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Symptom and functional networks of patients with cancer in different latent risk subgroups based on patient-reported outcomes

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Abstract

Background Currently, risk stratification and effective management of heterogeneous patients with cancer based on patient-reported outcomes (PROs), used to evaluate clinical efficacy and outcomes, are relatively rare and urgently needed. We aimed to explore latent risk subgroups and delineate multidimensional networks of symptoms and functions based on PROs in this study.

Methods Patients with cancer were recruited from eight hospitals in two Provinces in China. The PROs measure for patients with cancer (CA-PROM) was used to measure patients' HRQoL, symptoms, and functions. Latent profile analysis (LPA) was used to explore latent risk subgroups using four fitting indicators on the patients' HRQoL. Network model (NM) of multidimensional symptoms and functions was applied at the item level of the CA-PROM. The expected influence (EI), bridge EI, and predictability of each node were used to evaluate the centrality and predictability of NM. Network accuracy and stability were tested using a case-dropping bootstrap procedure. Finally, a network comparison test (NCT) was conducted to examine whether network characteristics differed among the various risk subgroups.

Results In total, 1,404 valid questionnaires were collected. Three latent risk subgroups were determined based on the four fitting indicators. Considering the mean difference in HRQoL, subgroups 1, 2, and 3 were indicated as high-risk ($n=196$), low-risk ($n=716$), and medium-risk ($n=492$) subgroups, respectively. There were statistically significant differences in most demographic data, disease conditions, and treatment among three latent risk subgroups. Network analysis revealed that some symptoms and functions (e.g., despair, gastrointestinal abnormalities, care and support from their families and friends, appetite, and so on) played more important roles in the heterogeneity of HRQoL for Chinese patients w ith cancer. But the performance of these symptoms and functions reported by patients varied among three subgroups. Network accuracy and stability basically met the preset criteria. NCT results showed that edge differences were observed in five nodes, and seven nodes with different EI values could be informative for targeted support for the patients of different clusters.

Conclusion Different central and bridge symptoms or functions in multidimensional networks of PROs may serve as potential targets for personalized interventions among patients with cancer who are at different risk levels of HRQoL.

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Keywords Patient-reported outcome, Risk stratification, Network analysis, HRQoL, Cancer

Background

According to global cancer statistics, there was an estimate of 20 million new cases worldwide and 9.7 million cancer-related deaths in 2022. Almost half of all new cases (49.2%) and most (56.1%) cancer-related deaths worldwide in 2022 were estimated to occur in Asia [1]. The incidence and mortality rate of cancer among Chinese residents are higher than the global average [2]. With the application of new anti-tumor drugs and technologies in clinical practice, median survival period of patients with cancer has increased [3]. Cancer and its treatment are associated with severe symptoms and functional impairments, leading to a continuous decline in survivors' health-related quality of life (HRQoL) [4].

The heterogeneity of patients is a well-known phenomenon due to cancer and its treatment, and others [5]. Various data (e.g., electronic health system, SEER cancer registries, and scale data) and analytical methods (e.g., item response theory and latent class profile analysis) were used to explore the heterogeneity of patients with cancer [6–8]. A shift from treating a single symptom or function to managing multiple symptom or functional clusters has commanded greater attention on health management [6]. Owing to different clusters, significant differences in the average baseline HRQoL of patients with cancer have been observed in multidimensional fields [9]. Patient-reported outcomes (PROs) are collected directly from patients' reports of their health status, functional status, behavioral psychology, and treatment experiences. The U.S. Food and Drug Administration has indicated that PROs can provide an accurate assessment of HRQoL [10]. In a study of the Pediatric PROs Measurement Information System, Chinese children with a low distress profile reported significantly greater HRQoL than those with other profiles [11]. Currently, risk stratification of adult patients with cancer-based on PROs is relatively rare. Therefore, exploring the heterogeneity of HRQoL based on baseline PROs of adult patients with cancer can guide stratified management of cancer survivors.

Focusing on average differences of of HRQoL among different clusters can not provide related information on the mechanisms of HRQoL heterogeneity [12]. The network model (NM) is one of primary approachs for analyzing the mechanisms of HRQoL heterogeneity [13]. A patient's HRQoL is formed by a network of mutually interacting symptoms and functions [14]. NM can construct a network structure and indentify important symptoms or functions of patients with cancer. It provides new breakthroughs in symptom management, and promotes entire network to change in a better direction [15–18]. Furthermore, co-occurring multidimensional symptom networks may differ across subgroups, such as different age, sexes, and cultural backgrounds. Understanding these differences may provide more tailored interventions after subgroup stratification [19]. Individual symptoms or functions and HRQoL can be obtained through the systematic use of PROs in routine cancer care.

In this study, we aimed to explore the heterogeneity of HRQoL among adult patients with cancer, and construct multidimensional symptom and functional networks of latent subgroups based on PROs. This could help identify distinct subgroups of patients who experienced greater symptom severity and functional impairment, and provide targeted supportive care to match specific profiles of patients with cancer.

Methods

Study design

This cross-sectional study was conducted in Shanxi and Henan, China. Figure 1 shows the study flow chart.

Sample

Patients diagnosed with cancer between May 2018 and October 2018 were recruited from eight hospitals. The inclusion criteria were a diagnosis of cancer, age > 18 years, a life expectancy predicted to be ≥ 6 months post-diagnosis, and the ability to read and understand the questionnaire. The exclusion criteria were a presence of cognitive impairment or mental disorder and a history of another serious disease before the survey.

Measure

Patients with cancer would fill in the questionnaire within half an hour via the Wenjuanxing APP when being willing to participate in the questionnaire survey. The questionnaire included cancer patient's demographic data (age, gender, height, weight, and so on), disease situation (smoking, alcohol drinking, diagnosis, metastasis, treatment, and so on), and PRO Measure for Patients with Cancer (CA-PROM). CA-PROM was used to measure the HRQoL of adult patients with cancer at any stage. It included four domains, 13 subdomains, and 49 items, with a five-point Likert rating. Reported return rate and effective rate were 89.93% and 88.87%, respectively [20]. To conveniently calculate HRQoL, positive items were recoded as the original score plus one, whereas negative items were recoded as five minus the original score. The higher the total CA-PROM score, the better the patient's HRQoL. Because of small difference in the therapeutic domain for patients with cancer, only physiological, psychological, and social domains with corresponding

