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Predictors for quality of life in older patients with breast cancer: A cross-sectional research from China

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Abstract

Background

The quality of life(QoL) of older patients with cancer is affected by more factors than that of young people, and their requirements for QoL are often higher than the treatment effect. Understanding what really matters to patients in nowadays contributes to the propensity of care resources. The purpose of this study was to investigate the QoL of Chinese older breast cancer patients and to further explore the association of functions, symptoms, financial burden, comorbidities with global health/quality of life(gQoL).

Methods

This cross-sectional study was conducted at the two centers in Beijing from October 2021 to

November 2022. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Charlson Comorbidity Index(CCI) were assessed in breast cancer patients aged over 65 years. Data were analyzed using network analysis and path analysis.

Results

481 patients were included in the final analysis. Network analysis showed that "fatigue" was the central symptom and indirectly decreased the gQoL mediated by increasing "financial difficulties", "CCI" and "role function"(β =-0.35, $p < 0.001$) . "Physical function" is also an important and direct intervention node, and it is indirectly related to gQoL mediated by "role function"(β =-0.15; p =0.006). The path analysis accounts for 32.0% of the total effect.

Conclusions

Focusing on both fatigue symptoms and physical function status may be a particularly worthwhile effort to reduce financial burden, improve patients' functional status and promote QoL.

Keywords: network analysis, path analysis, older breast cancer, fatigue, quality of life

1. INTRODUCTION

Breast cancer is a typical age-related disease in western countries. Although the current proportion of older breast cancer patients in China is much lower than that in Europe and the United States, it is estimated that by 2030, 41.4% of breast cancer patients in China will be aged 60 years or older[1]. Contemporary breast cancer treatment is already the most advanced biomedical treatment, patients can still have a long survival time after treatment, but it can not solve the survival-related quality of life(QoL) issues[2]. And older patients themselves are often combined with a variety of underlying diseases, the body function is weak, facing the risk of weakness. The QoL of older patients is affected by more factors than that of young people, and their requirements for QoL are often higher than the treatment effect[3].

In today's era of progressive chronic cancer treatment, patient QoL has become an important outcome measure and research endpoint in oncology medicine[4]. Different cancer patients may have very different needs. By measuring QoL, valuable information about disease symptoms and treatment side effects can be obtained from patients. Previous studies on the QoL of older breast cancer patients were mostly conducted in developed countries, and most of them were reported more than ten years ago[5][6]. With the development of the treatment measure, the QoL was also promoted[7]. Patients' demands for QoL may change. Understanding what really matters to patients in nowadays contributes to the propensity of care resources.

Network analysis is often used in the study of multiple scales to understand the interrelationships between scales. The approach illustrates what is an important target for clinical intervention by intuitively identifying the “central symptom” of the network[8]. However, network analysis cannot establish causality or directional relationships between nodes, which can be complemented by path analysis. Path analysis provides insight into the pathways between nodes (predictors and mediators) that lead to the resulting variables. By exploring the interaction of different dimensions of QoL and comorbidities, we can identify the specific processes that affect QoL. In addition, path analysis can provide a preliminary explanation and conjecture of the relationship between variables. It can also provide valuable insights for further research and practice[9].

Factors influencing the QoL in older Chinese patients with breast cancer have not been fully investigated. The purpose of this study was to understand the QoL of older Chinese patients with breast cancer using network and path analysis, and to understand the potentially important concerns of this group.

2. PATIENTS AND METHODS

2.1 Patients

This is a cross-sectional enrollment study conducted in the outpatient and inpatient departments of at the Cancer Hospital of Chinese Academy of Medical Sciences and Beijing

Chao Yang District San Huan Cancer Hospital from October 2021 to November 2022. The inclusion criteria were as follows: (1) pathologically confirmed breast cancer; (2) over 65 years of age at the time of the survey; (3) able to understand the purpose and content of the survey and cooperate with the survey; (4) complete medical records. A total of 510 questionnaires were sent out and 491 were returned, of which 10 were incomplete. Finally, the examination results of 481 patients were included in the analysis.

2.2 Measures

This study is divided into two parts, including a questionnaire survey and clinical data collection.

QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30(EORTC QLQ-C30)[10]. It consists of several programmes: five functional domains (physical, role, cognitive, emotional, and social); three domains of physical symptoms (fatigue, nausea/vomiting, pain); several individual symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties), and global health/quality of life (gQoL). The gQoL includes two questions, namely the subjective assessment of the patient's physical health status and the overall QoL. Each item scale is then converted into a standard score for analysis. Higher scores for functional domains and general health indicate better functional status and QoL. Higher scores for symptom domains indicate more symptoms or problems (and poorer QoL).

The Charlson Comorbidity Index (CCI) is currently the most widely used comorbidity index with a total of 14 items listed in **Supplementary Table S1**. The total score is calculated by adding the weights. To avoid duplicate assessment, breast cancer is included in the clinical data for statistics, but not in the CCI.

Clinicopathological data of the included patients were collected after questionnaire survey, including age at the time of the survey, education level, stage, molecular subtype and treatment. The treatment was identified as the treatment the patients had received at the time of the survey.

2.3 Ethical approval and informed consent

This study is part of a multi-centre, cross-sectional registry study(registration number: ChiCTR2200056070). All participants were informed of the aim of the study and signed an informed consent form. The study was carried out in line with a named standard approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval number: 22/216-3418).

2.4 Data analysis

2.4.1 Clinical data statistics

SPSS 26.0 software was used for descriptive statistical analyses, using means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

2.4.2 Network estimation

Network analysis was performed using the qgraph, networktools, ggplot, mgm and bootnet packages of R software (version 4.1.2; using the R Foundation for Statistical Computing). The least absolute shrinkage and selection operator (LASSO) and the extended Bayesian information criteria (EBIC) are used to regularize the correlation matrix to reduce the margin of possible spurious correlations[11]. Blue connections between nodes represent positive connections and red connections represent negative connections. The network is visualized using the Fruchterman-Reingold algorithm, and strongly connected nodes are usually close to each other. The importance of each node is quantified by calculating the expected influence [11]. The higher the expected influence, the more important the node is in the network model. To more intuitively identify specific symptoms that are directly related to gQoL, we used the "flow" function in the R package qgraph for plotting[12]. Predictability refers to the extent to which the variance of a node can be explained by all of its neighboring nodes[12]. The average predictability of all nodes in the network reflects the extent to which the network is affected by external factors.

To estimate the stability of the centrality measure, the case-drop subset bootstrap method was used, in which an increasing proportion of subjects were randomly removed

from the dataset and the centrality index was recalculated. In order to quantify the stability of the centrality index, the correlation stability (CS) coefficient was calculated. Ideally, centrality estimates should be greater than 0.5. In addition, to measure the accuracy of the edge, estimated 95% confidence intervals for the region containing the true regularized partial correlation (edge) were calculated by "nonparametric" bootstrapping (n bootstrap = 1000)[13].

2.4.3 Path analysis

Based on the results of the network analysis, multiple linear analysis was performed on factors directly related to gQoL to identify independently related factors. Path analysis is used to identify direct and indirect effects between viables and to determine the overall fit of the model. A well-fitting model must meet the following conditions: test chi-square, chi-square/degrees of freedom ratio (CMIN/DF) <3, goodness of fit index (GFI) > 0.90, comparative fit index (CFI) > 0.90, adjustment goodness of fit index (AGFI) > 0.95, and root mean square error of approximation (RMSEA) < 0.10[14]. Based on the multivariate Lagrangian multiplier (LM) test, the model was modified twice to add new paths where necessary. The significance of all direct and indirect effects was assessed to determine which variables had direct and indirect effects on gQoL. The significance level was set at 0.05. Standardized beta coefficients (β) are derived for each explanatory variable to allow comparison and estimation of the relative importance of each measure. The R-squared value is calculated to determine the proportion of variance that the model is able to explain[15].

Path analysis was performed using IBM SPSS Amos® software version 23.

3. RESULTS

3.1 Clinicopathological characteristics

A total of 481 patients were included in the final analysis (**Table 1**). The median age at enrolment was 69 (range 65-91) years. There were higher frequency(33.7%) of patients with 10-12 years of education and fewer patients(9.4%) with 6 years of education. Molecular subtype was predominantly HR+/HER2- (68.6%). The majority of patients had undergone surgery (91.1%). More than half had received chemotherapy and endocrine therapy (56.5% and 65.3%, respectively). 30.1% had received radiotherapy.

3.2 Distribution of function and symptom scores

The distribution of the function and symptom scores is showed in **Table 2.** The highest function scores were found for social function(86.9±22.7) whereas cognitive function(80.2±21.3) were rated much lower. Most of the patients' functional scores were greater than 50, and only a small number of patients were less than 50, among whom the role function ratio was the highest, reaching 9.6%. Insominia and fatigue were the relatively frequently reported symptoms with the highest scores(32.3±33.6 and 20.1±22.7).

3.3 Network analysis result

As shown in **Figure 1B**, there were a large number of connections between nodes. The strongest correlation between the variables in the network analysis was -0.722("fatigue" and "social function") and between the variables in the network analysis and gQoL was -0.513 ("fatigue" and "gQoL")(**Supplementary Table S2**). The symptom with the largest expected influence was "fatigue"(1.617), followed by "role function"(1.052) and "social function"(0.873)(**Figure 1A, Supplementary Table S3**), indicating that these symptoms had the largest impact in the overall network. In contrast, the least expected effects were "age"(0.048), "CCI"(0.382) and "diarrhea"(0.492). Moreover, node predictability values ranged from 45.0% to 96.5% with an average of 77.2%, indicating that, on average, 77.2% of the variance in nodes from the network could be explained by their neighboring nodes (**Supplementary Table S3**). "Age"(0.965), "CCI"(0.901) and "diarrhea"(0.893) had the highest predictability in the model, while the "fatigue"(0.450), "role function"(0.625) and "physical function"(0.665) had the lowest predictability.

To better illustrate the relationship between all symptoms and QoL scores, we plotted the QoL flow network (**Figure 2**). Of the total symptoms, 11 were directly related to the gQoL and the remaining symptoms include age were indirectly related to it. Multiple linear regression analysis shows that "CCI", "financial difficulties" and "role function" are independently correlated with "gQoL"(**Supplementary Table S4).**

The expected influence of the bridge and the strength of the bridge also had high stability,

and the correlation stability coefficient CS values were both 0.672 (**Supplementary Figure S1**) . The accuracy of edge weight estimation between nodes is shown in **Supplementary Figure S2** .

3.4 Path analysis model

Based on network analysis and multiple linear regression analysis results, we further examined the relationship between "fatigue", "physical function", "CCI", "financial difficulties", "role function" and "gQoL". The final model shows that significant correlations among them(**Figure 3**). The "financial difficulties" ($\beta = -0.11$, $p = 0.009$) and "role function" ($\beta = 0.26$; $p < 0.001$) have a direct effect on "gQoL". "CCI" has a indirect effect on "gQoL" being mediated by "financial difficulties"($\beta = -0.12$; $p < 0.001$). "Fatigue"($\beta = -0.35$, $p < 0.001$) has indirect effect on "gQoL" being mediated by "financial difficulties", "role function" and "CCI". "Physical function" have indirect effect on "gQoL" being mediated by "role function" ($\beta = -0.15$; $p = 0.006$) (**Table 3**). "Physical function" and "fatigue" were also significantly correlated($\beta = 0.69$; $p < 0.001$). The multivariate linear regression final model for the mediation showed a good global adjustment: Fit indices: $\chi 2$ (9) =3.870 (p>0.424); $\chi 2$ / df = 0.968; GFI = 0.997; AGFI = 0.986; CFI =1.000; RMSEA = 0.000 (95%CI = (0.000; 0.068)). R-square indicates that this model can explain 32.0% of the variance general health score.

4. DISCUSSION

The balance between treatment effectiveness and QoL in older breast cancer patients is an important issue for clinicians to consider. To our knowledge, this is the first cross-sectional study to investigate QoL in Chinese older breast cancer patients in the real world using a network and path analysis to help understand factors influencing the QoL in order to guide and inform social, health and education policies. As expected, functions, symptoms, and comorbidities had a significant impact on gQoL through different paths.

The results of the network analysis visualized the complex network of variables and provided clues to further understand of the relationship between functions, symptoms, comorbidities and gQoL. “Fatigue” as the central symptom was closely related to patient function including “role function” , “physical function” and “social function”. A recent meta-analysis showed that the incidence of fatigue after chemotherapy in cancer patients was about 49%[16]. Studies have shown that there are more and more severe levels of fatigue exist in older subgroups[17]. The high centrality of fatigue in this study indicates that it is highly associated with other symptoms, which has very important clinical intervention value. Compared to changing sociodemographic and clinical factors (which were difficult to do), it seems more preferable to change fatigue and systemic therapy side effects to improve long-term survivors' QoL. Therefore, the assessment and management of fatigue should be considered in daily nursing practice.

As for the means to improve fatigue, in addition to clinical drug intervention, the results

of path analysis also provide us with certain insights. Physical function and fatigue were significantly correlated. The low predictability of physical function indicates that it is also a good direct intervention node, and it is also independently related to role function. Previous studies have also shown that physical activity can have a positive impact on patients' quality of life through the prevention of decline in physical function[18]. In addition, chronic disease management is also important. In this pathway analysis, fatigue was an independent variable and comorbidities were the regulators. However, in cross-sectional studies, this is not absolute. These results suggest that fatigue in older patients can be improved by addressing comorbidities.

