherapy rarely experience a single symptom. Rather, clustering of more than ten symptoms is common.[3] This clustering can exacerbate the negative impact on patients through reinforcement or synergistic effects, thereby intensifying their overall disease burden.[6] Several studies have examined symptom composition among lymphoma patients during or before chemotherapy. For instance, Meng identified a cluster of psychological, disease-related, and lymphoma B symptoms in patients before chemotherapy.[7] A cross-sectional study from Turkey reported that fatigue, dry mouth, anxiety, and lack of appetite were prevalent among patients undergoing chemotherapy for lymphoma.[8] Siri A. Eikeland found that patients highly reported peripheral neuropathy symptoms after chemotherapy, such as numbness and tingling.[9] However, the composition and burden of symptoms among lymphoma patients during the intermittent periods of chemotherapy remain underexplored. Additionally, the symptom experience in time model (SET) posits that the symptom experience of cancer patients changes over time and can influence other symptoms.[10] This suggests that symptom research should focus on both the onset of patient symptoms and their temporal changes, thereby identifying symptoms that are persistent and sensitive during treatment, which will ultimately help guide clinical practice. Findings from a preliminary investigation showed that the symptom structure in lymphoma patients is complex and variable in the early stages of chemotherapy but stabilizes after the third cycle.[7] In a longitudinal study, Chih-Jung Wu identified different symptom clusters across chemotherapy cycles in lymphoma patients.[11] Nevertheless, most studies have employed cluster analysis or exploratory factor analysis, which assumes that symptoms cluster due to a common underlying factor,[12] thus limiting the exploration of interactions among symptoms. Understanding these interaction patterns, the relative importance of symptoms, and the drivers of overall symptom burden could help develop more desired care plans and discharge preparation programs.

Currently, network analysis (NA) has emerged as a valuable tool in psychological and cancer medicine research. This technique hypothesizes that network nodes (i.e., symptoms) interact with one another, assigning roles based on their positions within the network model, which allows for a more comprehensive evaluation of the relationships among complex symptoms.[13] Accordingly, we aim to provide a comprehensive analysis of symptom interconnections for lymphoma chemotherapy patients through network analysis. The objectives of this study are to (1) describe the prevalence and severity of symptoms at home during the intermittent period of chemotherapy for lymphoma; (2) construct and visualize symptom networks to identify core and bridge symptoms using NA; and (3) explore how the symptom structure and central indices change over time through network comparison tests to prioritize symptoms for targeted intervention.

Methods

Study design and sample

This study is a single-center prospective observational study conducted at a specialized oncology hospital in Sichuan, China, from December 2019 to December 2020. In this study, purposive cluster sampling was employed, with clusters formed based on the diagnosis of lymphoma. We defined clusters as groups of patients diagnosed with lymphoma who were scheduled to undergo chemotherapy for the first time. Inclusion criteria were as follows: (1) patients diagnosed with lymphoma according to World Health Organization (WHO) clinical criteria, including Non-Hodgkin Lymphoma (NHL) and Hodgkin Disease (HD); (2) patients scheduled to undergo chemotherapy for lymphoma for the first time; and (3) patients with accessible clinical data. We excluded individuals with mental illnesses or severe comorbidities and those who required continued supportive treatment in the hospital after chemotherapy. The intermittent chemotherapy period was defined as the period from 24 hours after chemotherapy to 24 hours before the start of the next chemotherapy cycle in our study. Treatment protocols for the included patients adhered to the guidelines for lymphoma diagnosis and treatment issued by the Chinese Society of Clinical Oncology.[14] Standardized regimens were applied to 77.4% of participants, while the remaining 21.6% received individualized protocols in accordance with CSCO recommendations for refractory or rare subtypes. Before chemotherapy, patients received premedication, including antiemetic patches, tropisetron, metoclopramide, and lansoprazole for gastric protection. For sample size calculation, there is no consensus on a gold standard for symptom network analysis. This study employs the fuzzy estimation method, and according to metrological principles, the sample size should be 10 times the number of variables. Given that this study includes 13 symptom nodes and accounts for a 10% attrition rate, the minimum required sample size is 145. The adequacy of the sample size for network analysis will also be evaluated using stability tests via non-parametric bootstrapping methods.[15]

Measurements

General information

We use a self-designed questionnaire to collect demographic information and clinical data, including age, gender, education level, income, marital status, employment status, height, weight, clinical diagnosis, tumor stage, and medical history.