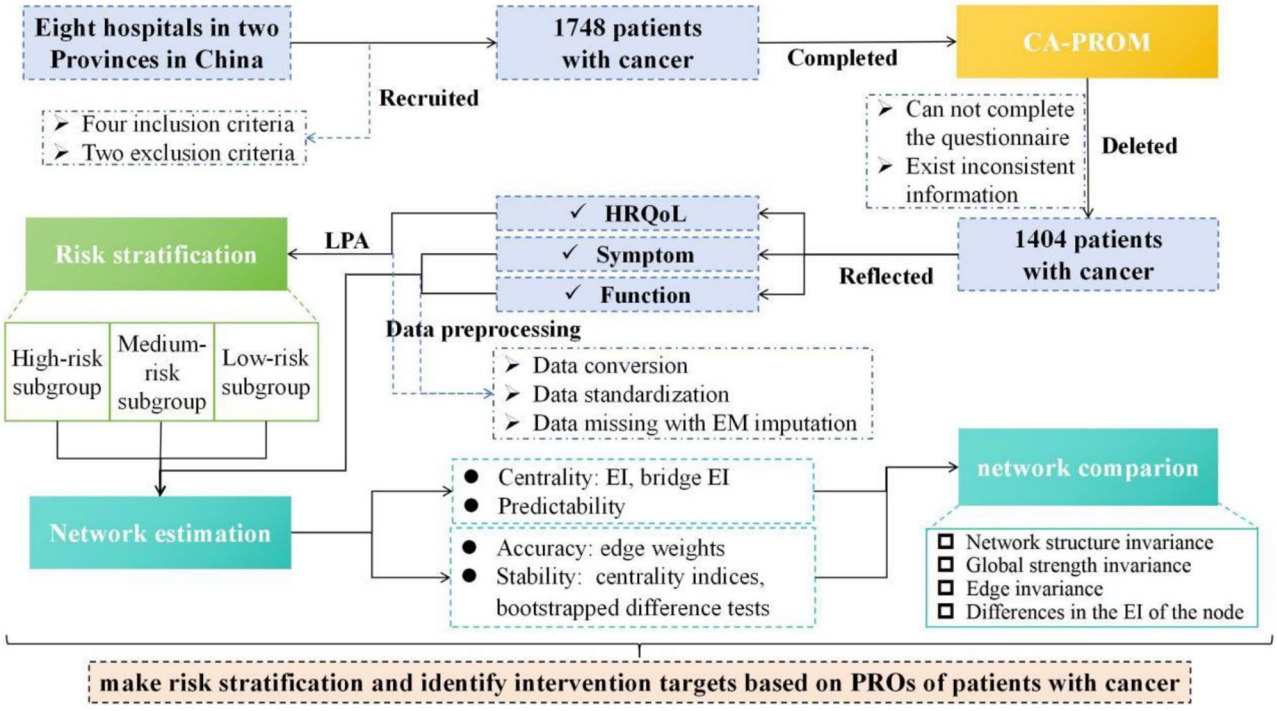

Fig. 1 Flow chart of this study

subdomains and items were selected in this study (See Additional file 1).

Data preprocessing

The collected questionnaires were numbered, and corresponding digital database was conducted via the Epidata. Demographic data and disease situation of patients with cancer was checked in the hospital medical record system. Little' missing completely at random test was used to evaluate whether the data of CA-PROM were missing at random. Dummy values were to substitute in for missing data by the expectation-maximization algorithm [21]. The scores of each item were added to obtain the raw score for each subdomain. Because different subdomains have different numbers of items, a min-max normalization was used to obtain a standardized score for each subdomain [22]. After standardization, the highest score for each subdomain was 100, whereas the lowest score was 0. To obtain intervention targets based on PROs, a reverse scoring method for calculating HRQoL was adopted in the NM [23].

Risk stratification based on the baseline HRQoL of patients with cancer

Latent Profile Analysis (LPA) was performed based on the standardized HRQoL scores for eight subdomains of the CA-PROM using the R package mclust (version 6.0.0) [24]. It can identify the latent risk subgroups to which patients were most likely to belong [8]. The following fitting indicators were used to evaluate the performance of the latent classification. The smaller the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, the better classification performance of the k-category model. Entropy is often used to evaluate the accuracy of latent classification. When the Entropy value is 0.8, the classification accuracy of the k-category model exceeds 90%. When the p-value of the Bootstrapped Likelihood Ratio Test (BLRT (p)) is <0.05, the k-category model is considered more suitable than the k-1-category model [4, 11]. After determining the optimal number of subgroups, each subgroup was named based on average HRQoL scores. In each subgroup, continuous variables were presented as mean ± standard deviation (Mean ± SD). Categorical variables were described using frequencies (n) and percentages (%). Analysis of variance and the chi-square test were used to analyze the demographic differences of patients among the latent risk subgroups. Bonferroni method was used for multiple comparison correction. Statistical significance was set at $p = 0.05$.

Network estimation of the items of the CA-PROM under risk stratification

In the NM, each item of the CA-PROM was indicated as a node, and partial association of items was regarded as an edge. The tuning parameter was set to 0.5 to obtain a sparser network. It is easier to interpret for clinical researchers [25]. The Fruchterman-Reingold algorithm

and spring layout were used in the estimated NM [26]. Centrality indices of the NM were expected influence (EI) and Bridge EI. A node with a higher EI value indicates a central symptom or function [27]. A node with a bridge EI value > 0.2 indicates a bridge symptom or function [28]. Node predictability is expressed as the area in the rings around each node in the NM layout. It represents the extent to which a node is associated with its neighboring nodes [29]. The accuracy of edge weights, node strength stability, and bootstrapped difference tests were used to estimate the network structure. The accuracy of edge weights and difference test in each pair of edges was evaluated by generating a new dataset with a 95% confidence interval (CI) based on nonparametric bootstrapping [30]. Node strength stability was evaluated using the Correlation Stability Coefficient (CS-C). CS-C should not be < 0.25 and should preferably be > 0.5 [31]. Network Comparison Test (NCT) was used to compare network properties between two subgroups [32]. Four indices were used to evaluate the NCT results: (1) differences in network structure invariance, (2) global strength invariance, (3) edge invariance, and (4) differences in the EI of the node [12, 33]. Statistical significance was set at $p = 0.05$. Network estimation was computed using the R package qgraph (version 1.9.5), qgraph mgm (version 1.2–13), Bootnet (version 1.5.3), and NetworkComparisonTest (version 2.2.1).