Moreover, the presence of chronic disease had a negative impact on the gQoL through "financial difficulties". This suggests that financial burden is an important factor to consider among older cancer patients, especially those with chronic diseases. Previous studies have shown that greater financial burden is associated with patients' anxiety and depression, which is also shown in our **Figure 1**, and patients' compliance with treatment is also poor [19][20]. We included patients over 65 years of age, almost all of whom were retired and did not have high sources of income, and they were likely to experience greater financial burden[21]. It not only causes patients to delay seeking care and to forgo necessary treatments, but also affects treatment decisions and patient compliance[22]. Of course, this requires the participation of the whole society's medical insurance to improve the financial burden of cancer patients. This is not easy, but it may partly explain why the QoL of breast cancer patients in China is relatively lower than in western countries[23] [24].

All identified core symptoms had a high predictive value, with an average predictive value of 74.8% for all nodes in the network. In other words, most of the nodes in the network can be interpreted and controlled by their neighbours. The CS was greater than 0.5, which means the network has good repeatability. The model evaluation indices of the path analysis also meet the expected requirements and show that the overall fit of the model is good.

The shortcoming of this study is that it was a cross-sectional study which are not directional. They cannot confirm the causal relationship between symptoms. Path analysis compensates for this to some extent, but time series data should still be collected in the future. Second, participants in this study were recruited from two hospitals, which may not be representative of the older breast cancer population across different regions of China.

5. CONCLUSION

In conclusion, this study provides a clinical pathway to improve the quality of life for older breast cancer patients. We found that fatigue and physical function indirectly affects gQoL by influencing financial difficulties, CCI or role function, accounting for 32.0% of the total effect. Focusing on both fatigue symptom and physical function status may be a particularly worthwhile effort to reduce financial burden, improve patients' functional status and promote QoL.

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ABBREVIATIONS

QoL	quality of life
gQoL	global health/quality of life
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life questionnaire Core 30

CCI	Charlson Comorbidity Index
LASSO	Least Absolute Shrinkage and Selection Operator
EBIC	Extended Bayesian Information Criteria
CS	correlation stability
CMIN/DF	chi-square/degrees of freedom ratio
GFI	goodness of fit index
CFI	comparative fit index
AGFI	adjusted goodness of fit index
RMSEA	root mean square error of approximation
LM	Lagrangian multiplier
β	Standardized beta coefficients
HR	Hormone receptor
HER2	Human epidermal growth factor receptor 2
SD	Standard Deviation
AIDS	Acquired Immune Deficiency Syndrome

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FIGURE LEGENGS

Figure 1 A. Expected influence of each node of the quality of life and characteristics network. B. Network structure of quality of life and characteristics.

Figure 2 Flow network of quality of life and characteristics.

Figure 3 Path analysis with standardized direct effects. Note: Ftg, fatigue; PhF, physical function; CCI, Charlson Comorbidity Index; Fnd, financial difficulties; gQoL, global health/quality of life; RlF, role function.

SUPPLEMENTARY FIGURE LEGENGS

Supplementary Figure S1 Network stability: bridge expected influence and bridge strength.

Supplementary Figure S2 Bootstrapped confidence intervals of edge weights.

Supplementary Figure S3 Comparison of network properties between early and advanced stage group.

Table 1 Clinicopathological data

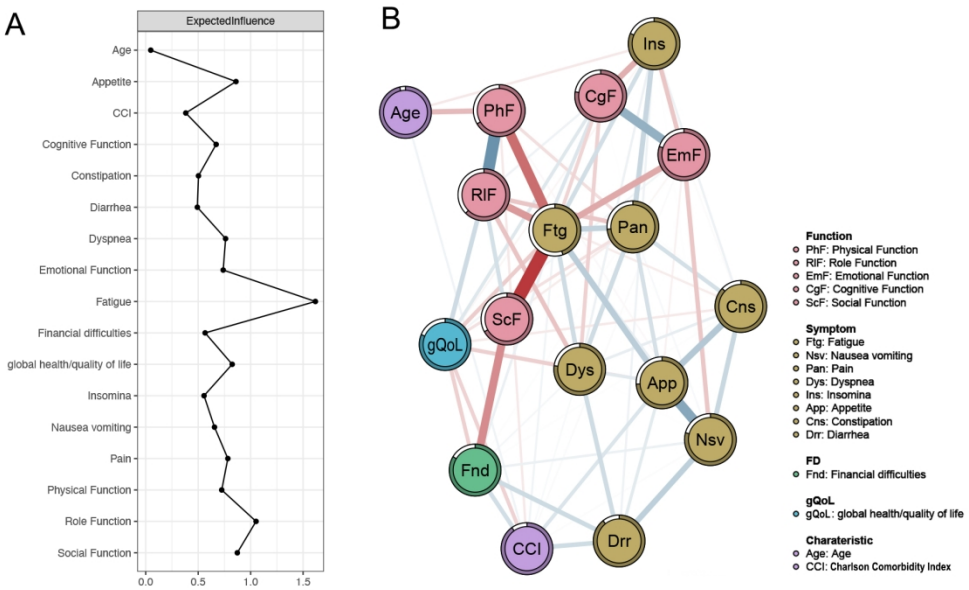
	All(n=481)	%
Age(year, range)	69	65-91
Year at diagnosis		
1979-2000	13	2.7
2000-2009	24	5.0
2010-2019	199	41.4
2000-2022	245	50.9
Education(year)		
≤6	45	9.4
7-9	133	27.7
10-12	162	33.7
≥13	141	29.3
CCI(median, range)	2	0-11
Stage		
Tis	8	1.7
I	151	31.4
II	133	27.7
III	69	14.3
IV	107	22.2
unknown	13	2.7
Molecular subtype		
HR+/HER2-	330	68.6
HER2+	95	19.8
HR-/HER2-	43	8.9
unknown	13	2.7
Surgery		
yes	438	91.1
no	43	8.9
Chemotherapy		
yes	272	56.5
no/unknown	209	43.5
Radiotherapy		
yes	145	30.1
no/unknown	336	69.9
Endocrine therapy		
yes	314	65.3
no/unknown	167	34.7

Abbreviate: CCI, Charlson Comorbidity Index; HR, Hormone receptor; HER2, Human epidermal growth factor receptor 2.

Table 2 Scores of EORTC QLQ-C30 questionnaires

	Mean±SD	Proportion of cases with
EORTC QLQ-C30		Scores < 50 (%)
gQoL	69.1±21.3	13.5
Function scores		
Physical Function	82.4±21.4	7.5
Role Function	84.9±26.2	9.6
Emotion Function	81.9±20.0	4.2
Cognitive Function	80.2±21.3	6.0
Social Function	86.9±22.7	6.2
Symptoms		Scores ≥ 50 (%)
Fatigue	20.1±22.7	10.6
Nausea/vomiting	4.7±14.3	3.5
Pain	16.4±24.3	13.5
Dyspnea	15.5±24.4	9.4
Insomina	32.3±33.6	27.9
Appetite	15.0±25.5	11.0
Constipation	15.5±26.3	11.6
Diarrhea	6.6±18.5	5.0
Financial difficulties	15.2±27.1	11.0

Abbreviate: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; SD, Standard Deviation; gQoL, Global health/quality of life



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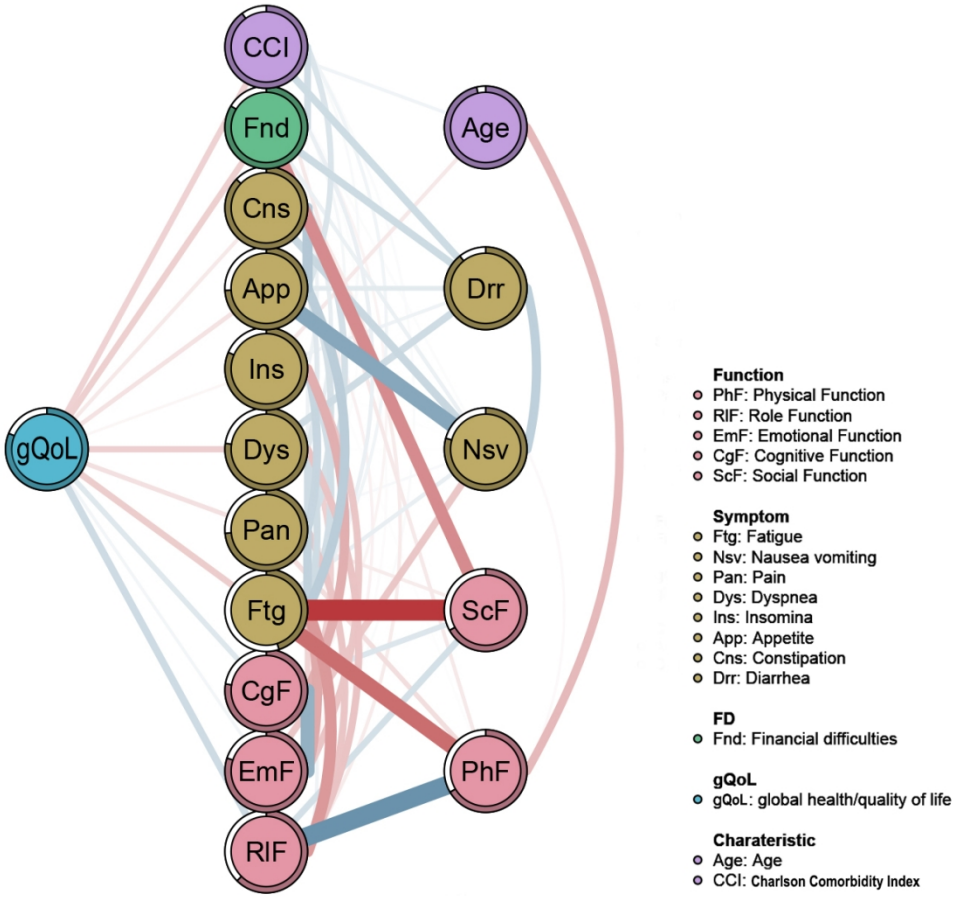

Figure 2 Flow network of quality of life and characteristics.

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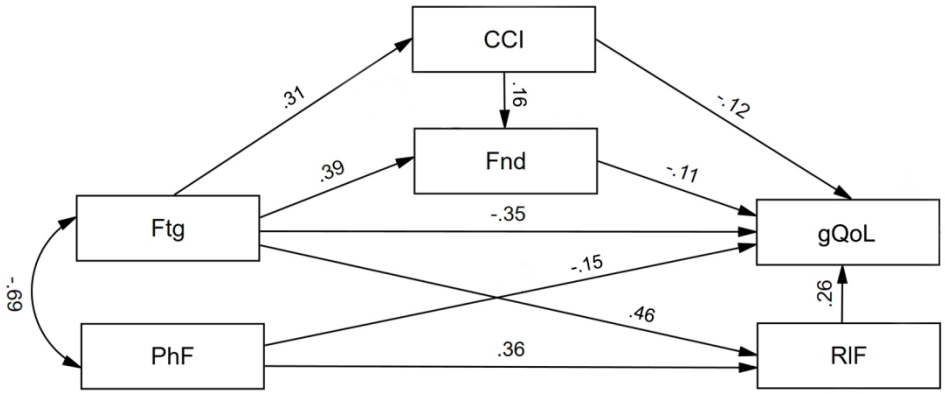


Figure 3 Path analysis with standardized direct effects. Note: Ftg, fatigue; PhF, physical function; CCI, Charlson Comorbidity Index; Fnd, financial difficulties; gQoL, global health/quality of life; RlF, role function.

621x287mm (72 x 72 DPI)

Supplementary Table S1 Scoring of different diseases in Charlson Comorbidity Index

Scoring	Comorbidity
1	Ischemic heart disease; congestive heart failure; peripheral vascular disease; cerebrovascular disease; dementia; chronic pulmonary disease; mild liver disease; diabetes without chronic complication
2	Diabetes with chronic complication; renal impairment; tumor without metastasis
3	Moderate or severe liver disease
6	Metastatic solid tumor; AIDS

Abbreviate: AIDS, Acquired Immune Deficiency Syndrome

Supplementary Table S2 Correlation coefficient of symptoms, functions, financial difficulties, charateristics and gQoL

	Physical Function	Role Function	Emotional Function	Cognitive Function	Social Function	Fatigue	Nausea/ vomiting	Pain	Dyspnea	Insomina	Appetite	Constipation	Diarrhea	Financial difficulties	gQoL	Age	CCI
Physical Function	1.000																
Role Function	0.680	1.000															
Emotional Function	0.282	0.324	1.000														
Cognitive Function	0.352	0.417	0.486	1.000													
Social Function	0.491	0.564	0.380	0.429	1.000												
Fatigue	-0.688	-0.709	-0.524	-0.512	-0.722	1.000											
Nausea vomiting	-0.322	-0.301	-0.348	-0.165	-0.247	0.430	1.000										
Pain	-0.488	-0.536	-0.368	-0.368	-0.469	0.607	0.343	1.000									
Dyspnea	-0.368	-0.491	-0.285	-0.385	-0.351	0.542	0.313	0.458	1.000								
Insomina	-0.254	-0.282	-0.381	-0.408	-0.298	0.462	0.260	0.406	0.336	1.000							
Appetite	-0.396	-0.427	-0.358	-0.306	-0.408	0.555	0.512	0.455	0.410	0.270	1.000						
Constipation	-0.287	-0.324	-0.252	-0.165	-0.213	0.347	0.351	0.357	0.308	0.254	0.415	1.000					
Diarrhea	-0.213	-0.188	-0.166	-0.116	-0.188	0.290	0.327	0.220	0.301	0.212	0.305	0.184	1.000				
Financial difficulties	-0.310	-0.340	-0.230	-0.285	-0.467	0.434	0.277	0.308	0.304	0.140	0.273	0.214	0.285	1.000			
gQoL	0.329	0.469	0.331	0.364	0.397	-0.513	-0.265	-0.407	-0.404	-0.302	-0.379	-0.283	-0.213	-0.336	1.000		
Age	-0.230	-0.138	0.007	-0.015	-0.120	0.129	-0.016	0.022	0.052	-0.053	0.062	0.045	0.014	0.026	-0.086	1.000	
CCI	-0.264	-0.240	-0.070	-0.138	-0.225	0.308	0.220	0.202	0.238	0.099	0.288	0.170	0.157	0.277	-0.277	0.123	1.000