Symptoms assessment

The study utilized the MD Anderson Symptom Inventory-Chinese version (MDASI-C), developed by the MD Anderson Cancer Center in the United States.[16] The first section of this symptom checklist includes 13 items representing the symptom dimension, while the second section includes 6 items addressing life disturbances. To focus on establishing a symptom network based on the severity of symptoms, this study only utilized the first part of the MDASI-C scale to assess the incidence and severity of symptoms experienced by malignant lymphoma patients at home during intermittent chemotherapy. The severity of each symptom is rated on an 11-point Likert scale (0 = “not at all” to 10 = “as bad as you can imagine”). The Cronbach's α of the MDASI-C was 0.86. The retest reliability of the scale in this study was 0.92.

Data collection and analysis

Data collection was conducted by trained research team members via telephone or WeChat. Based on preliminary evidence, it was suggested that the symptom structure in lymphoma patients is complex and variable in the early stages of chemotherapy but stabilizes after the third cycle, patients were followed up after 7 days from the end of the first (T1), second (T2), and third (T3) cycles of chemotherapy.

Data analysis was carried out using R version 4.4.0 for data cleaning and statistical analysis. Descriptive statistics included median and interquartile range or means and standard deviations for continuous variables and composition ratios for categorical variables. Line graphs and bar graphs were utilized to visualize the prevalence and severity of the thirteen symptoms across the three time points. The symptom network analysis in this work proceeded as follows: 1) Symptom network estimation and visualization. We developed a Gaussian graphical model (GGM) to represent the relationships among the thirteen symptoms. To minimize spurious connections and visualize the estimated network, we applied the graphical least absolute shrinkage and selection operator

(GLASSO) algorithm. The accuracy of the estimated network was assessed by calculating the 95% confidence intervals for edge weights through bootstrapping. 2) Centrality analysis. This study presented three note centrality indices, including strength (r_s), which is indicative of core symptoms within each network model. Closeness (r_c), which reflects the connectivity to other symptoms. Betweenness (r_b), which reflects the bridge role of the symptom node. The stability of these centrality indices was evaluated using the correlation stability coefficient (CS). A CS value below 0.25 indicates poor stability. 3) Symptom network comparison. We evaluated differences in network connectivity across the three time points by comparing global strengths and the weighted absolute sums of all edges. Statistical significance was determined by a two-sided test ($\alpha = 0.05$).

Results

General information of participants

Fig. 1 illustrates the selection process. A total of 220 patients were assessed for eligibility. 208 eligible patients agreed to participate and completed the initial survey, 168 participants completed the assessment at the second time point, and 135 completed the final follow-up. Among the participants, 9 (4.3%) reported having B symptoms, including fever, pruritic rash, weight loss, and night sweats. The characteristics of the participants are detailed in Table 1.

Prevalence and severity of symptoms at home

As illustrated in Fig. 2, fatigue was the most prevalent symptom at T1 (42.8%), T2 (41.1%), and T3 (39.2%). Overall, the incidence of all symptoms, except for numbness, exhibited a downward trend over time. In terms of severity, vomiting was reported as the most severe symptom across all three time points (T1 = 2.79, T2 = 2.67, T3 = 3.33). Apart from the severity of vomiting, which aggravated at T3, the severity of other symptoms remained consistent across the time points.

Overall symptom networks structure

Fig. 3 depicts the estimated symptom network comprising thirteen nodes for patients during chemotherapy at each time point. Nodes represent symptoms, while edges illustrate the relationships between these symptoms. The thickness of each edge indicates the strength of the interaction between two symptom nodes, with thicker edges signifying stronger correlations. Green edge represents a positive correlation, while brown represents a negative correlation. The symptom network densities were 0.54, 0.47, and 0.54 for T1, T2, and T3, respectively. The global strength values for the individual networks were 5.02, 5.55, and 5.75 at T1, T2, and T3, respectively. The 95% confidence intervals for the estimated edge weights, computed through bootstrapping, indicate a degree of overlap, suggesting good accuracy of the network estimates (Appendix A).