Results

In total, 1748 patients with cancer were recruited in this study to complete the CA-PROM. Notably, 344 questionnaires were eliminated because the patients could not complete the scale and responded with incorrect information. Finally, 1404 samples were selected for this study. Cronbach's α coefficients for eight dimensions of the CA-PROM were > 0.7. The Root-Mean-Square Error of Approximation value was 0.08 with a 95% CI of 0.089–0.099 in the confirmatory factor analysis. It indicated good reliability, validity, and feasibility of the CA-PROM.

Latent classification based on the patients' HRQoL in ten subdomains of the CA-PROM

Considering the heterogeneity of baseline HRQoL of patients with cancer, latent models were sequentially established using the LPA method. All the BLRT (p) of six models were < 0.05 in the Table 1. It indicated that the k-th category model was significantly better than the k-1th category model. The entropy value of three subgroups was maximized. The corresponding AIC and BIC decreased by 1.78% and 1.62% for three subgroups compared with those for two subgroups, respectively. Considering four fitting indicators, the optimization model was ultimately determined to be three subgroups. Sample sizes across subgroups were 196 (Class 1), 716 (Class 2), and 492 (Class 3).

Differences in the standardized scores for each domain and subdomain of the CA-PROM among three subgroups

As shown in Figure 2A, the standardized mean scores for the physiological (56.05±13.14) and psychological (59.39±19.38) domains of Class 1 were lower than those for the physiological (87.67±8.67) and psychological (90.35±9.51) domains of Class 2. The standardized mean scores of Class 1 were also lower than those for the physiological (75.62±11.45) and psychological (66.28±14.79) domains of Class 3. The standardized mean scores for the social domain of Classes 1 (66.58±14.57) and 3 (66.67±13.55) were very close but lower than those for the social domain of Class 2 (79.72±15.50). As shown in Figure 2B, the standardized mean scores for each subdomain began to cross when the subgroups were stratified into the three. The standardized mean scores for the social influence of Class 2 (82.56±21.03) were higher than those for the social influence of Class 1 (50.96±26.86). A diametrically opposite pattern is observed in the social adjustment. The higher the standardized mean score of CA-PROM, the higher the HRQoL of patients with cancer. Therefore, Classes 1, 2, and 3 were designated as high-, low-, and medium-risk subgroups, respectively. The standardized mean sore for pain subdomain was significantly lower in the high-risk group (41.11±15.60) than that in the medium-risk subgroups (86.90±12.63) and low-risk subgroups (94.86±9.47).

Comparison of demographic data among the three latent risk subgroups

Table 2 presented the results of the comparison of demographic data among the three latent risk subgroups. No

Table 1 Fit statistics for latent profile analysis from one to six classes

Model	AIC	BIC	Entropy	BLRT(p)	Number of each subgroup	The percentage of each subgroup
1	99929.06	100013.02	1.00	-	1404	1.00
2	97916.40	98047.58	0.82	0.01	1058/346	0.75/0.25
3	**97349.06**	**97527.46**	**0.86**	**0.01**	**716/492/196**	**0.51/0.35/0.14**
4	97143.86	97369.49	0.80	0.01	693/419/160/132	0.49/0.30/0.12/0.09
5	97035.47	97308.32	0.79	0.01	587/424/163/135/95	0.42/0.30/0.11/0.10/0.07
6	96606.04	96926.11	0.83	0.01	554/431/112/109/89/89	0.41/0.32/0.08/0.07/0.06/0.06

Note: AIC, akaike information criterion; BIC, bayesian information criterion; BLRT(p), p value of bootstrapped likelihood ratio test

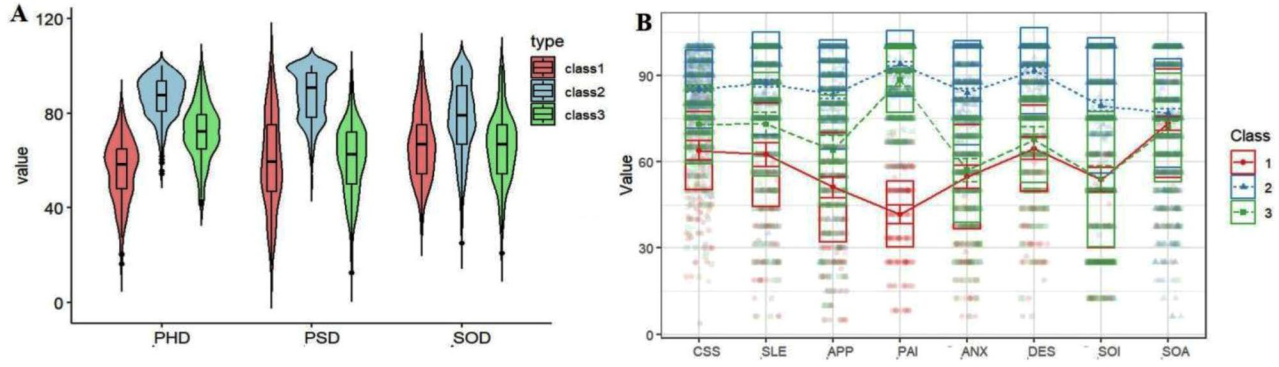

Fig. 2 **A** Differences between standard scores for three subdomains of CA-PROM in three latent classifications. PHD: physiological domain, PSD: psychological domain, SOD: social domain. **B** Differences between trajectories of standard scores for eight subdomains of CA-PROM in three latent subgroups. The scores of each domain and subdomain had been standardized, which ranged from 0 to 100. CSS: common symptoms, SLE: sleep, APP: appetite, PAI: pain influence, ANX: anxiety, DES: Despair, SOI: social influence, SOA: social adjustment

statistically significant differences in sex, blood type, marital status, smoking, alcohol consumption, or disease systems was observed. There were significant differences in age, height, weight, education level, average monthly income, medical insurance, occupation, family history, history of allergies, comorbidities, cancer staging, metastasis, and therapy among three latent risk subgroups, with the significance level < 0.05. After multiple comparisons of analysis of variance among three latent subgroups, mean difference of age (-2.208, $P = 0.015$), height (1.188, $P = 0.032$), and weight (2.4497, $P = 0.001$) between low-risk and medium-risk subgroup were statistically significant ($P = 0.015$). The significant mean difference of age (-2.910, $p = 0.022$) and weight (3.6680, $p < 0.001$) also existed between low-risk and high-risk subgroup. After multiple comparisons of chi-square test among three latent subgroups, the high-risk subgroup showed significantly lower education levels and monthly income compared with those of the low-risk subgroup. The high-risk subgroup comprised 43 patients reported work occupational exposure. This subgroup demonstrated different percentage of family and allergy history, comorbidity, and metastatic disease. Notably, The high-risk subgroup received multiple treatment modalities.