Abbreviate: gQoL, Global health/quality of life; CCI, Charlson Comorbidity Index;

Supplementary Table S3 Descriptive statistics of the items

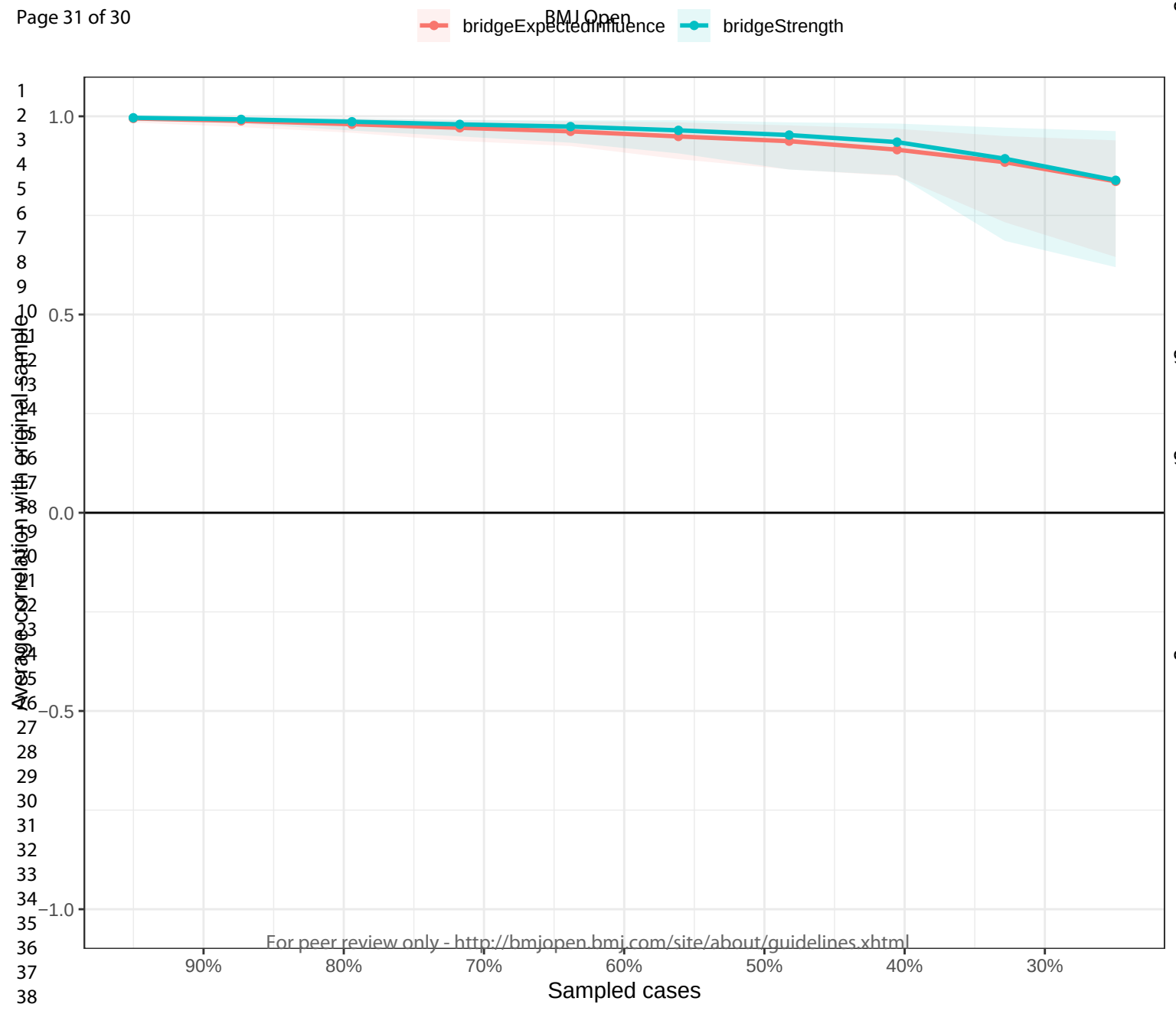
Item content	Expected influence	Predictability
Age	0.048	0.965
CCI	0.382	0.901
gQoL	0.824	0.813
Physical Function	0.724	0.665
Role Function	1.052	0.625
Emotional Function	0.739	0.801
Cognitive Function	0.671	0.776
Social Function	0.873	0.669
Fatigue	1.617	0.450
Nausea/vomiting	0.656	0.793
Pain	0.783	0.736
Dyspnea	0.761	0.773
Insomina	0.556	0.815
Appetite loss	0.860	0.742
Constipation	0.503	0.872
Diarrhea	0.492	0.893
Financial difficulties	0.566	0.837

Abbreviate: CCI, Charlson Comorbidity Index; gQoL, Global health/quality of life

Supplementary Table S4 Multiple linear analysis related to gQoL

	Unstandardized		Standardized	P-value	F	adj R^2
	β (95%CI)	SE	β			
				<0.001	22.4	0.329
Role function	0.131(0.042-0.220)	0.045	0.161	**0.004**		
Emotional function	0.068(-0.031-0.167)	0.050	0.064	0.177		
Cognitive function	0.070(-0.023-0.164)	0.048	0.070	0.139		
Fatigue	-0.096(-0.224-0.033)	0.065	-0.102	0.144		
Pain	-0.046(-0.133-0.041)	0.044	-0.053	0.296		
Dyspnea	-0.078(-0.159-0.002)	0.041	-0.090	0.057		
Insomnia	-0.034(-0.091-0.022)	0.029	-0.054	0.232		
Appetite	-0.049(-0.128-0.030)	0.040	-0.059	0.223		
Constipation	-0.036(-0.104-0.032)	0.035	-0.044	0.303		
Financial difficulties	-0.076(-0.142--0.010)	0.034	-0.097	**0.024**		
CCI	-0.988(-1.749--0.227)	0.387	-0.104	**0.011**		

Abbreviate: gQoL, Global health/quality of life; CCI, Charlson Comorbidity Index



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Association of quality of life in older patients with breast cancer: A cross-sectional study from China

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Association of quality of life in older patients with breast cancer: A cross-sectional study from China

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Running title: QoL in Older Breast Cancer Patients in China

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Abstract

Objectives

The purpose of this study was to investigate the quality of life (QoL) of older Chinese patients with breast cancer and to further explore the associations of functions, symptoms, financial burdens, and comorbidities with global health/quality of life (gQoL).

Methods

This was a cross-sectional study. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and the Charlson Comorbidity Index (CCI) were used to assess QoL and comorbidities in patients with breast cancer aged over 65 years. The data were analysed using network analysis and path analysis.

Results

A total of 481 patients were included in the final analysis. Out of the 136 possible edges in the final networks, 84 (61.8%) were non-zero. “Fatigue” was the central symptom and indirectly decreased the gQoL, which was mediated by increasing “financial difficulties”, “CCI” and “role function” ($\beta = -0.35$, $p < 0.001$). “Physical function” was also an important and direct intervention node that was indirectly related to gQoL, and this was mediated by “role function” ($\beta = -0.15$; $p = 0.006$). Path analysis accounted for 32.0% of the total effect.

Conclusions

The various dimensions of QoL are highly interrelated and mutually reinforcing. These results highlight the importance of improving the fatigue and physical function of older patients with breast cancer. Interventions targeting these symptoms may lead to overall improvement in gQoL.

Strengths and limitations of this study

- The study was supported by a national project with good preliminary design.
- Data were collected using standardized and validated procedures and instruments, increasing its credibility.

- Both network and path analysis methods were used to leverage their respective strengths and address their limitations.
- One limitation of our study is that it employed a cross-sectional study design with heterogeneous subjects.
- The combined analysis of metastatic and nonmetastatic patients underestimated these differences.

Introduction

With increased awareness of the importance of individualized, patient-centred care, as well as the increased rates and duration of breast cancer survival, quality of life (QoL) is becoming the central parameter of breast cancer survivorship[1][2]. QoL is affected by a variety of factors in older breast cancer patients, as they face tremendous declines in both physical and psychological functions, with issues ranging from organ failure and neuropathy to depression[3][4]. Moreover, with the rapid ageing of the population, 41.4% of patients with breast cancer in China are estimated to be aged 60 years or older by 2030[5]. There is a need to focus on this group of patients in China.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is a widely validated scale for assessing QoL, and it includes multidimensional concepts such as symptoms, functions and financial burden[6][7]. Most previous studies have focused on how specific factors affect QoL, such as the impact of cognitive function and physical function on QoL, the impact of comorbidities on QoL, and the impact of treatment-related symptoms on QoL[8][9][10]. However, the different dimensions of QoL tend to influence each other and are highly correlated, but there have been no studies that fully illustrate this relationship. Network analysis is often used in the study of multiple items to understand the interrelationships among them and to identify important targets called “central symptoms” for clinical intervention[11]. However, network analysis cannot establish causality or directional relationships between nodes; this limitation can be overcome by path analysis. Path analysis provides insight into the pathways between nodes (predictors and mediators) that lead to the resulting variables. By exploring the interaction of different dimensions of QoL, we can identify the specific processes that affect QoL.

Thus, the purpose of this study was to understand the relationships among multiple dimensions of QoL in older Chinese patients with breast cancer using network and path analysis. Specifically, we used network analysis to examine the relationships among

the QoL subscales and to identify the core symptoms. Next, we used path analysis to investigate the relationships between core symptoms and global health/quality of life (gQoL). By elucidating the symptom-function-financial burden-comorbidity-gQoL relationship, we hope to provide insights for developing effective interventions and rehabilitation programs for older patients with breast cancer to ensure their QoL.

Patients and methods

Study design and setting

This study was part of a multicentre, prospective, cross-sectional, registry study designed to establish a clinical database for older patients. This breast cancer cohort included 510 participants from two hospitals in Beijing from October 2021 to November 2022. The reporting in this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross-sectional studies (**Table S1**)[12].

Participants

The inclusion criteria for the participants were as follows: (1) had pathologically confirmed breast cancer; (2) were over 65 years of age; (3) were able to understand the purpose and content of the survey and cooperate with the survey; and (4) had complete medical records.

The exclusion criteria were as follows: (1) refused to complete the scale; (2) incomplete questionnaires; and (3) medical records that were incomplete and could not be analysed statistically.

Measures

QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[6]. It consists of several programs: five functional domains (physical, role, cognitive, emotional, and social); three domains of physical symptoms (fatigue, nausea/vomiting, and pain);

several individual symptoms (dyspnoea, insomnia, appetite, constipation, diarrhoea, and financial difficulties); and global health/quality of life (gQoL). The gQoL includes two questions, namely, the subjective assessment of the patient's physical health status and the overall QoL. Each item scale is then converted into a standard score for analysis. Higher scores for functional domains and general health indicate better functional status and QoL. Higher scores for symptom domains indicate more symptoms or problems (and poorer QoL).

The Charlson Comorbidity Index (CCI) is currently the most widely used comorbidity index, with a total of 14 items (**Table S2)**. The total score is calculated by adding the weights. To avoid duplicate assessments, breast cancer was included in the clinical data for statistical analysis but not in the CCI. The above sinicization scales have been validated in the Chinese population[13][14].

Clinicopathological data, including age at the time of the survey, education level, stage, molecular subtype and treatment, were collected from the included patients after the questionnaire survey. The treatment was identified as the treatment the patients had received at the time of the survey.

Patient and public involvement

All the participants were informed of the aim of the study and signed an informed consent form. The survey was completed by participants voluntarily and no input from patients was sought in interpreting or writing up the results. The results of the research will not be disseminated to the patients.

Data analysis

Clinical data statistics

SPSS 26.0 software was used for descriptive statistical analyses, with means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

Network estimation

Network analysis was performed using the qgraph, networktools, ggplot, mgm and bootnet packages of R software (version 4.1.2; using the R Foundation for Statistical Computing). The least absolute shrinkage and selection operator (LASSO) and extended Bayesian information criterion (EBIC) were used to regularize the correlation matrix to reduce the margin of possible spurious correlations. The blue connections between nodes represent positive connections, and the red connections represent negative connections. The network was visualized using the Fruchterman–Reingold algorithm, and strongly connected nodes were usually close to each other. The importance of each node was quantified by calculating the expected influence[15]. The greater the expected influence was, the more important the node was in the network model. To more intuitively identify specific symptoms that are directly related to gQoL, we used the "flow" function in the R package qgraph for plotting[16]. Predictability refers to the extent to which the variance of a node can be explained by all of its neighbouring nodes[16]. The average predictability of all nodes in the network reflects the extent to which the network was affected by external factors.