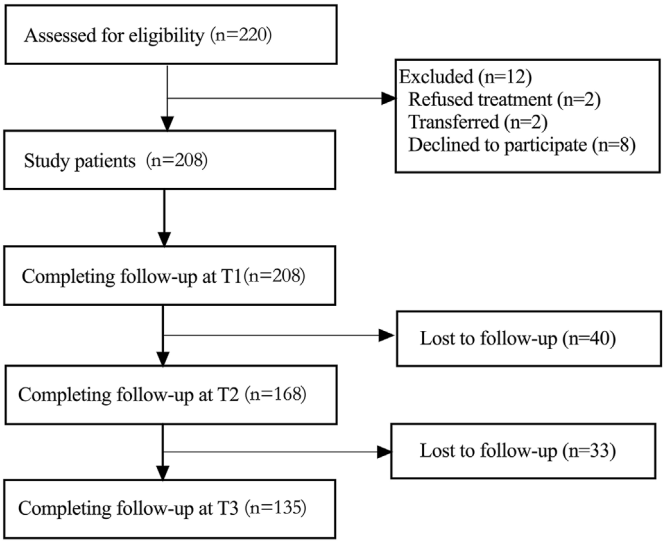

Fig. 1. Patient flow chart.

Table 1
General information ($N = 208$).

Characteristics	*n* (%)
Sex	
Male	119 (57.2)
Female	89 (42.8)
Age (years, median [IQR])	53.5 [44.0, 65.0]
Category	
Classical Hodgkin lymphoma	18 (8.7)
B-cell lymphoma	153 (73.6)
T-cell lymphoma	37 (17.8)
Staging	
I	13 (6.2)
II	33 (15.9)
III	33 (15.9)
IV	49 (23.5)
Unstaged/Unknown	80 (38.5)
Treatment protocols	
ABVD	13 (6.3)
R-CHOP	122 (58.7)
P-GemOx	14 (6.7)
CVAD	9 (4.3)
EPOCH	5 (2.4)
Others	45 (21.6)
Marital status	
Married	184 (88.5)
Single	21 (10.1)
Education level	
Illiterate	24 (11.5)
Primary	102 (49.0)
High or above	79 (38.0)
Working status	
Working	154 (74.0)
Not working	54 (26.0)
Monthly income (RMB)	
< 3000	26 (12.5)
3000-4999	107 (51.4)
5000-6999	60 (28.8)
> 7000	13 (6.3)
Comorbidities	
Yes	71 (34.1)
No	137 (65.9)
ECOG	
0	152 (73.1)
1	36 (17.3)
≥ 2	17 (8.2)
BMI (kg/m^2, median [IQR])	23.0 [20.6, 25.0]

Note centrality indices

Fig. 3 displays the three node centrality indices at the three time points, including strength, betweenness, and closeness. Lack of appetite, sadness, and nausea were the core symptoms with the highest strength centrality at T1 ($r_s = 1.13$), T2 ($r_s = 1.20$), and T3 ($r_s = 1.13$), respectively. Regarding betweenness and closeness, lack of appetite, distress, and dry mouth exhibited higher values at T1 ($r_b = 21$, $r_c = 0.01$), T2 ($r_b = 25$, $r_c = 0.01$), and T3 ($r_b = 11$, $r_c = 0.01$), respectively. The correlation stability coefficients for each symptom network are plotted in Appendix B. The results of CS for expected influence were 0.51, 0.44, and 0.21 at T1, T2, and T3, respectively, indicating good stability of centrality at T1 and T2, while poor stability performance at T3.