Symptom and functional networks in the three latent risk subgroups

Figure 3 showed the multidimensional symptom and functional networks estimation of the three latent risk subgroups. The network densities of the low-, medium-, and high-risk subgroups were 12.69% (59/465), 11.61% (54/465), and 10.32% (48/465), respectively, with the average weights ranging from 0.099 to 0.107.

Figure 4 showed the centrality plots of the multidimensional symptom and functional networks in the three latent risk subgroups. It depicted the values of EI and bridge EI for the 31 items of the CA-PROM. There were higher values of EI for two nodes (SOA2 (i.e., My neighbors and friends all care about my illness.) and APP3 (i.e., I feel full after a little eating.)) of low-risk subgroups, three nodes (SOA2 (i.e., My neighbors and friends all care about my illness.), SLE3 (i.e., I am easy to wake up in the midnight.), and DES3 (i.e., I have no confidence in defeating my disease.)) of medium-risk subgroups, and one node (DES4 (i.e., I have lost my confidence in the future.))of high-risk subgroups, respectively. This results suggested that five individual symptoms and functions were the most influential within the three NMs in terms of the variance explained using PROs. These nodes were viewed as short-term intervention targets. After sorting the bridge EI of the estimated networks in three latent risk subgroups, these values of bridge EI > 0.2 were observed for two nodes (CSS4 [bridge EI = 0.254] and DES2 [bridge EI = 0.399]) in the low-risk subgroup, one node (DES2 [bridge EI = 0.222]) in the medium-risk subgroup, and two nodes (CSS4 [bridge EI = 0.355] and DES4 [bridge EI = 0.339]) in the high-risk subgroup. Based on the results of bridge EI, there were five cross-sectional connection pathways across different subdomains or domains based on PROs in three subgroups (see Additional file 2). Average predictability among the 31 items of the CA-PROM were 0.269, 0.322, and 0.243 in the low-, medium-, and high-risk subgroup respectively. There were the highest predictability for the node "SOA2 (i.e., My neighbors and friends all care about my illness.)", the node "SLE3 (i.e., I am easy to wake up in the midnight.)", and two nodes "SLE3" and DES4 (i.e., I have lost my confidence in the future.) in the low-, medium- and high- risk subgroups, respectively (see Additional file 3).

Stability and accuracy of the network

The gray areas for edge weights were small among three network analysis processes (see Additional file 4). It indicated that the estimated edge weights were all accurate and stable. The stability of EI and bridge EI of the nodes were showed in the Additional file 5–6. The CS-C values

Table 2 Comparison of basic data among three subgroups

Variable	Value	Group			F/ x^2	*P*
		High-risk (*n* = 196)	Low-risk (*n* = 716)	Medium-risk (*n* = 492)		
Age		58.53 ± 13.15	55.62 ± 14.20	57.83 ± 12.29	5.838	0.003
Sex	Male	107 (12.6%)	444 (52.2%)	299 (35.2%)	3.295	0.192
	Female	89 (15.9%)	272 (49.3%)	193 (34.8%)		
Height(cm)		165.74 ± 7.62	166.83 ± 7.91	165.64 ± 7.79	3.782	0.023
Weight(kg)		59.99 ± 11.48	63.66 ± 11.27	61.21 ± 11.18	11.489	< 0.001
Blood type	A	30 (16.1%)	97 (52.2%)	59 (31.7%)	12.548	0.250
	B	43 (16.2%)	145 (54.7%)	77 (29.1%)		
	AB	16 (16.3%)	49 (50.0%)	33 (33.7%)		
	O	38 (14.4%)	138 (52.5%)	87 (33.1%)		
	No known	67 (11.7%)	284 (49.3%)	224 (39.0%)		
Level of education	Primary school and below	58 (16.9%)	157 (45.8%)	128 (37.3%)	14.484	0.025
	Middle school	86 (15.3%)	282 (50.2%)	194 (34.5%)		
	High school	36 (11.3%)	176 (55.2%)	107 (33.5%)		
	Bachelor and above	14 (8.4%)	99 (59.3%)	54 (32.3%)		
Marital status	Unmarried	8 (14.3%)	36 (64.3%)	12 (21.4%)	11.937	0.154
	Married	173 (13.9%)	642 (51.5%)	432 (34.6%)		
	Divorced	2 (14.3%)	4 (28.6%)	8 (57.1%)		
	Widowed	12 (15.8%)	33 (43.4%)	31 (40.8%)		
Average monthly income	Low	134 (15.0%)	426 (47.7%)	333 (37.3%)	13.181	0.010
	Middle	60 (12.3%)	283 (57.9%)	146 (29.9%)		
	High	1 (11.1%)	5 (55.6%)	3 (33.3%)		
Medical insurance	Self funded	7 (11.1%)	34 (54.0%)	22 (34.9%)	0.466	0.792
	Non self funded	187 (14.0%)	681 (51.2%)	463 (34.8%)		
Occupation	peasant	117 (14.9%)	369 (46.9%)	300 (38.2%)	27.734	0.006
	worker	43 (16.0%)	150 (56.0%)	75 (28.0%)		
	Institution	6 (20.0%)	13 (43.3%)	11 (36.7%)		
	Other	29 (9.4%)	183 (59.0%)	98 (31.6%)		
Family history	No	161 (13.3%)	645 (53.2%)	407 (33.6%)	10.301	0.036
	Yes	32 (21.5%)	66 (44.3%)	51 (34.2%)		
Allergy history	No	169 (13.4%)	657 (52.2%)	432 (34.3%)	8.145	0.017
	Yes	24 (22.6%)	55 (51.9%)	27 (25.5%)		
Smoking	No	116 (15.4%)	394 (52.3%)	245 (32.4%)	6.318	0.388
	Smoking	28 (14.7%)	97 (50.8%)	66 (34.6%)		
	Given up smoking	45 (11.3%)	208 (52.4%)	144 (36.3%)		
Drink	No	129 (15.8%)	417 (51.2%)	269 (33.0%)	10.028	0.123
	Occasionally drinking	21 (10.8%)	112 (57.4%)	62 (31.8%)		
	Regularly drinking	10 (17.9%)	24 (42.9%)	22 (39.3%)		
	Given up drinking	29 (10.5%)	146 (52.9%)	101 (36.6%)		
Comorbidity	No	38 (33.9%)	42 (37.5%)	32 (28.6%)	41.023	< 0.001
	Yes	157 (12.2%)	674 (52.2%)	461 (35.6%)		
Cancer staging	I	9 (11.8%)	35 (46.1%)	32 (42.1%)	39.764	< 0.001
	II	44 (16.4%)	94 (34.9%)	131 (48.7%)		
	III	59 (9.2%)	392 (60.9%)	193 (30.0%)		
	IV	81 (20.4%)	191 (48.0%)	126 (31.6%)		
Metastasis	No	118 (11.6%)	569 (56.2%)	326 (32.2%)	24.222	< 0.001
	Yes	57 (21.2%)	112 (41.6%)	100 (37.2%)		
Disease systems	Respiratory system	40 (11.6%)	180 (52.2%)	125 (36.2%)	11.649	0.168
	Digestive system	93 (16.4%)	252 (44.5%)	221 (39.0%)		
	Hematological system	27 (13.0%)	115 (55.3%)	66 (31.7%)		
	Endocrine system	19 (12.2%)	63 (48.1%)	52 (39.7%)		
	other	16 (12.2%)	63 (48.1%)	52 (39.7%)		