To estimate the stability of the centrality measure, the case–drop subset bootstrap method was used, in which an increasing proportion of subjects were randomly removed from the dataset and the centrality index was recalculated. To quantify the stability of the centrality index, the correlation stability (CS) coefficient was calculated. Ideally, centrality estimates should be greater than 0.5. In addition, to measure the accuracy of the edge, estimated 95% confidence intervals for the region containing the true regularized partial correlation (edge) were calculated by "nonparametric" bootstrapping (n bootstrap = 1000)[17].

Path analysis

Based on the results of the network analysis, multiple linear analyses were performed on factors directly related to gQoL to identify independently related factors. Path

analysis was used to identify direct and indirect effects between variables and to determine the overall fit of the model. A well-fitting model needed to meet the following conditions: test chi-square, chi-square/degrees of freedom ratio (CMIN/DF) <3, goodness-of-fit index (GFI) > 0.90, comparative fit index (CFI) > 0.90, adjustment goodness-of-fit index (AGFI) > 0.95, and root mean square error of approximation (RMSEA) < 0.10[18]. Based on the multivariate Lagrangian multiplier (LM) test, the model was modified twice to add new paths where necessary. The significance of all direct and indirect effects was assessed to determine which variables had direct or indirect effects on gQoL. The significance level was set to 0.05. Standardized beta coefficients (β) were derived for each explanatory variable to allow comparison and estimation of the relative importance of each measure. The R-squared value was calculated to determine the proportion of variance that the model was able to explain[19]. Path analysis was performed using IBM SPSS Amos® software version 23.

Results

Clinicopathological characteristics

A total of 510 questionnaires were sent out, and 491 were returned, of which 10 were incomplete. Therefore, the examination results of 481 patients were included in the analysis. The median age at enrolment was 69 (range 65-91) years. There was a greater percentage (33.7%) of patients with 10-12 years of education and fewer patients (9.4%) with only 6 years of education. Most participants (76.7%) had early-stage BC, and HR+/HER2- BC accounted for the majority of cases (68.6%). Most patients had undergone surgery (91.1%). More than half of the patients had received chemotherapy or endocrine therapy (56.5% and 65.3%, respectively). A total of 30.1% had received radiotherapy. Among the 369 patients with early-stage breast cancer, 86 (23.3%) were in the pre-chemotherapy phase of treatment, and only 40 (10.8%) were in the chemotherapy phase. A total of 243 (65.9%) patients were in the post-chemotherapy phase or had already received endocrine therapy at the time of enrolment. The median time from active treatment was 44 (1-336) months (**Table 1**).

Distribution of function and symptom scores

The distributions of the function and symptom scores are shown in **Table 2.** The highest score was found for social function (86.9±22.7), whereas cognitive function (80.2±21.3) was rated much lower. Most of the patients' functional scores were greater than 50, and only a small number of patients had scores less than 50, among whom the role function ratio was the highest (9.6%). Insomnia and fatigue were the most frequently reported symptoms, with the highest scores (32.3±33.6 and 20.1±22.7, respectively).

Network analysis results

As shown in **Figure 1A**, 84 of the 136 possible edges (61.8%) were non-zero, indicating significant interconnectedness between symptoms. The strongest correlation between the variables in the network analysis was between "fatigue" and "social function" (-0.722), and the strongest relationship between the variables in the network analysis and gQoL was "fatigue" and "gQoL" (-0.513)(**Table S3**). The symptom with the greatest expected influence was "fatigue" (1.617), followed by "role function" (1.052) and "social function" (0.873), indicating that these symptoms and functions had the greatest impact on the overall network(**Figure 1B, Table S4**). In contrast, the variables with the least expected effects were "age" (0.048), "CCI" (0.382) and "diarrhoea" (0.492). Moreover, the node predictability values ranged from 45.0% to 96.5%, with an average of 77.2%, indicating that, on average, 77.2% of the variance in nodes from the network could be explained by their neighbouring nodes (**Table S4**). "Age" (0.965), "CCI" (0.901) and "diarrhoea" (0.893) had the highest predictability in the model, whereas "fatigue" (0.450), "role function" (0.625) and "physical function" (0.665) had the lowest predictability.

To better illustrate the relationships between the items and gQoL scores, we plotted the QoL flow network (**Figure 2**). Among the total symptoms, 11 were directly related to gQoL, and the remaining symptoms, including age, were indirectly related to gQoL. Multiple linear regression analysis revealed that "CCI", "financial difficulties"

and "role function" were independently correlated with "gQoL"(**Table S5).**

The expected influence of the bridge and the strength of the bridge also had high stability, and the correlation stability coefficient CS values were both 0.672 (**Figure S1**). The accuracy of edge weight estimation between nodes is shown in **Figure S2**.

Path analysis model

Based on network analysis and multiple linear regression analysis results, we further examined the relationships between "fatigue", "physical function", "CCI", "financial difficulties", "role function" and "gQoL". The final model revealed significant correlations among the variables (**Figure 3**). "Financial difficulties" ($\beta = -0.11$, $p = 0.009$) and "role function" ($\beta = 0.26$; $p < 0.001$) had direct effects on "gQoL". "CCI" had an indirect effect on "gQoL" and was mediated by "financial difficulties" ($\beta = -0.12$; $p < 0.001$). "Fatigue" ($\beta = -0.35$, $p < 0.001$) had an indirect effect on "gQoL" and was mediated by "financial difficulties", "role function" and "CCI". "Physical function" had an indirect effect on "gQoL", which was mediated by "role function" ($\beta = -0.15$; $p = 0.006$). "Physical function" and "fatigue" were also significantly correlated ($\beta = 0.69$; $p < 0.001$). The multivariate linear regression final model for the mediation showed good global adjustment: fit indices: $\chi 2$ (9) =3.870 ($p>0.424$); $\chi 2/df = 0.968$; GFI = 0.997; AGFI = 0.986; CFI =1.000; RMSEA = 0.000 (95% CI = (0.000; 0.068)). The R-square value indicated that this model explained 32.0% of the variance in the general health score.

Discussion

The balance between treatment effectiveness and QoL in older patients with breast cancer is an important issue for clinicians. To our knowledge, this is the first cross-sectional study to investigate QoL in older Chinese patients with breast cancer in the real world using network and path analyses to help understand the factors influencing QoL to guide and inform social, health and education policies. As expected, functions, symptoms, and comorbidities had a significant impact on gQoL through different paths.

The results of the network analysis visualized the complex network of variables and provided clues to further understand the relationships among functions, symptoms, comorbidities and gQoL. “Fatigue” as the central symptom was closely related to patient function, including “role function”, “physical function” and “social function”. A recent meta-analysis revealed that the incidence of fatigue after chemotherapy in patients with cancer was approximately 49%[20]. Studies have shown that older subgroups experience increasingly severe levels of fatigue[21]. The high centrality of fatigue in this study indicates that it is highly associated with other symptoms, which has very important clinical intervention value. Compared with changing sociodemographic and clinical factors, which can be challenging, it seems more effective to address fatigue and systemic therapy side effects to improve long-term survivors' QoL. Therefore, the assessment and management of fatigue should be considered in daily nursing practice.

In addition to clinical drug interventions, the results of the path analysis also provide valuable insights into ways to improve fatigue. Physical function and fatigue were significantly correlated. The low predictability of the physical function indicates that it is also a good direct intervention node, and it is independently related to the “role function”. Previous studies have also shown that physical activity can have a positive effect on patients' quality of life by preventing a decline in physical function[22]. In addition, chronic disease management has also been shown to be important. In this pathway analysis, fatigue was an independent variable, and comorbidities were the regulators. However, in cross-sectional studies, this is not absolute. These results suggest that fatigue in older patients can be improved by addressing comorbidities.

Women with breast cancer have a similar risk of developing chronic diseases or comorbidities as women without cancer because of the natural effects of ageing. However, comorbidities have a significant effect on cancer treatment decisions and health care costs. These patients are likely to experience inadequate treatment or

perioperative complications[23]. Our data also revealed that the presence of chronic disease had a negative effect on gQoL that is mediated by “financial difficulties”. We included patients over 65 years of age, almost all of whom were retired, did not have high sources of income, and were likely to experience greater financial burden[20]. This not only causes patients to delay seeking care and to forgo necessary treatments but also affects treatment decisions and patient compliance[24]. This requires the participation of the whole society's medical insurance to reduce the financial burden on patients with cancer. This is not easy, but it may partly explain why the QoL of patients with breast cancer in China is lower than that of patients in Western countries[22][23].

All identified core symptoms had a high predictive value, with an average predictive value of 74.8% for all nodes in the network. In other words, most of the nodes in the network could be interpreted and controlled by their neighbours. When the CS was greater than 0.5, the network had good repeatability. The model evaluation indices of the path analysis also met the expected requirements and showed that the overall fit of the model was good.

The limitation of this study is that it was a cross-sectional study, meaning that the relationships observed are not directional. They cannot confirm the causal relationship between symptoms. Path analysis compensates for this to some extent, but time series data should still be collected in the future. Second, the drivers of quality of life differ according to metastatic status. The combined analysis of metastatic and nonmetastatic patients underestimated these differences. Finally, the participants in this study were recruited from two hospitals, and this group may not be representative of the older breast cancer population across different regions of China.

Conclusion

The various dimensions of QoL are highly interrelated and mutually reinforcing. These results highlight the importance of improving the fatigue and physical function of older patients with breast cancer. Interventions targeting these symptoms may lead to overall

improvement in gQoL.

Ethics Approval Statement

This study was part of a multicentre, cross-sectional registry study (registration number: ChiCTR2200056070). The study was carried out according to a named standard approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Data Sharing Statement

In order to protect patient data privacy, we do not share data unless the request is reasonable and with the consent of the corresponding author.

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Abbreviations

QoL	quality of life
gQoL	global health/quality of life
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life questionnaire Core 30
CCI	Charlson Comorbidity Index
LASSO	Least Absolute Shrinkage and Selection Operator
EBIC	Extended Bayesian Information Criteria
CS	correlation stability
CMIN/DF	chi-square/degrees of freedom ratio
GFI	goodness of fit index
CFI	comparative fit index
AGFI	adjusted goodness of fit index
RMSEA	root mean square error of approximation
LM	Lagrangian multiplier
β	Standardized beta coefficients
HR	Hormone receptor
HER2	Human epidermal growth factor receptor 2
SD	Standard Deviation
AIDS	Acquired Immune Deficiency Syndrome

Author contributions

Pin Zhang: Conceptualization, Methodology, Supervision, Writing-Review & Editing. Min Xiao: Software, Formal analysis, Investigation, Data Curation, Writing-Original Draft. Xi Chen, Lei Ji, Xiaoyan Qian, Meng Xiu, Zhuoran Li, Jintao Zhang and Heng Cao: Data Curation, Investigation. Zhuoran Li, Qing Li, Qiao Li, Xiang Wang, Jiani Wang, Yiqun Li ,Shanshan Chen, Xiaojuan Zheng, Jintao Zhang: Resources. The guarantor of the study is Pin Zhang, who takes full responsibility for the final work and the conduct of the study, had access to the data, and controlled the decision to publish.

Conflict of interest statement

The authors declare no conflicts of interest.

Figure legends

Figure 1 A. Network structure of quality of life and characteristics. B. Expected influence of each node of the quality of life and characteristics network.

Figure 2 Flow network of quality of life and characteristics.

Figure 3 Path analysis with standardized direct effects. Note: Ftg, fatigue; PhF, physical function; CCI, Charlson Comorbidity Index; Fnd, financial difficulties; gQoL, global health/quality of life; RlF, role function.

Table 1 Clinicopathological data

	All(n=481)	%
Age(year, range)	69	65-91
Year at diagnosis		
1979-2000	13	2.7
2000-2009	24	5.0
2010-2019	199	41.4
2000-2022	245	50.9
Education(year)		
≤6	45	9.4
7-9	133	27.7
10-12	162	33.7
≥13	141	29.3
CCI(median, range)	2	0-11
Stage		
early	369	76.7
metastatic	112	23.3
Molecular subtype		
HR+/HER2-	330	68.6
HER2+	95	19.8
HR-/HER2-	43	8.9
unknown	13	2.7
Surgery		
yes	438	91.1
no	43	8.9
Chemotherapy		
yes	272	56.5
no/unknown	209	43.5
Radiotherapy		
yes	145	30.1
no/unknown	336	69.9
Endocrine therapy		
yes	314	65.3
no/unknown	167	34.7
Step of treatment[a]	369	
pre-chemotherapy	86	23.3
during chemtherapy	40	10.8
post-chemotherapy/ during endocrine therapy	243	65.9

Median time from enrolment to active treatment(month, range)[b]	44(1-336)

Abbreviate: CCI, Charlson Comorbidity Index; HR, Hormone receptor; HER2, Human epidermal growth factor receptor 2.
a. This point applies to early stage patients(n=369). b. This point applies to early stage patients after chemotherapy or during endocrine therapy(n=243).