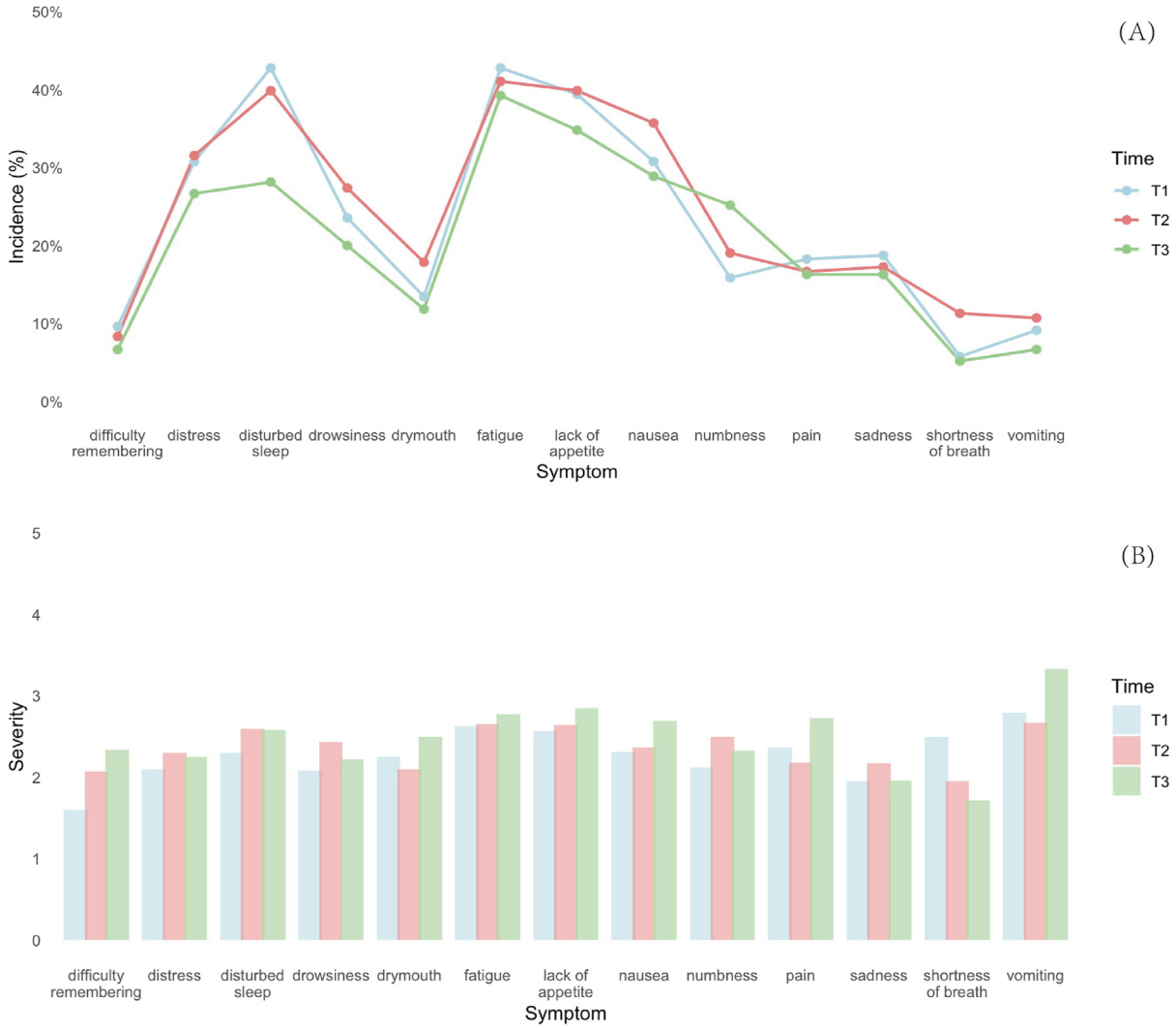

Fig. 2. The prevalence and severity of symptoms. The changing trends of the prevalence and severity of thirteen symptoms at three time points are shown in (A) and (B), respectively. The blue, red, and green colors in the figures represent T1, T2, and T3, respectively.

Results of network comparison

The results of NCT indicate no statistically significant differences in the maximum edge weights (T1 vs. T2, $P = 0.87$; T2 vs. T3, $P = 0.49$; T1 vs. T3, $P = 0.06$) or global strength (T1 vs. T2, $P = 0.32$; T2 vs. T3, $P = 0.78$; T1 vs. T3, $P = 0.44$) among three networks. These findings suggest that the overall network structure remained similar over time. For centrality indices, the results show that sadness exhibited higher betweenness and closeness in the network of T2 (T1 vs. T2, $P_c = 0.03$, $P_b = 0.03$; T2 vs. T3, $P_c = 0.01$, $P_b = 0.03$), indicating that, although the strengths of sadness have no statistical difference across three points, sadness lies on the path of many associations and was more influenced by other symptoms at T2 than at T1 and T3.