Table 2 (continued)

Variable	Value	Group			F/ x^2	*P*
		High-risk (*n* = 196)	Low-risk (*n* = 716)	Medium-risk (*n* = 492)		
Primary treatment modality	Surgery	103 (14.7%)	388 (55.3%)	210 (30.0%)	48.582	< 0.001
	chemotherapy	55 (17.8%)	127 (41.1%)	127 (41.1%)		
	Radiotherapy	132 (15.0%)	440 (49.9%)	310 (35.1%)		
	Other	11 (11.7%)	25 (26.6%)	58 (61.7%)		

of the EI for patients with cancer in the low-, medium-, and high-risk subgroups were 0.750, 0.595, and 0.363, respectively. They were greater than 0.25. It demonstrated the consistency of the EI values in three latent risk subgroups even after significant chunks of the sample were dropped by the case-dropping subset bootstrap approach. The CS-C of the bridge EI for patients with cancer in the low-risk subgroup was 0.517. However, the CS-C of the bridge EI in the high- and medium-risk subgroups had slightly lower stability (0.126 and 0.207, respectively).

Network comparisons among the three latent risk subgroups

Figure 5 showed the network comparisons between the low- and medium-risk subgroups. The maximum difference in all edge weights was significant (M = 0.24, $p = 0.035$). No significant differences in the network global strength were observed (S = 1.57, $p = 0.616$). The three significantly different edges were SOI1-SOI2 ($p = 0.009$), SOA1-SOA2 ($p = 0.003$), and PAI1-PAI2 ($p = 0.043$). Significant differences in the EI of node "SOA1" were observed ($p = 0.012$). Additional figure files show the network comparisons among the other pairwise subgroups (see Additional files 7a, 7b). One individual edge (DES2-DES4 [$p < 0.001$]) and the EI of the node "DES4" [$p = 0.015$] differed significantly between the low- and high-risk subgroups. Furthermore, one individual edge (SOI1-SOI2 [$p = 0.013$]) and the EI of five nodes (APP3 [$p = 0.043$], APP4 [$p = 0.021$], PAI2 [$p = 0.013$], PAI3 [$p = 0.049$], and SOA3 [$p = 0.003$]) differed significantly between the high- and medium-risk subgroups.

Discussion

Considering the heterogeneity of general cancer patients' HRQoL, three latent subgroups (i.e., high-, low-, and medium-risk) were identified to perform risk stratification. Moreover, multidimensional networks of symptoms and functions among three subgroups were constructed based on PROs to explore the mechanisms of HRQoL heterogeneity. After comparing network properties of three subgroups, it was found that some symptoms and functions played important roles in the hierarchical risk stratification of disease management. Despair was common central symptom in three multidimensional networks of symptoms and functions, but the performance of depair reported by patients varied among three subgroups. Gastrointestinal abnormalities is common bridge symptom in the networks of low- and high- risk subgroups. It indicated that there was a greater probability of contagion from the subdomain of common symptoms to the subdomain of appetite by the symptom "gastrointestinal abnormalities". SOA2 (My neighbors and friends all care about my illness) was common central function in the low- and medium- risk subgroups, indicating that patients of two subgroups were more concerned about the care and support from their families and friends. The identification of HRQoL patterns and network analysis of interaction mechanisms of symptoms and functions can help clinical practitioners identify different risk groups of patients with cancer and initiate therapeutic interventions based on PROs that are more timely and supportive.

In clinical trials or personalized cancer care, existing published guidelines [34–36] indicated that direct and prompt care can be provided to patients based on PROs. Data collection of PROs can be standardized to reduce workload. And Risk stratification based on patients' HRQoL levels can be implemented. Furthermore, clinicians immediately focus on high-risk patients requiring urgent intervention. For lower-risk patients, ongoing monitoring must be established through scheduled follow-ups [37]. Therefore, we used LPA to stratify the risk based on eight subdomains of the CA-PROM. However, a systematic perspective was lacking. García Abejas et al. [38] reported that PROs pose a complex research problem. It includes the complex interplay between symptoms and functions, and the mechanism by which physiological, psychological, and social symptoms or functions affect HRQoL. The existence and specificity of these interactions were identified using network assessment. Multidimensional symptom and functional network research based on PROs can provide a systemic perspective to capture the complex interactions between crucial symptom and functional targets and other symptoms or functions [39]. Central symptoms or functions in the NM may contribute heavily to the development and continuation of other symptoms and functions. Therefore, focusing on central symptoms may be more efficient to optimize disease management strategies [40].