Table 2 Scores of EORTC QLQ-C30 questionnaires

	Mean±SD	Number of cases with scores < 50 (%)
EORTC QLQ-C30		
gQoL	69.1±21.3	65(13.5)
Function scores		
Physical Function	82.4±21.4	36(7.5)
Role Function	84.9±26.2	46(9.6)
Emotion Function	81.9±20.0	19(4.0)
Cognitive Function	80.2±21.3	28(5.8)
Social Function	86.9±22.7	29(6.0)
Symptoms		Number of cases with scores ≥ 50 (%)
Fatigue	20.1±22.7	51(10.6)
Nausea/vomiting	4.7±14.3	17(3.5)
Pain	16.4±24.3	37(7.7)
Dyspnea	15.5±24.4	45(9.4)
Insomina	32.3±33.6	134(27.9)
Appetite	15.0±25.5	53(11.0)
Constipation	15.5±26.3	56(11.6)
Diarrhea	6.6±18.5	24(5.0)
Financial difficulties	15.2±27.1	53(11.0)

Abbreviate: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; SD, Standard Deviation; gQoL, Global health/quality of life

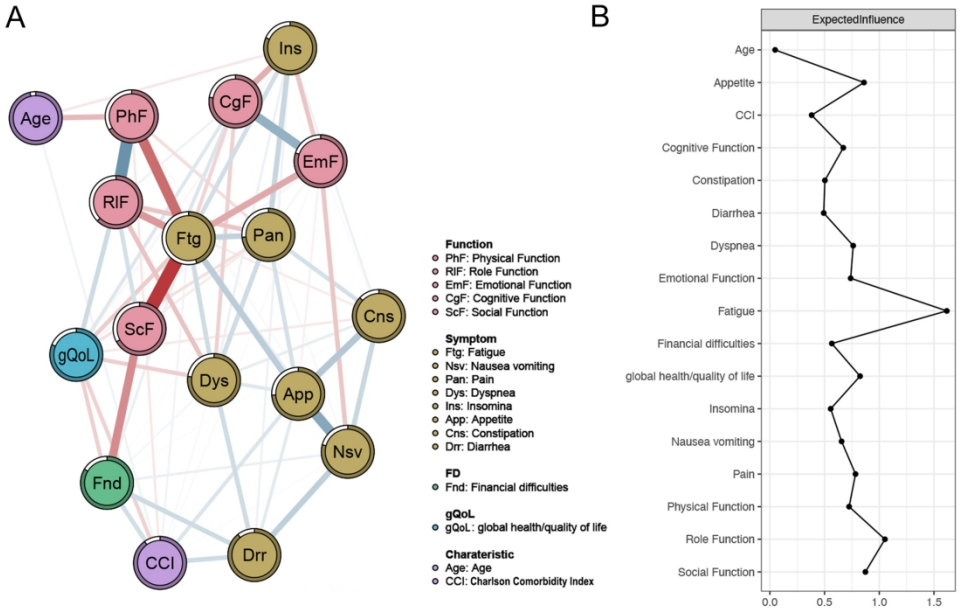

Figure 1 A. Network structure of quality of life and characteristics. B. Expected influence of each node of the quality of life and characteristics network.

872x557mm (72 x 72 DPI)

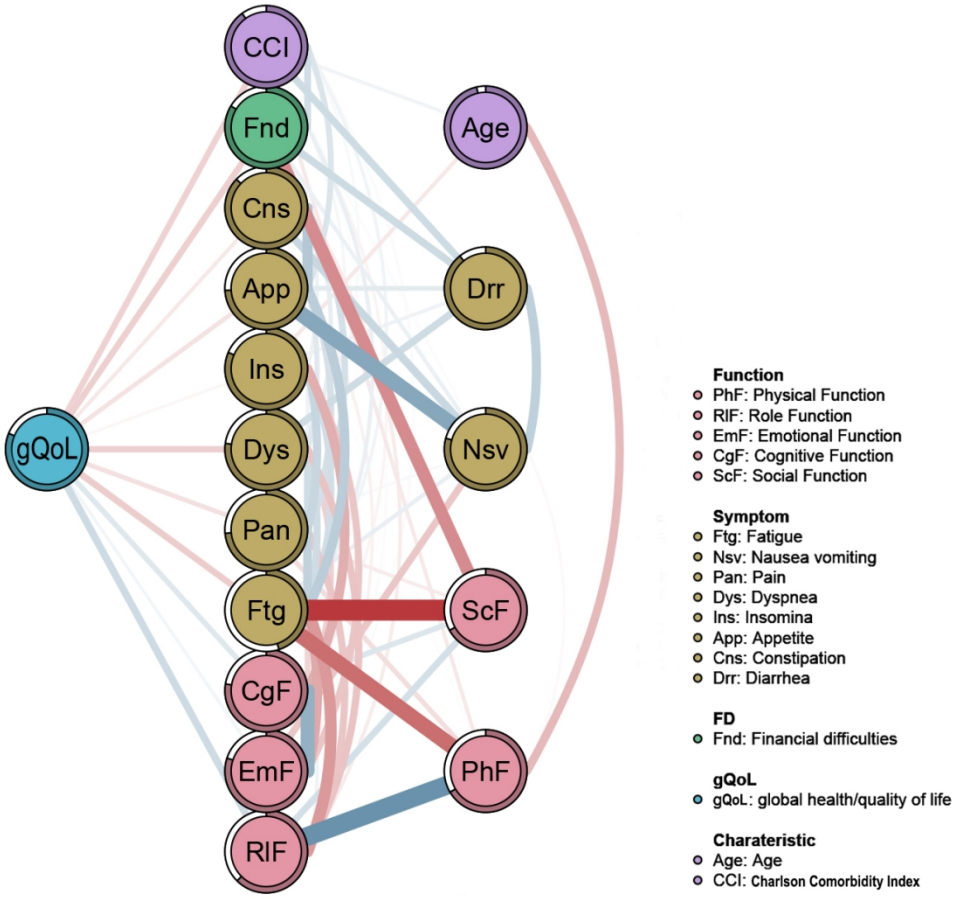

Figure 2 Flow network of quality of life and characteristics.

478x452mm (72 x 72 DPI)

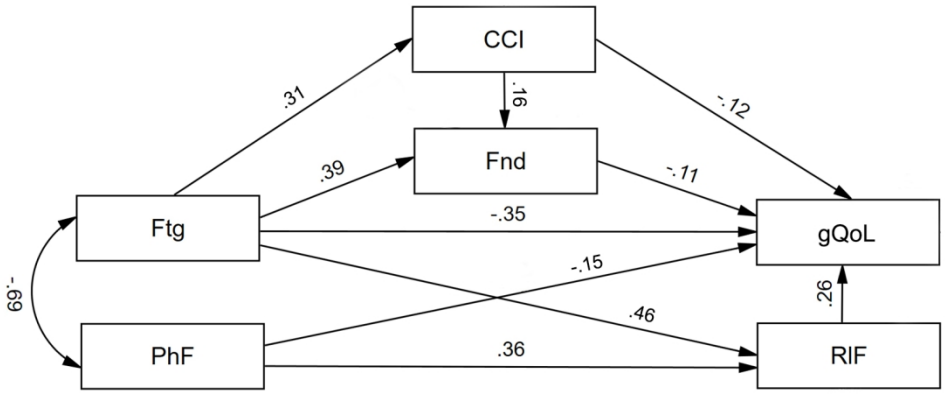

Figure 3 Path analysis with standardized direct effects. Note: Ftg, fatigue; PhF, physical function; CCI, Charlson Comorbidity Index; Fnd, financial difficulties; gQoL, global health/quality of life; RlF, role function.

621x287mm (72 x 72 DPI)

Table S1 STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

STROBE guidelines

Section/topic	Item number	Recommendation	Page No
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the manuscript	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	Cohort study - give the eligibility criteria, and the sources and methods of selection of participants; describe methods of follow-up Case-control study - give the eligibility criteria, and the sources and methods of case ascertainment and control selection; give the rationale for the choice of cases and controls Cross-sectional study - give the eligibility criteria, and the sources and methods of selection of participants Cohort study - for matched studies, give matching criteria and number of exposed and unexposed Case-control study - for matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; give diagnostic criteria, if	6-7

STROBE guidelines

Section/topic	Item number	Recommendation	Page No
		applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement); describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses; if applicable, describe which groupings were chosen and why	6
Statistical methods	12	Describe all statistical methods, including those used to control for confounding Describe any methods used to examine subgroups and interactions Explain how missing data were addressed Cohort study - if applicable, explain how loss to follow-up was addressed Case-control study - if applicable, explain how matching of cases and controls was addressed Cross-sectional study - if applicable, describe analytical methods taking account of sampling strategy Describe any sensitivity analyses	8-9
Results			
Participants	13*	Report numbers of individuals at each stage of study - e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed Give reasons for nonparticipation at each stage Consider use of a flow diagram	9
Descriptive data	14*	Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	9-10

STROBE guidelines

Section/topic	Item number	Recommendation	Page No
		Indicate number of participants with missing data for each variable of interest Cohort study - summarize follow-up time (e.g., average and total amount)	
Outcome data	15*	Cohort study - report numbers of outcome events or summary measures over time Case-control study - report numbers in each exposure category, or summary measures of exposure Cross-sectional study - report numbers of outcome events or summary measures	10
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval); make clear which confounders were adjusted for and why they were included Report category boundaries when continuous variables were categorized If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done - e.g., analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarize key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision; discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalizability	21	Discuss the generalizability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of	17

STROBE guidelines

Section/topic	Item number	Recommendation	Page No
		the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies

Table S2 Scoring of different diseases in Charlson Comorbidity Index

Scoring	Comorbidity
1	Ischemic heart disease; congestive heart failure; peripheral vascular disease; cerebrovascular disease; dementia; chronic pulmonary disease; mild liver disease; diabetes without chronic complication
2	Diabetes with chronic complication; renal impairment; tumor without metastasis
3	Moderate or severe liver disease
6	Metastatic solid tumor; AIDS

Abbreviate: AIDS, Acquired Immune Deficiency Syndrome

Table S3 Correlation coefficient of symptoms, functions, financial difficulties, charateristics and gQoL

	Physical Function	Role Function	Emotional Function	Cognitive Function	Social Function	Fatigue	Nausea/ vomiting	Pain	Dyspnea	Insomina	Appetite	Constipa- -tion	Diarrhea	Financial difficulties	gQoL	Age	CCI
Physical Function	1.000																
Role Function	0.680	1.000															
Emotional Function	0.282	0.324	1.000														
Cognitive Function	0.352	0.417	0.486	1.000													
Social Function	0.491	0.564	0.380	0.429	1.000												
Fatigue	-0.688	-0.709	-0.524	-0.512	-0.722	1.000											
Nausea vomiting	-0.322	-0.301	-0.348	-0.165	-0.247	0.430	1.000										
Pain	-0.488	-0.536	-0.368	-0.368	-0.469	0.607	0.343	1.000									
Dyspnea	-0.368	-0.491	-0.285	-0.385	-0.351	0.542	0.313	0.458	1.000								
Insomina	-0.254	-0.282	-0.381	-0.408	-0.298	0.462	0.260	0.406	0.336	1.000							
Appetite	-0.396	-0.427	-0.358	-0.306	-0.408	0.555	0.512	0.455	0.410	0.270	1.000						
Constipation	-0.287	-0.324	-0.252	-0.165	-0.213	0.347	0.351	0.357	0.308	0.254	0.415	1.000					
Diarrhea	-0.213	-0.188	-0.166	-0.116	-0.188	0.290	0.327	0.220	0.301	0.212	0.305	0.184	1.000				
Financial difficulties	-0.310	-0.340	-0.230	-0.285	-0.467	0.434	0.277	0.308	0.304	0.140	0.273	0.214	0.285	1.000			
gQoL	0.329	0.469	0.331	0.364	0.397	-0.513	-0.265	-0.407	-0.404	-0.302	-0.379	-0.283	-0.213	-0.336	1.000		
Age	-0.230	-0.138	0.007	-0.015	-0.120	0.129	-0.016	0.022	0.052	-0.053	0.062	0.045	0.014	0.026	-0.086	1.000	
CCI	-0.264	-0.240	-0.070	-0.138	-0.225	0.308	0.220	0.202	0.238	0.099	0.288	0.170	0.127	0.277	-0.277	0.123	1.000

Abbreviate: gQoL, Global health/quality of life; CCI, Charlson Comorbidity Index;

Table S4 Descriptive statistics of the items

Item content	Expected influence	Predictability
Age	0.048	0.965
CCI	0.382	0.901
gQoL	0.824	0.813
Physical Function	0.724	0.665
Role Function	1.052	0.625
Emotional Function	0.739	0.801
Cognitive Function	0.671	0.776
Social Function	0.873	0.669
Fatigue	1.617	0.450
Nausea/vomiting	0.656	0.793
Pain	0.783	0.736
Dyspnea	0.761	0.773
Insomina	0.556	0.815
Appetite loss	0.860	0.742
Constipation	0.503	0.872
Diarrhea	0.492	0.893
Financial difficulties	0.566	0.837

Abbreviate: CCI, Charlson Comorbidity Index; gQoL, Global health/quality of life

Table S5 Multiple linear analysis related to gQoL

	Unstandardized		Standardized	P-value	F	adj R^2
	β (95%CI)	SE	β			
				<0.001	22.4	0.329
Role function	0.131(0.042-0.220)	0.045	0.161	**0.004**		
Emotional function	0.068(-0.031-0.167)	0.050	0.064	0.177		
Cognitive function	0.070(-0.023-0.164)	0.048	0.070	0.139		
Fatigue	-0.096(-0.224-0.033)	0.065	-0.102	0.144		
Pain	-0.046(-0.133-0.041)	0.044	-0.053	0.296		
Dyspnea	-0.078(-0.159-0.002)	0.041	-0.090	0.057		
Insomnia	-0.034(-0.091-0.022)	0.029	-0.054	0.232		
Appetite	-0.049(-0.128-0.030)	0.040	-0.059	0.223		
Constipation	-0.036(-0.104-0.032)	0.035	-0.044	0.303		
Financial difficulties	-0.076(-0.142--0.010)	0.034	-0.097	**0.024**		
CCI	-0.988(-1.749--0.227)	0.387	-0.104	**0.011**		