Discussion

This study investigated the symptoms experienced at home in patients during the intermittent periods of chemotherapy for lymphoma. Specifically, we calculated the prevalence and severity of symptoms, developed a symptom network model at each observation point, and identified core symptoms along with the interconnections between the symptom network through network analysis. Our results indicated that fatigue was the most common symptom, and vomiting was reported as the most severe symptom across all three time points, which were similar to, but less prevalent than, findings from previous studies on symptoms in lymphoma patients undergoing chemotherapy.[1,11] The downward trend in symptom severity observed across the three time points may indicate a degree of adaptation among patients throughout the course of chemotherapy, consistent with previous research.[17] However, further investigation is needed to explore the associations between patient adaptation and the impact of supportive interventions on symptom management in lymphoma patients. In the presented network, all nodes are interconnected, and the network density is 0.47–0.54, which is similar to that of lung cancer patients receiving chemotherapy, with network densities of 0.55.[18] This suggests that the symptoms of lymphoma chemotherapy patients may also be highly correlated. Particularly, lack of appetite, distress, and nausea were identified as core symptoms at each time point, pointing to the potential utility of addressing these in early intervention. Furthermore, while there were no significant differences in the overall structure of the symptom network across the three time points, notable inconsistencies were observed in the centrality metrics. These findings suggest that, although the severity and prevalence of symptoms during the stay-at-home period were lower than those experienced during chemotherapy, a significant symptom burden remains that cannot be overlooked. Despite the overall stability of the symptom network, fluctuations in centrality metrics indicate that the relative importance of

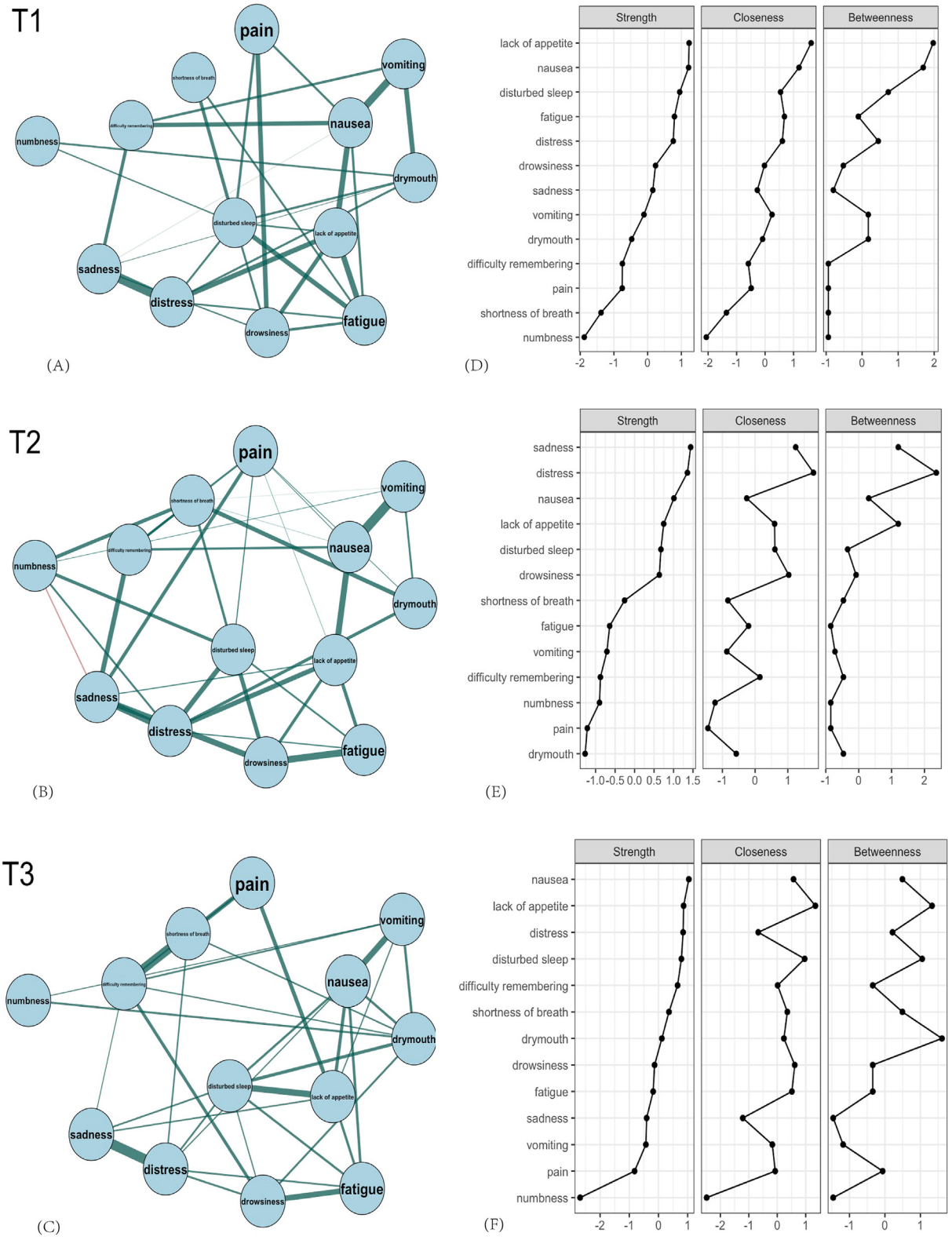

Fig. 3. Symptom network and centrality indices. The estimated symptom networks of T1, T2, and T3 were illustrated in (A), (B), and (C), respectively. Centrality indices of T1, T2, and T3 were illustrated in (D), (E), and (F).