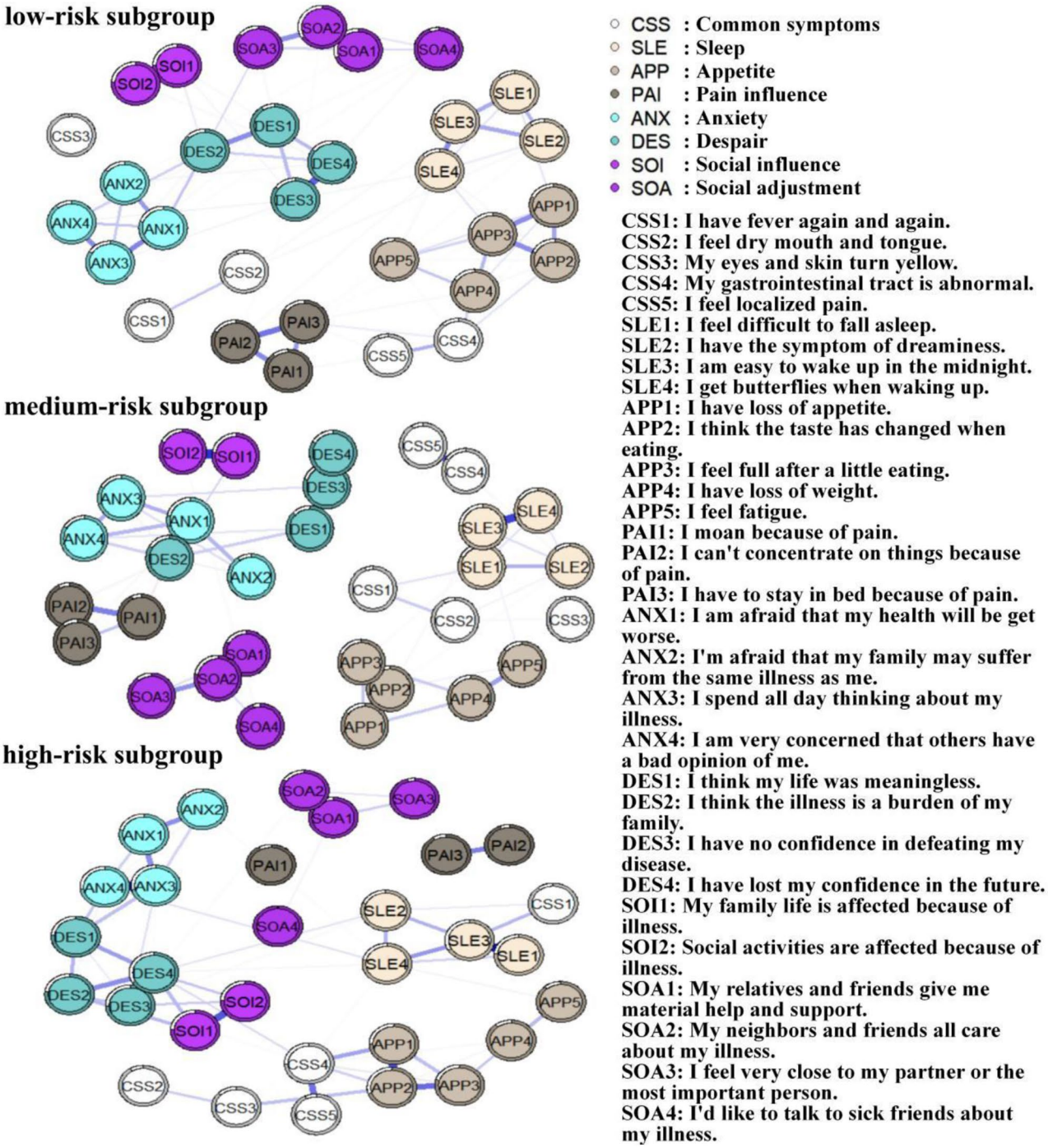

Fig. 3 Estimated symptom and functional networks of each item of CA-PROM for cancer patients in three latent subgroups. The network structure was a Gaussian graphical model, which was a network of partial correlation coefficients. Nodes represent symptoms or functions. The outermost grey rings of nodeds represent the predictability of symptoms or functions. Edges represent pairwise dependencies between the symptoms or functions under controlling for all of other correlations of a given node. Blue line indicates a positive correlation. The thicker the lines are, the stronger the correlation

Researchers can identify bridge symptoms as catalysts for various syndromes using network analyses. Therefore, a network perspective could potentially yield more clinically applicable insights into the role of early symptoms in estimating the likelihood of future interventions [13].

The observed disparities in socio-demographic and clinical variables among latent risk subgroups underscored the multifactorial nature of cancer outcomes. The high-risk subgroup showed significantly older age (mean 58.53 ± 13.15 years), lighter weight group (mean

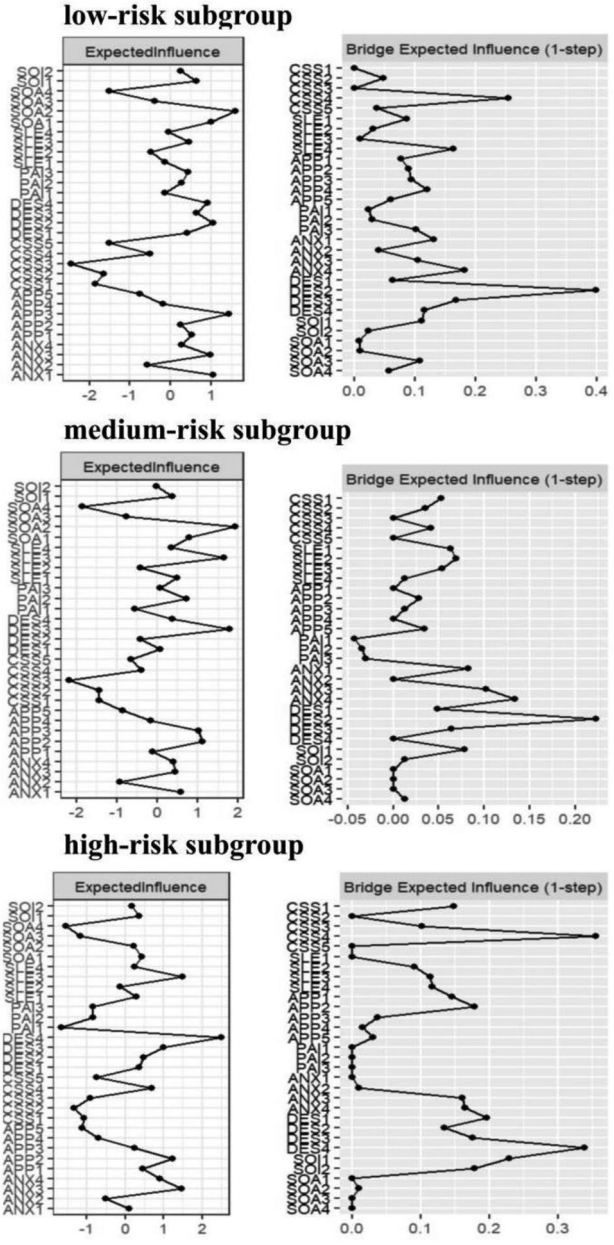

Fig. 4 Centrality plot depicted the expected influence (EI) and bridge EI (z-score) for each item of CA-PROM chosen in cancer patients of three latent subgroups. CSS, common symptoms; SLE, sleep; APP, appetite; PAI, pain influence; ANX, anxiety; DES, despair; SOI, social influence; SOA, social adjustment