Abbreviate: gQoL, Global health/quality of life; CCI, Charlson Comorbidity Index

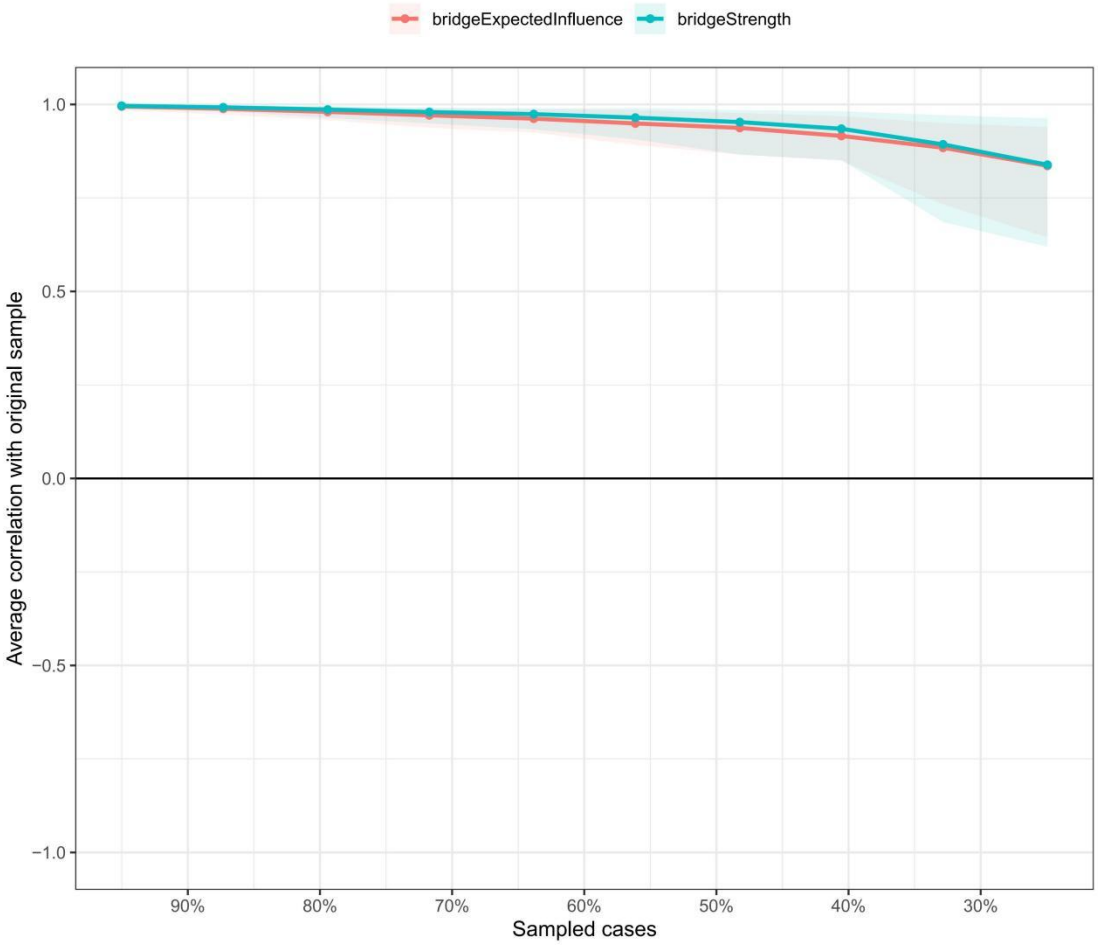

Figure S1 Network stability: bridge expected influence and bridge strength.

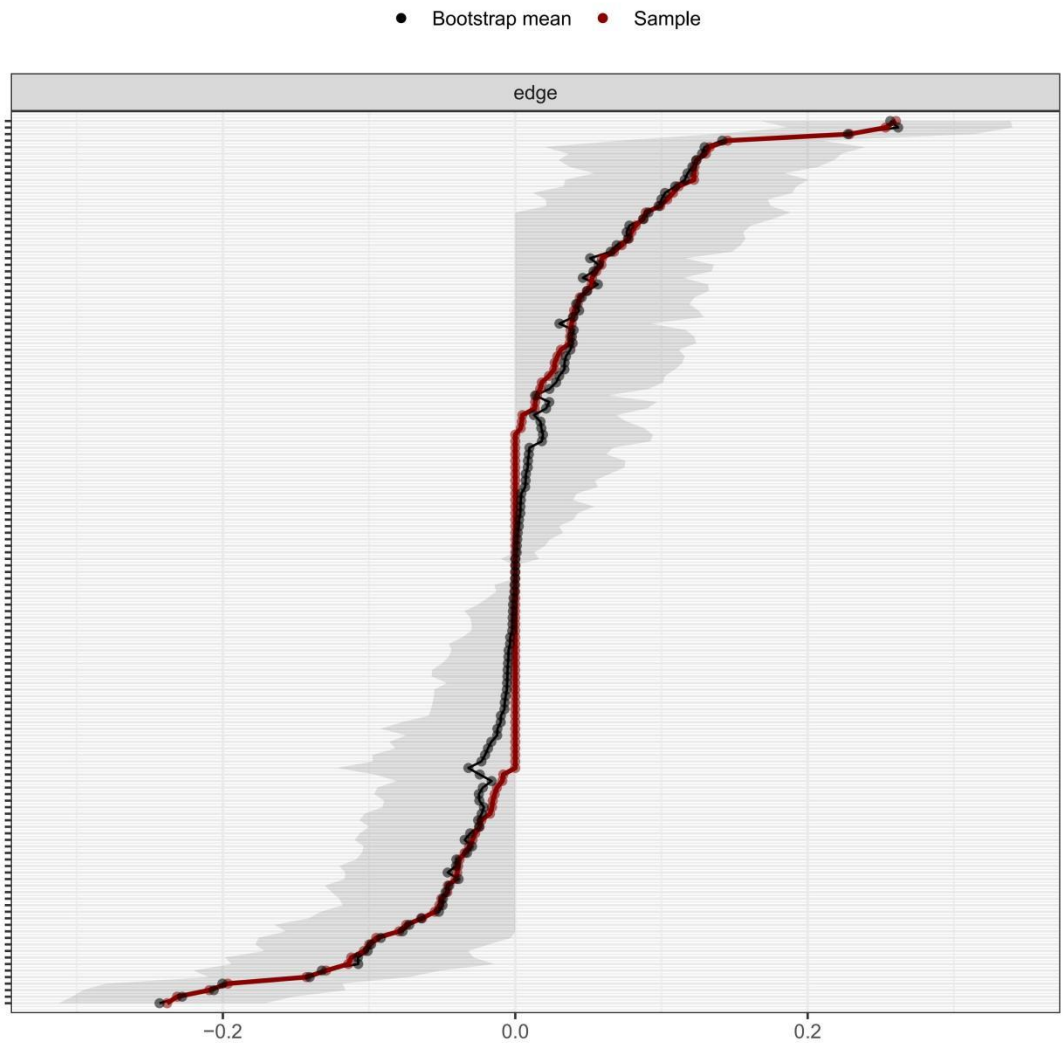

Figure S2 Bootstrapped confidence intervals of edge weights.

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Association of quality of life in older patients with breast cancer: A cross-sectional study from China

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Association of quality of life in older patients with breast cancer: A cross-sectional study from China

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Running title: QoL in Older Breast Cancer Patients in China

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Abstract

Objectives The purpose of this study was to investigate the quality of life (QoL) of older Chinese patients with breast cancer and to further explore the associations of functions, symptoms, financial burdens, and comorbidities with global health/quality of life (gQoL).

Design This was a cross-sectional study carried out following the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

Setting This study was conducted in two hospitals in Beijing from October 2021 to November 2022.

Participants Patients with breast cancer aged over 65 years were included in the final analysis, which comprised a total of 481 patients.

Primary and secondary outcome measures The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and the Charlson Comorbidity Index (CCI) were used to assess patients' QoL and comorbidities. The data were analysed using network analysis and path analysis.

Results Out of the 136 possible edges in the final networks, 84 (61.8%) were non-zero. "Fatigue" was the central symptom and indirectly decreased the gQoL, which was mediated by increasing "financial difficulties", "CCI" and "role function" (β =-0.35, $p < 0.001$). "Physical function" was also an important and direct intervention node that was indirectly related to gQoL, and this was mediated by "role function" (β =-0.15; p =0.006). Path analysis accounted for 32.0% of the total effect.

Conclusions The various dimensions of QoL are highly interrelated and mutually reinforcing. These results highlight the importance of improving the fatigue and physical function of older patients with breast cancer. Interventions targeting these symptoms may lead to overall improvement in gQoL.

Strengths and limitations of this study

- The study was supported by a national project with good preliminary design.
- Data were collected using standardized and validated procedures and instruments, increasing its credibility.

- Both network and path analysis methods were used to leverage their respective strengths and address their limitations.
- One limitation of our study is that it employed a cross-sectional study design with heterogeneous subjects.
- The combined analysis of metastatic and nonmetastatic patients underestimated these differences.

Introduction

With increased awareness of the importance of individualized, patient-centred care, as well as the increased rates and duration of breast cancer survival, quality of life (QoL) is becoming the central parameter of breast cancer survivorship[1][2]. QoL is affected by a variety of factors in older breast cancer patients, as they face tremendous declines in both physical and psychological functions, with issues ranging from organ failure and neuropathy to depression[3][4]. Moreover, with the rapid ageing of the population, 41.4% of patients with breast cancer in China are estimated to be aged 60 years or older by 2030[5]. There is a need to focus on this group of patients in China.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is a widely validated scale for assessing QoL, and it includes multidimensional concepts such as symptoms, functions and financial burden[6][7]. Most previous studies have focused on how specific factors affect QoL, such as the impact of cognitive function and physical function on QoL, the impact of comorbidities on QoL, and the impact of treatment-related symptoms on QoL[8][9][10]. However, the different dimensions of QoL tend to influence each other and are highly correlated, but there have been no studies that fully illustrate this relationship. Network analysis is often used in the study of multiple items to understand the interrelationships among them and to identify important targets called “central symptoms” for clinical intervention[11]. However, network analysis cannot establish causality or directional relationships between nodes; this limitation can be overcome by path analysis. Path analysis provides insight into the pathways between nodes (predictors and mediators) that lead to the resulting variables. By exploring the interaction of different dimensions of QoL, we can identify the specific processes that affect QoL.

Thus, the purpose of this study was to understand the relationships among multiple dimensions of QoL in older Chinese patients with breast cancer using network and path analysis. Specifically, we used network analysis to examine the relationships among

the QoL subscales and to identify the core symptoms. Next, we used path analysis to investigate the relationships between core symptoms and global health/quality of life (gQoL). By elucidating the symptom-function-financial burden-comorbidity-gQoL relationship, we hope to provide insights for developing effective interventions and rehabilitation programs for older patients with breast cancer to ensure their QoL.

Patients and methods

Study design and setting

This study was part of a multicentre, prospective, cross-sectional, registry study designed to establish a clinical database for older patients. This breast cancer cohort included 510 participants from two hospitals in Beijing from October 2021 to November 2022. The reporting in this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross-sectional studies (**Table S1**)[12]. All the participants were informed of the aim of the study and signed an informed consent form.

Participants

The inclusion criteria for the participants were as follows: (1) had pathologically confirmed breast cancer; (2) were over 65 years of age; (3) were able to understand the purpose and content of the survey and cooperate with the survey; and (4) had complete medical records.

The exclusion criteria were as follows: (1) refused to complete the scale; (2) incomplete questionnaires; and (3) medical records that were incomplete and could not be analysed statistically.

Measures

QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[6]. It consists of several programs: five functional domains (physical, role, cognitive, emotional, and

social); three domains of physical symptoms (fatigue, nausea/vomiting, and pain); several individual symptoms (dyspnoea, insomnia, appetite, constipation, diarrhoea, and financial difficulties); and global health/quality of life (gQoL). The gQoL includes two questions, namely, the subjective assessment of the patient's physical health status and the overall QoL. Each item scale is then converted into a standard score for analysis. Higher scores for functional domains and general health indicate better functional status and QoL. Higher scores for symptom domains indicate more symptoms or problems (and poorer QoL).

The Charlson Comorbidity Index (CCI) is currently the most widely used comorbidity index, with a total of 14 items (**Table S2)**. The total score is calculated by adding the weights. To avoid duplicate assessments, breast cancer was included in the clinical data for statistical analysis but not in the CCI. The above sinicization scales have been validated in the Chinese population[13][14].

Clinicopathological data, including age at the time of the survey, education level, stage, molecular subtype and treatment, were collected from the included patients after the questionnaire survey. The treatment was identified as the treatment the patients had received at the time of the survey.

Data analysis

Clinical data statistics

SPSS 26.0 software was used for descriptive statistical analyses, with means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables. Additionally, the median were provided for the QoL subscales to facilitate comparison with other published data[15].

Network estimation

Network analysis was performed using the qgraph, networktools, ggplot, mgm and bootnet packages of R software (version 4.1.2; using the R Foundation for Statistical

Computing). The least absolute shrinkage and selection operator (LASSO) and extended Bayesian information criterion (EBIC) were used to regularize the correlation matrix to reduce the margin of possible spurious correlations. The blue connections between nodes represent positive connections, and the red connections represent negative connections. The network was visualized using the Fruchterman–Reingold algorithm, and strongly connected nodes were usually close to each other. The importance of each node was quantified by calculating the expected influence[16]. The greater the expected influence was, the more important the node was in the network model. To more intuitively identify specific symptoms that are directly related to gQoL, we used the "flow" function in the R package qgraph for plotting[17]. Predictability refers to the extent to which the variance of a node can be explained by all of its neighbouring nodes[17]. The average predictability of all nodes in the network reflects the extent to which the network was affected by external factors.