specific symptoms may change over time. Therefore, oncological caregivers should take these fluctuations into account when developing individualized care plans for lymphoma patients. Based on our results, this article will discuss the prevalence and severity of symptoms, the structure of the symptom network at each time point, and the implications of these findings for clinical oncology nursing and home care practices.

At the first observation time point, lack of appetite was identified as both a core and bridge symptom, while fatigue was the most prevalent symptom and vomiting was reported as the most severe symptom.

Previous studies have indicated that many lymphoma survivors experience long-term fatigue, with prevalence rates ranging from 11% to 76%.[19] The etiology of chemotherapy-related fatigue remains unclear and is probably multifactorial, often correlating with other cancer-related symptoms.[20] A previous meta-analysis concluded that fatigue is significantly associated with nausea, emesis, and lack of appetite.[21] In this study, the analysis of the symptom network suggests that fatigue and vomiting are likely to interact with lack of appetite, leading to an exacerbation of the overall symptom experience. This underscores the importance of addressing lack of appetite, fatigue, and vomiting simultaneously in clinical practice to enhance patient outcomes. Comprehensive exercise programs have been found to improve fatigue. A meta-analysis of RCTs shows that mind-body exercises, such as yoga and qigong, are more effective than aerobic exercise in alleviating fatigue in lymphoma patients.[22] Regarding lack of appetite, to our knowledge, there is no formal definition of lack of appetite that specifically includes early satiety or a reduced physiological desire to eat. While nausea and vomiting often receive significant attention from medical staff, addressing lack of appetite is currently not incorporated into the routine supportive pathway for chemotherapy patients.[23] These findings highlight the necessity of more effective interventions targeting lack of appetite to reduce the overall symptom burden when appetite disorders exist, such as aromatherapy practices,[24] using hawthorn[25] and pharmacological treatment,[26] which warrants further high-quality RCTs to verify this hypothesis.

At the second observation time point, fatigue and vomiting remained highly reported. Interestingly, although the prevalence and severity of distress and sadness were low to moderate, network calculations indicated that sadness and distress served as the core and bridging symptoms of the T2 symptom network, respectively. Additionally, the results of NCT revealed that the centrality of sadness was statistically different across the three time points. This may be explained by a combination of the young and middle-aged Chinese patients' tendency to withhold negative emotions during follow-ups, making it challenging to capture the distressing symptoms in this group, which similar to early research.[27] In reality, much research has found that psychological distress may be quite common in lymphoma patients during the early stages of chemotherapy,[28,29] and could be more closely related to other symptoms.[30] Recent meta-analysis of RCTs demonstrated the effectiveness of positive psychological interventions (e.g., dignity therapy, meaning therapy, life review, and expressive writing intervention) in improving health outcomes in cancer patients but could not make definitive conclusions about reducing overall symptom burden.[31] Our results inform future research on the role of psychological interventions in alleviating overall symptom burden, particularly in relation to changes in network structure among lymphoma patients. It is also important to note that the MDASI measures “distress” and “sadness” as broad psychological terms. Further examination of psychological distress branches using standardization scales, such as anxiety, depression, and fear, is necessary to understand their specific impacts on this symptom group. In short, the prevalence of a symptom alone is not sufficient to confirm its impact on patients. The centrality of the symptom within the network should also be considered. During this period, a comprehensive assessment of patients’ self-reported fatigue and vomiting is essential. In addition to chemotherapy-related physiological reactions, these issues may be partly attributed to the negative effects of emotional distress. Encouraging patients to confess their emotional experiences may help facilitate timely access to appropriate psychological and family support.