59.99 ± 11.48 kg), lower education levels and monthly income, aligning with the WHO's framework on social determinants of health [41]. Limited health literacy correlates with poor symptom recognition and delayed screening uptake [42]. Mobile health platforms with low-literacy-adapted content (e.g., video-based instructions for chemotherapy adherence) could mitigate this gap, as trialed in rural cancer cohorts [43]. Forty-three patients with cancer of high-risk subgroup worked in industries with occupational exposure, echoing the findings of International Agency for Research on Cancer on occupational cancers [44]. Targeted workplace screening programs (e.g., annual low-dose CT for asbestos-exposed workers) should be prioritized. Higher prevalence of familial cancer in the high-risk subgroup suggested potential genetic susceptibility [45]. Paradoxically, allergy history was inversely associated with high-risk, possibly due to enhanced immune surveillance-a phenomenon observed in glioma cohorts [46]. High-risk patients had higher rates of comorbidity and metastatic disease, negatively correlated with patients' HRQoL. The high-risk subgroup received multiple treatment modalities and fewer targeted therapies, likely due to cost barriers and biomarker testing inequities. Co-payment assistance for genetic testing could increase targeted therapy access [47].

In the present study, over half of patients with cancer ($n = 716$) were classified into the low-risk subgroup. And average of three domains and eight subdomains of the CA-PROM reflected higher HRQoL in this group than in the other two subgroups. Network analysis in the low-risk subgroup revealed node "SOA2 (My neighbors and friends care about my illness)" and "APP3 (I feel full after eating a little)" as reflecting the most influential social support functions and dietary symptoms. The importance of social support has been confirmed by the research results of Li et al. [15]. They found that with more social support, patients with low-grade gastric cancer could obtain sufficient positive resources to cope with the disease burden. Because of the burden of therapeutic treatments for patients with cancer, social support is imperative to encourage patients' medical compliance. Patients with cancer receiving family support in the form of informational, instrumental, emotional, and self-esteem support can improve their HRQoL [48]. The central symptoms (node "APP3 (I feel full after eating a little)") in the present study differed from the results of a Chinese gastric cancer study on the chemotherapy-related symptom networks of distinct subgroups. They found that fatigue and lack of appetite were the two most severe symptoms in the moderate group. This discrepancy may be partly due to differences in the participants' focus. Notably, patients with cancer who underwent chemotherapy, radiation therapy, or surgery were recruited in the present study. Multiple treatments and various types of cancer have different effects on the HRQoL of patients with cancer [49]. Rha et al. found that lack of appetite is strongly associated with changes in taste in the symptom network [50]. Lack of appetite may predict poor patient survival and cause significant distress to both patients and family members in later stages [51]. Providing patients with dietary advice, such as small frequent meals, nutritional supplementation, and

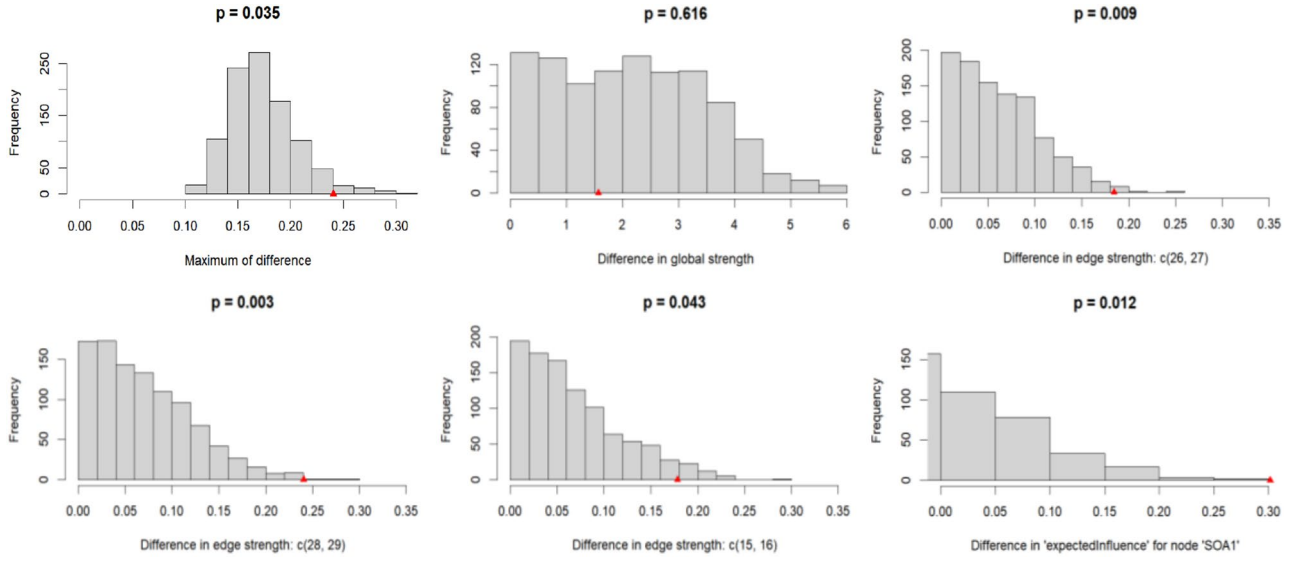

Fig. 5 Comparison of network properties between the low- and medium- risk group. Vertical axis indicated sample size; Horizontal axis indicated proportion of p-values < 0.05; Maximum of difference, maximum difference across network structure of two subgroups; Difference in global strength, difference for the overall level of connectivity across two subgroups' networks; Difference in edge strength, difference in individual edges across two subgroups' networks; c(26,27) represents the edge weight between node "SOI1 (My family life is affected because of illness.)" and node "SOI2 (Social activities are affected because of illness.)". c(28,29) represents the edge weight between node "SOA1 (My relatives and friends give me material help and support.)" and node "SOA2 (My neighbors and friends all care about my illness.)". c(15,16) represents the edge weight between node "PAI1 (I moan because of pain.)" and node "PAI2 (I can't concentrate on things because of pain.)"

consuming hawthorn to stimulate the appetite, may help alleviate gastrointestinal symptoms [52].