To estimate the stability of the centrality measure, the case–drop subset bootstrap method was used, in which an increasing proportion of subjects were randomly removed from the dataset and the centrality index was recalculated. To quantify the stability of the centrality index, the correlation stability (CS) coefficient was calculated. Ideally, centrality estimates should be greater than 0.5. In addition, to measure the accuracy of the edge, estimated 95% confidence intervals for the region containing the true regularized partial correlation (edge) were calculated by "nonparametric" bootstrapping (n bootstrap = 1000)[18].

Path analysis

Based on the results of the network analysis, multiple linear analyses were performed on factors directly related to gQoL to identify independently related factors. Path analysis was used to identify direct and indirect effects between variables and to determine the overall fit of the model. A well-fitting model needed to meet the following conditions: test chi-square, chi-square/degrees of freedom ratio (CMIN/DF) <3, goodness-of-fit index (GFI) > 0.90, comparative fit index (CFI) > 0.90, adjustment

goodness-of-fit index (AGFI) > 0.95, and root mean square error of approximation (RMSEA) < 0.10[19]. Based on the multivariate Lagrangian multiplier (LM) test, the model was modified twice to add new paths where necessary. The significance of all direct and indirect effects was assessed to determine which variables had direct or indirect effects on gQoL. The significance level was set to 0.05. Standardized beta coefficients (β) were derived for each explanatory variable to allow comparison and estimation of the relative importance of each measure. The R-squared value was calculated to determine the proportion of variance that the model was able to explain[20]. Path analysis was performed using IBM SPSS Amos® software version 23.

Patient and Public Involvement

Patient and Public Involvement statement

None.

Results

Clinicopathological characteristics

A total of 510 questionnaires were sent out, and 491 were returned, of which 10 were incomplete. Therefore, the examination results of 481 patients were included in the analysis. The median age at enrolment was 69 (range 65-91) years. There was a greater percentage (33.7%) of patients with 10-12 years of education and fewer patients (9.4%) with only 6 years of education. Most participants (76.7%) had early-stage BC, and HR+/HER2- BC accounted for the majority of cases (68.6%). Most patients had undergone surgery (91.1%). More than half of the patients had received chemotherapy or endocrine therapy (56.5% and 65.3%, respectively). A total of 30.1% had received radiotherapy. Among the 369 patients with early-stage breast cancer, 86 (23.3%) were in the pre-chemotherapy phase of treatment, and only 40 (10.8%) were in the chemotherapy phase. A total of 243 (65.9%) patients were in the post-chemotherapy phase or had already received endocrine therapy at the time of enrolment. The median time from active treatment was 44 (1-336) months (**Table 1**).

Distribution of function and symptom scores

The distributions of the function and symptom scores are shown in **Table 2.** The highest score was found for social function (86.9±22.7), whereas cognitive function (80.2±21.3) was rated much lower. Most of the patients' functional scores were greater than 50, and only a small number of patients had scores less than 50, among whom the role function ratio was the highest (9.6%). Insomnia and fatigue were the most frequently reported symptoms, with the highest scores (32.3±33.6 and 20.1±22.7, respectively).

Network analysis results

As shown in **Figure 1A**, 84 of the 136 possible edges (61.8%) were non-zero, indicating significant interconnectedness between symptoms. The strongest correlation between the variables in the network analysis was between "fatigue" and "social function" (-0.722), and the strongest relationship between the variables in the network analysis and gQoL was "fatigue" and "gQoL" (-0.513)(**Table S3**). The symptom with the greatest expected influence was "fatigue" (1.617), followed by "role function" (1.052) and "social function" (0.873), indicating that these symptoms and functions had the greatest impact on the overall network(**Figure 1B, Table S4**). In contrast, the variables with the least expected effects were "age" (0.048), "CCI" (0.382) and "diarrhoea" (0.492). Moreover, the node predictability values ranged from 45.0% to 96.5%, with an average of 77.2%, indicating that, on average, 77.2% of the variance in nodes from the network could be explained by their neighbouring nodes (**Table S4**). "Age" (0.965), "CCI" (0.901) and "diarrhoea" (0.893) had the highest predictability in the model, whereas "fatigue" (0.450), "role function" (0.625) and "physical function" (0.665) had the lowest predictability.

To better illustrate the relationships between the items and gQoL scores, we plotted the QoL flow network (**Figure 2**). Among the total symptoms, 11 were directly related to gQoL, and the remaining symptoms, including age, were indirectly related to gQoL. Multiple linear regression analysis revealed that "CCI", "financial difficulties"

and "role function" were independently correlated with "gQoL"(**Table S5).**

The expected influence of the bridge and the strength of the bridge also had high stability, and the correlation stability coefficient CS values were both 0.672 (**Figure S1**). The accuracy of edge weight estimation between nodes is shown in **Figure S2**.

Path analysis model

Based on network analysis and multiple linear regression analysis results, we further examined the relationships between "fatigue", "physical function", "CCI", "financial difficulties", "role function" and "gQoL". The final model revealed significant correlations among the variables (**Figure 3**). "Financial difficulties" ($\beta = -0.11$, $p = 0.009$) and "role function" ($\beta = 0.26$; $p < 0.001$) had direct effects on "gQoL". "CCI" had an indirect effect on "gQoL" and was mediated by "financial difficulties" ($\beta = -0.12$; $p < 0.001$). "Fatigue" ($\beta = -0.35$, $p < 0.001$) had an indirect effect on "gQoL" and was mediated by "financial difficulties", "role function" and "CCI". "Physical function" had an indirect effect on "gQoL", which was mediated by "role function" ($\beta = -0.15$; $p = 0.006$). "Physical function" and "fatigue" were also significantly correlated ($\beta = 0.69$; $p < 0.001$). The multivariate linear regression final model for the mediation showed good global adjustment: fit indices: $\chi 2$ (9) =3.870 ($p>0.424$); $\chi 2/df = 0.968$; GFI = 0.997; AGFI = 0.986; CFI =1.000; RMSEA = 0.000 (95% CI = (0.000; 0.068)). The R-square value indicated that this model explained 32.0% of the variance in the general health score.

Discussion

The balance between treatment effectiveness and QoL in older patients with breast cancer is an important issue for clinicians. To our knowledge, this is the first cross-sectional study to investigate QoL in older Chinese patients with breast cancer in the real world using network and path analyses to help understand the factors influencing QoL to guide and inform social, health and education policies. As expected, functions, symptoms, and comorbidities had a significant impact on gQoL through different paths.

The results of the network analysis visualized the complex network of variables and provided clues to further understand the relationships among functions, symptoms, comorbidities and gQoL. “Fatigue” as the central symptom was closely related to patient function, including “role function”, “physical function” and “social function”. A recent meta-analysis revealed that the incidence of fatigue after chemotherapy in patients with cancer was approximately 49%[21]. Studies have shown that older subgroups experience increasingly severe levels of fatigue[22]. The high centrality of fatigue in this study indicates that it is highly associated with other symptoms, which has very important clinical intervention value. Compared with changing sociodemographic and clinical factors, which can be challenging, it seems more effective to address fatigue and systemic therapy side effects to improve long-term survivors' QoL. Therefore, the assessment and management of fatigue should be considered in daily nursing practice.

In addition to clinical drug interventions, the results of the path analysis also provide valuable insights into ways to improve fatigue. Physical function and fatigue were significantly correlated. The low predictability of the physical function indicates that it is also a good direct intervention node, and it is independently related to the “role function”. Previous studies have also shown that physical activity can have a positive effect on patients' quality of life by preventing a decline in physical function[23]. In addition, chronic disease management has also been shown to be important. In this pathway analysis, fatigue was an independent variable, and comorbidities were the regulators. However, in cross-sectional studies, this is not absolute. These results suggest that fatigue in older patients can be improved by addressing comorbidities.

Women with breast cancer have a similar risk of developing chronic diseases or comorbidities as women without cancer because of the natural effects of ageing. However, comorbidities have a significant effect on cancer treatment decisions and health care costs. These patients are likely to experience inadequate treatment or

perioperative complications[24]. Our data also revealed that the presence of chronic disease had a negative effect on gQoL that is mediated by “financial difficulties”. We included patients over 65 years of age, almost all of whom were retired, did not have high sources of income, and were likely to experience greater financial burden[21]. This not only causes patients to delay seeking care and to forgo necessary treatments but also affects treatment decisions and patient compliance[25]. This requires the participation of the whole society's medical insurance to reduce the financial burden on patients with cancer. This is not easy, but it may partly explain why the QoL of patients with breast cancer in China is lower than that of patients in Western countries[23][24].

All identified core symptoms had a high predictive value, with an average predictive value of 74.8% for all nodes in the network. In other words, most of the nodes in the network could be interpreted and controlled by their neighbours. When the CS was greater than 0.5, the network had good repeatability. The model evaluation indices of the path analysis also met the expected requirements and showed that the overall fit of the model was good.

The limitation of this study is that it was a cross-sectional study, meaning that the relationships observed are not directional. They cannot confirm the causal relationship between symptoms. Path analysis compensates for this to some extent, but time series data should still be collected in the future. Second, the drivers of quality of life differ according to metastatic status. The combined analysis of metastatic and nonmetastatic patients underestimated these differences. Finally, the participants in this study were recruited from two hospitals, and this group may not be representative of the older breast cancer population across different regions of China.

Conclusion

The various dimensions of QoL are highly interrelated and mutually reinforcing. These results highlight the importance of improving the fatigue and physical function of older patients with breast cancer. Interventions targeting these symptoms may lead to overall

improvement in gQoL.

Ethics Approval Statement

This study was part of a multicentre, cross-sectional registry study (registration number: ChiCTR2200056070). The study was carried out according to a named standard approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College(approval number: 22/216-3418).

Data Sharing Statement

In order to protect patient data privacy, we do not share data unless the request is reasonable and with the consent of the corresponding author.

Funding Statement

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payments with health-related quality of life among breast, prostate and colorectal cancer patients. Acta Oncol, 2019. 58(7): p. 1062-1068.

Abbreviations

QoL	quality of life
gQoL	global health/quality of life
EORTC QLQ-	European Organization for Research and Treatment of Cancer
C30	Quality of Life questionnaire Core 30
CCI	Charlson Comorbidity Index
LASSO	Least Absolute Shrinkage and Selection Operator
EBIC	Extended Bayesian Information Criteria
CS	correlation stability
CMIN/DF	chi-square/degrees of freedom ratio
GFI	goodness of fit index
CFI	comparative fit index
AGFI	adjusted goodness of fit index
RMSEA	root mean square error of approximation
LM	Lagrangian multiplier
β	Standardized beta coefficients
HR	Hormone receptor
HER2	Human epidermal growth factor receptor 2
SD	Standard Deviation
AIDS	Acquired Immune Deficiency Syndrome

Author contributions

Pin Zhang: Conceptualization, Methodology, Supervision, Writing-Review & Editing. Min Xiao: Software, Formal analysis, Investigation, Data Curation, Writing-Original Draft. Xi Chen, Lei Ji, Xiaoyan Qian, Meng Xiu, Zhuoran Li, Jintao Zhang and Heng Cao: Data Curation, Investigation. Zhuoran Li, Qing Li, Qiao Li, Xiang Wang, Jiani

Wang, Yiqun Li ,Shanshan Chen, Xiaojuan Zheng, Jintao Zhang: Resources. The guarantor of the study is Pin Zhang, who takes full responsibility for the final work and the conduct of the study, had access to the data, and controlled the decision to publish.

Conflict of interest statement

The authors declare no conflicts of interest.

Figure legends

Figure 1 A. Network structure of quality of life and characteristics. B. Expected influence of each node of the quality of life and characteristics network.

Figure 2 Flow network of quality of life and characteristics.

Figure 3 Path analysis with standardized direct effects. Note: Ftg, fatigue; PhF, physical function; CCI, Charlson Comorbidity Index; Fnd, financial difficulties; gQoL, global health/quality of life; RlF, role function.

Table 1 Clinicopathological data

	All(n=481)	%
Age(year, range)	69	65-91
Year at diagnosis		
1979-2000	13	2.7
2000-2009	24	5.0
2010-2019	199	41.4
2000-2022	245	50.9
Education(year)		
≤6	45	9.4
7-9	133	27.7
10-12	162	33.7
≥13	141	29.3
CCI(median, range)	2	0-11
Stage		
early	369	76.7
metastatic	112	23.3
Molecular subtype		
HR+/HER2-	330	68.6
HER2+	95	19.8
HR-/HER2-	43	8.9
unknown	13	2.7
Surgery		
yes	438	91.1
no	43	8.9
Chemotherapy		
yes	272	56.5
no/unknown	209	43.5
Radiotherapy		
yes	145	30.1
no/unknown	336	69.9
Endocrine therapy		
yes	314	65.3
no/unknown	167	34.7
Step of treatment[a]	369	
pre-chemotherapy	86	23.3
during chemtherapy	40	10.8

post-chemotherapy/ during endocrine therapy	243	65.9
Median time from enrolment to active treatment(month, range)[b]	44(1-336)	

Abbreviate: CCI, Charlson Comorbidity Index; HR, Hormone receptor; HER2, Human epidermal growth factor receptor 2.

a. This point applies to early stage patients(n=369). b. This point applies to early stage patients after chemotherapy or during endocrine therapy(n=243).