At the third observation time point, the network calculations indicated that nausea was the core symptom of the T3 symptom network, underscoring its significant impact on other symptoms. Inadequate control of nausea may elevate the overall symptom burden at home. The worsening of gastrointestinal reactions may be attributed to the increase in chemotherapy-related side effects as the chemotherapy course increases. In terms of severity, vomiting was reported as the most severe symptom across all three time points, despite its relatively lower incidence rates. This pattern likely arises from standardized prophylactic antiemetics (e.g., 5-HT3 antagonists), which suppress frequency but incompletely mitigate severity, particularly in delayed chemotherapy-induced nausea and vomiting (CINV) involving central neurotransmitter dysregulation.[32] Additionally, we recommend future studies to investigate how personal factors may contribute to vomiting severity exacerbation after discharge. Some studies have explored acupuncture,[33] ginger therapy,[34] and structured nursing interventions[35] for relieving delayed CINV. However, the evidence supporting these approaches is generally low to moderate upon review. The delayed CINV remains challenging to control after discharge, necessitating collaboration between oncology caregivers and patients to make recommendations that can be integrated into a home-based care regime. Additionally, dry mouth was identified as a bridging symptom with the highest tightness and mediating effect in our study. Previous research has shown that xerostomia forms a symptom cluster in lymphoma chemotherapy patients,[8,11] adversely affecting their nutritional status and quality of life by causing discomfort during eating, including restricted mouth opening, difficulty swallowing, and trouble chewing. Further research is needed in this area, as there is currently insufficient evidence to support the effectiveness of interventions targeting xerostomia in minimizing the overall symptom burden experienced by lymphoma patients.

Implications for nursing practice and research

In terms of clinical implications, the current network analysis enables oncology nurses to identify core symptoms among lymphoma patients at home, such as lack of appetite, sadness, and nausea. This information can be combined with patient self-reported outcomes to effectively prioritize symptom management strategies. The nature of symptom networks enhances caregivers’ understanding of the interconnections among symptoms, facilitating the development of tailored interventions that address multiple symptoms simultaneously. For instance, managing lack of appetite may also alleviate fatigue and nausea, leading to a more comprehensive approach to patient care. Additionally, nursing staff can utilize insights from network analysis to educate patients about the relationships between their symptoms, thereby enhancing their ability to cope with the challenges of their condition at home.

Limitations

Despite the findings presented above, we acknowledge several limitations in this study. First, the reduced sample size due to loss to follow-up, which includes health issues, the perceived burden associated with follow-up assessments, and decreased interest in the study, may introduce selection bias and compromise the stability of the estimated network at T3, potentially impacting the robustness of our results. Second, we cannot guarantee that all potential symptoms were captured using the MDASI-C scale, highlighting the need for more comprehensive symptom assessments in future research. Third, the single-center design of this study may limit the reproducibility and generalizability of our findings to a broader population, as the results may not be applicable to patients in different healthcare settings or regions. Additionally, we only observed follow-ups at three time points. Importantly, 38% of participants were classified as “unknown” due to delays in assessment or incomplete documentation at the time of enrollment. This lack of staging information may affect the interpretation of our findings. Finally, the symptom network analysis conducted in this study does not establish any causal links. We will consider employing the cross-lagged panel network (CLPN) model to explore cross-temporal predictability and potential causal relationships among symptoms. Therefore, our results should be interpreted with caution. Future studies should consider multi-center

designs with larger sample sizes and longer follow-up periods to validate and enhance our findings.

Conclusions

Lymphoma chemotherapy patients experienced a significant symptom burden at home during intermittent chemotherapy. This network analysis identifies lack of appetite, sadness, and nausea as core symptoms that are centrally correlated with other symptoms at each assessment. Addressing these core symptoms is crucial for reducing the overall symptom burden at home. Nursing staff should focus on these symptoms, enhance psychological and nutritional support, and provide discharge education for patients and their family caregivers regarding symptom management.

CRediT authorship contribution statement

Qinglu Li: Writing – original draft, Conceptualization, Methodology, Formal analysis. Lu Yang: Investigation, Data duration, Writing – review & editing. Nan Wang: Conceptualization, Methodology. Wenting Shi: Conceptualization, Methodology. Lei Luo: Investigation. Hui Chen: Writing – review & editing. Guorong Wang: Conceptualization, Writing – review & editing, Supervision, Funding acquisition. All authors have read and approved the final manuscript.

Ethics statement

The study protocol was reviewed and approved by the Medical Ethics Committee of Sichuan Cancer Hospital (Approval No. SCCHEC-02-2020-52) and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants provided written informed consent.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Prof. Guorong Wang, upon reasonable request.

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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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2025.100683.

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