Patients with cancer in the medium-risk subgroup in the present study reported symptom severity and functional impairment between the low and high-risk classes. Besides node "SOA2 (My neighbors and friends care about my illness)," nodes "SLE3 (I can be easily woken at midnight)" and "DES3 (I have no confidence in defeating my disease)" indicated a core symptom in this symptom network. In a study by Zhang et al., sleep disorders were a core symptom in the symptom cluster of 2966 survivors who participated in the 2020 National Health Interview Survey [53]. Han et al. described anxiety, despair, and sleep disturbances as a psychological symptom cluster [54]. According to the International Classification of Diseases, Tenth Revision, sadness is regarded as a core symptom [55]. Notably, most patients with cancer cannot take good care of themselves. They hardly meet the fundamental physiological needs of Maslow's hierarchy of needs. Psychological symptoms were inevitable when most basic needs were unmet. Patients may adopt some measures to alleviate their associated symptoms, including mindfulness meditation, music therapy, maintaining social connections with family and friends, and seeking psychological counseling when needed [56].

Patients with cancer in the high-risk group in the present study reported high levels of symptom severity and functional impairment. In particular, changes in the pain influence subdomain were observed. However, the results of the NM in this group showed that node "DES4 (I have lost my confidence in the future)" indicated the most central symptom, and its bridge EI and predictability values showed good performance. This node was related to two nodes "ANX1 (I am afraid that my health will be get worse.)" and "ANX2 (I'm afraid that my family may suffer from the same illness as me.)" of the anxiety subdomain. And it was also related to two nodes "SOI1 (i.e., My family life is affected because of illness.)" of social influence subdomain and "SOA3 (i.e., I feel very close to my partner or the most important person.)" of social adaptation subdomain. Cancer pain and physical limitations contribute to psychological symptoms over time. Feelings of despair may be a common experience among individuals with cancer, and these feelings contribute to anxiety symptoms. Fear of death may lead to avoidance of medical appointments or social activities, which can exacerbate feelings of despair [57]. Kleijn et al. reported that the despair subscale correlated significantly ($p < 0.001$) with HRQoL (r=-0.29), distress ($r = 0.44$), anxiety ($r = 0.47$), and depression ($r = 0.32$) in 107 patients with advanced cancer patients between 2009 and 2014 [58]. Social support has been shown to positively impact cancer prognosis by enabling patients to feel emotionally supported during treatment [59]. Patients should actively communicate with their physicians to identify appropriate pain management strategies [50]. Implementing mindfulness-based stress reduction techniques alongside cognitive

behavioral therapy (CBT) protocols can help patients alleviate emotional distress [60].

Among three subgroups in the present study, nodes "CSS4 (My gastrointestinal tract is abnormal.)," "DES2 (I think the illness is a burden to my family)," and "DES4 (I have lost my confidence in the future)" had greater bridge EI values than the other nodes. They were directly or indirectly related to other nodes in eight subdomains and three domains of the CA-PROM. The interconnection was indirectly confirmed by assessing differences in symptom clusters among 1,330 survivors. They found that there were consistent connections between fatigue, emotional symptoms, appetite loss, dyspnea, and pain across all cancer types [61]. In a study by Shim et al., somatic and psychological symptoms were strongly related particularly in patients with cancer experiencing more severe symptoms [62]. In the present study, the network properties of three latent risk subgroups were more similar than different. However, there were the observed edge differences between some nodes. These nodes could be informative regarding targeted support. A comparison of network structures among latent risk subgroups can reveal which nodes and associations differ among cancer patients at different HRQoL levels. This information could provide a valuable tool beyond assessing mean differences in CA-PROM in patients with cancer [12].

This study has some limitations. First, the CS-C of the bridge EI in the high- and medium-risk groups had slightly lower stability, which was lower than the minimum acceptable value of CS-C (0.25). Second, we constructed an NM of cross-sectional PROs; however, the explanation of the causal relationships between variables is limited. Third, self-reported approaches for evaluating the HRQoL of patients with cancer may provide skewed results and misinterpretations, which may compromise the accuracy of the analysis. Finally, our results should be interpreted with caution because the generated networks were based on group-level analysis, and whether group-level results can represent individual-level results remains unclear. Further, patients' trajectory was not captured through the CA-PROM in a cross-sectional survey. So the long-term effects of the central symptoms or functions and connection pathways need to be further confirmed. To address these limitations, we will further expand the sample size of patients with cancer and conduct regular follow-ups of PROs in future research.

Conclusion

To our knowledge, this is the first network analysis of multidimensional networks of symptoms and functions based on PROs in adult cancer patients with different risk subgroups. Considering the heterogeneity of HRQoL among patients with cancer, high-, low-, and medium-risk subgroups were identified by the method of LPA. Given the standardized mean scores of the physiological (56.05 ± 13.14), psychological (59.39 ± 19.38), and social (66.58 ± 14.57) domain, the patient with cancer will be very likely at risk of low HRQoL levels. To analyze the mechanisms of HRQoL heterogeneity, NM was used to delineate multidimensional networks of symptoms and functions based on PROs among three latent risk subgroups. Network analysis revealed despair was common central symptom. However, the performance of depair reported by patients varied among three subgroups. Gastrointestinal abnormalities is common bridge symptom in the networks of low- and high- risk subgroups. SOA2 (My neighbors and friends all care about my illness) was common central function in the low- and medium- risk subgroups. Focusing on mean differences in HRQoL and interference targets from the network analysis of PROs can provide sufficient information for precision medicine for patients with cancer.

Abbreviations

HRQoL	Health-Related Quality of Life
PROs	Patient-Reported Outcomes
LPA	Latent Profile Analysis
NM	Network Model
CA-PROM	Patient-Reported Outcome Measure for patients with Cancer
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BLRT	Bootstrapped Likelihood Ratio Test
CS-C	Correlation Stability Coefficient
CI	Confidence Interval
NCT	Network Comparison Test
EI	Expected Influence

Supplementary Information

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Supplementary Material 1

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Author contributions

All authors originated and designed the study. XH, ZD and XL were responsible for collecting the data. XH contributed to the drafting and rewriting of the paper. HC participated in the data analysis. HZ and YZ proposed the original concept for this study. All the authors take responsibility for the integrity of the data and the accuracy of the data. All the authors read and approved the final manuscript.

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Data availability

Please contact the corresponding author for the study data, which will be granted upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the declaration of Helsinki. All research procedures complied with the relevant guidelines and regulations. The medical Ethics Committee of Shanxi Medical University had approved this study (No. 2013099). All participants received sufficient explanation from research workers and signed informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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