Table 2 Scores of EORTC QLQ-C30 questionnaires

	Mean±SD	Number of cases with scores < 50 (%)
EORTC QLQ-C30		
gQoL	69.1±21.3	65(13.5)
Function scores		
Physical Function	82.4±21.4	36(7.5)
Role Function	84.9±26.2	46(9.6)
Emotion Function	81.9±20.0	19(4.0)
Cognitive Function	80.2±21.3	28(5.8)
Social Function	86.9±22.7	29(6.0)
Symptoms		Number of cases with scores ≥ 50 (%)
Fatigue	20.1±22.7	51(10.6)
Nausea/vomiting	4.7±14.3	17(3.5)
Pain	16.4±24.3	37(7.7)
Dyspnea	15.5±24.4	45(9.4)
Insomina	32.3±33.6	134(27.9)
Appetite	15.0±25.5	53(11.0)
Constipation	15.5±26.3	56(11.6)
Diarrhea	6.6±18.5	24(5.0)
Financial difficulties	15.2±27.1	53(11.0)

Abbreviate: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; SD, Standard Deviation; gQoL, Global health/quality of life

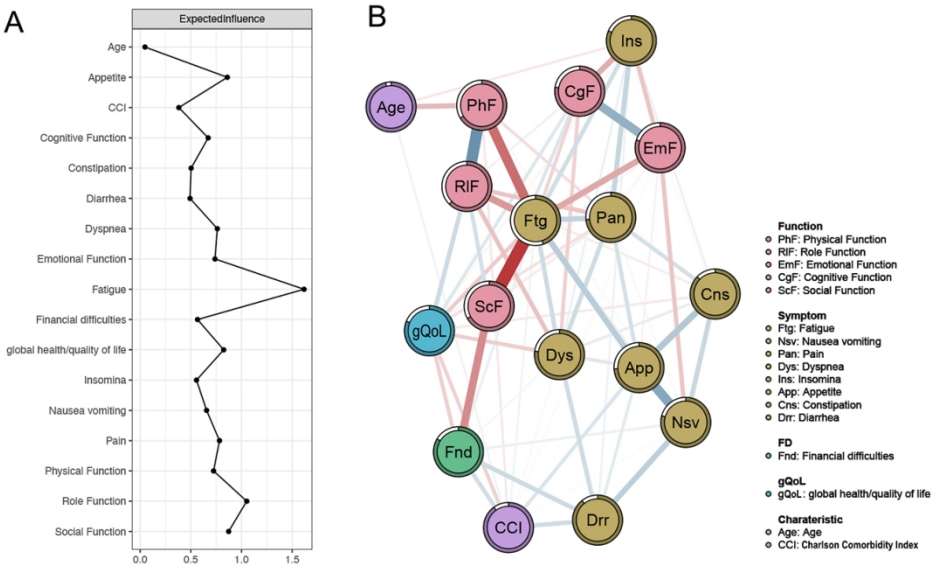

Figure 1 A. Network structure of quality of life and characteristics. B. Expected influence of each node of the quality of life and characteristics network.

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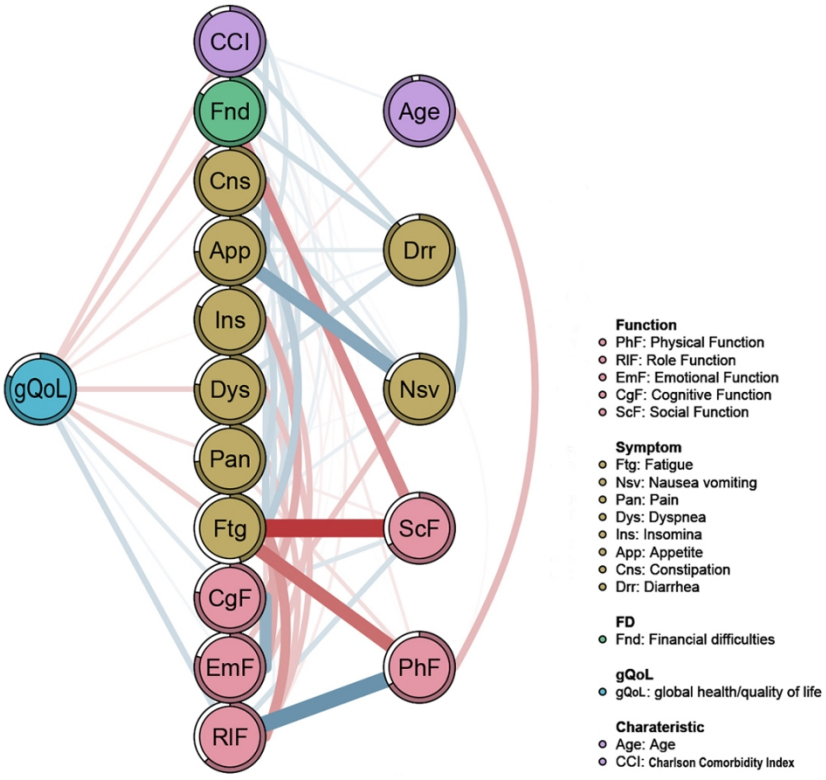

Figure 2 Flow network of quality of life and characteristics.

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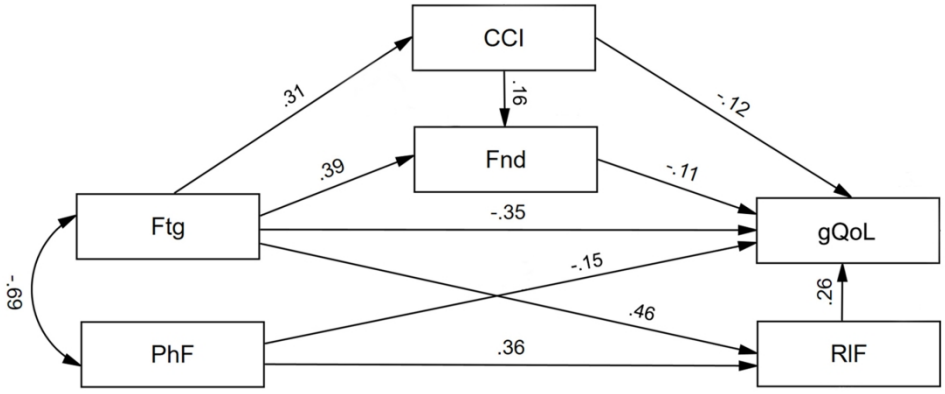

Figure 3 Path analysis with standardized direct effects. Note: Ftg, fatigue; PhF, physical function; CCI, Charlson Comorbidity Index; Fnd, financial difficulties; gQoL, global health/quality of life; RlF, role function.

750x416mm (72 x 72 DPI)

Table S1 STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

STROBE guidelines

Section/topic	Item number	Recommendation	Page No
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract Provide in the abstract an informative and balanced summary of what was done and what was found	2-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the manuscript	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	Cohort study - give the eligibility criteria, and the sources and methods of selection of participants; describe methods of follow-up Case-control study - give the eligibility criteria, and the sources and methods of case ascertainment and control selection; give the rationale for the choice of cases and controls Cross-sectional study - give the eligibility criteria, and the sources and methods of selection of participants Cohort study - for matched studies, give matching criteria and number of exposed and unexposed Case-control study - for matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; give diagnostic criteria, if	7-8

STROBE guidelines

Section/topic	Item number	Recommendation	Page No
		applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement); describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses; if applicable, describe which groupings were chosen and why	7
Statistical methods	12	Describe all statistical methods, including those used to control for confounding Describe any methods used to examine subgroups and interactions Explain how missing data were addressed Cohort study - if applicable, explain how loss to follow-up was addressed Case-control study - if applicable, explain how matching of cases and controls was addressed Cross-sectional study - if applicable, describe analytical methods taking account of sampling strategy Describe any sensitivity analyses	8-10
Results			
Participants	13*	Report numbers of individuals at each stage of study - e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed Give reasons for nonparticipation at each stage Consider use of a flow diagram	10
Descriptive data	14*	Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	10

STROBE guidelines

Section/topic	Item number	Recommendation	Page No
		Indicate number of participants with missing data for each variable of interest Cohort study - summarize follow-up time (e.g., average and total amount)	
Outcome data	15*	Cohort study - report numbers of outcome events or summary measures over time Case-control study - report numbers in each exposure category, or summary measures of exposure Cross-sectional study - report numbers of outcome events or summary measures	11
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval); make clear which confounders were adjusted for and why they were included Report category boundaries when continuous variables were categorized If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done - e.g., analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarize key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision; discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalizability	21	Discuss the generalizability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of	15

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Section/topic	Item number	Recommendation	Page No
		the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies

Table S2 Scoring of different diseases in Charlson Comorbidity Index

Scoring	Comorbidity
1	Ischemic heart disease; congestive heart failure; peripheral vascular disease; cerebrovascular disease; dementia; chronic pulmonary disease; mild liver disease; diabetes without chronic complication
2	Diabetes with chronic complication; renal impairment; tumor without metastasis
3	Moderate or severe liver disease
6	Metastatic solid tumor; AIDS

Abbreviate: AIDS, Acquired Immune Deficiency Syndrome

Table S3 Correlation coefficient of symptoms, functions, financial difficulties, charateristics and gQoL

	Physical Function	Role Function	Emotional Function	Cognitive Function	Social Function	Fatigue	Nausea/ vomiting	Pain	Dyspnea	Insomina	Appetite	Constipa--tion	Diarrhea	Financial difficulties	gQoL	Age	CCI
Physical Function	1.000																
Role Function	0.680	1.000															
Emotional Function	0.282	0.324	1.000														
Cognitive Function	0.352	0.417	0.486	1.000													
Social Function	0.491	0.564	0.380	0.429	1.000												
Fatigue	-0.688	-0.709	-0.524	-0.512	-0.722	1.000											
Nausea vomiting	-0.322	-0.301	-0.348	-0.165	-0.247	0.430	1.000										
Pain	-0.488	-0.536	-0.368	-0.368	-0.469	0.607	0.343	1.000									
Dyspnea	-0.368	-0.491	-0.285	-0.385	-0.351	0.542	0.313	0.458	1.000								
Insomina	-0.254	-0.282	-0.381	-0.408	-0.298	0.462	0.260	0.406	0.336	1.000							
Appetite	-0.396	-0.427	-0.358	-0.306	-0.408	0.555	0.512	0.455	0.410	0.270	1.000						
Constipation	-0.287	-0.324	-0.252	-0.165	-0.213	0.347	0.351	0.357	0.308	0.254	0.415	1.000					
Diarrhea	-0.213	-0.188	-0.166	-0.116	-0.188	0.290	0.327	0.220	0.301	0.212	0.305	0.184	1.000				
Financial difficulties	-0.310	-0.340	-0.230	-0.285	-0.467	0.434	0.277	0.308	0.304	0.140	0.273	0.214	0.285	1.000			
gQoL	0.329	0.469	0.331	0.364	0.397	-0.513	-0.265	-0.407	-0.404	-0.302	-0.379	-0.283	-0.213	-0.336	1.000		
Age	-0.230	-0.138	0.007	-0.015	-0.120	0.129	-0.016	0.022	0.052	-0.053	0.062	0.045	0.014	0.026	-0.086	1.000	
CCI	-0.264	-0.240	-0.070	-0.138	-0.225	0.308	0.220	0.202	0.238	0.099	0.288	0.170	0.127	0.277	-0.277	0.123	1.000

Abbreviate: gQoL, Global health/quality of life; CCI, Charlson Comorbidity Index;

Table S4 Descriptive statistics of the items

Item content	Expected influence	Predictability
Age	0.048	0.965
CCI	0.382	0.901
gQoL	0.824	0.813
Physical Function	0.724	0.665
Role Function	1.052	0.625
Emotional Function	0.739	0.801
Cognitive Function	0.671	0.776
Social Function	0.873	0.669
Fatigue	1.617	0.450
Nausea/vomiting	0.656	0.793
Pain	0.783	0.736
Dyspnea	0.761	0.773
Insomina	0.556	0.815
Appetite loss	0.860	0.742
Constipation	0.503	0.872
Diarrhea	0.492	0.893
Financial difficulties	0.566	0.837

Abbreviate: CCI, Charlson Comorbidity Index; gQoL, Global health/quality of life

Table S5 Multiple linear analysis related to gQoL

	Unstandardized		Standardized	P-value	F	adj R^2
	β (95%CI)	SE	β			
				<0.001	22.4	0.329
Role function	0.131(0.042-0.220)	0.045	0.161	**0.004**		
Emotional function	0.068(-0.031-0.167)	0.050	0.064	0.177		
Cognitive function	0.070(-0.023-0.164)	0.048	0.070	0.139		
Fatigue	-0.096(-0.224-0.033)	0.065	-0.102	0.144		
Pain	-0.046(-0.133-0.041)	0.044	-0.053	0.296		
Dyspnea	-0.078(-0.159-0.002)	0.041	-0.090	0.057		
Insomnia	-0.034(-0.091-0.022)	0.029	-0.054	0.232		
Appetite	-0.049(-0.128-0.030)	0.040	-0.059	0.223		
Constipation	-0.036(-0.104-0.032)	0.035	-0.044	0.303		
Financial difficulties	-0.076(-0.142--0.010)	0.034	-0.097	**0.024**		
CCI	-0.988(-1.749--0.227)	0.387	-0.104	**0.011**		

Abbreviate: gQoL, Global health/quality of life; CCI, Charlson Comorbidity Index

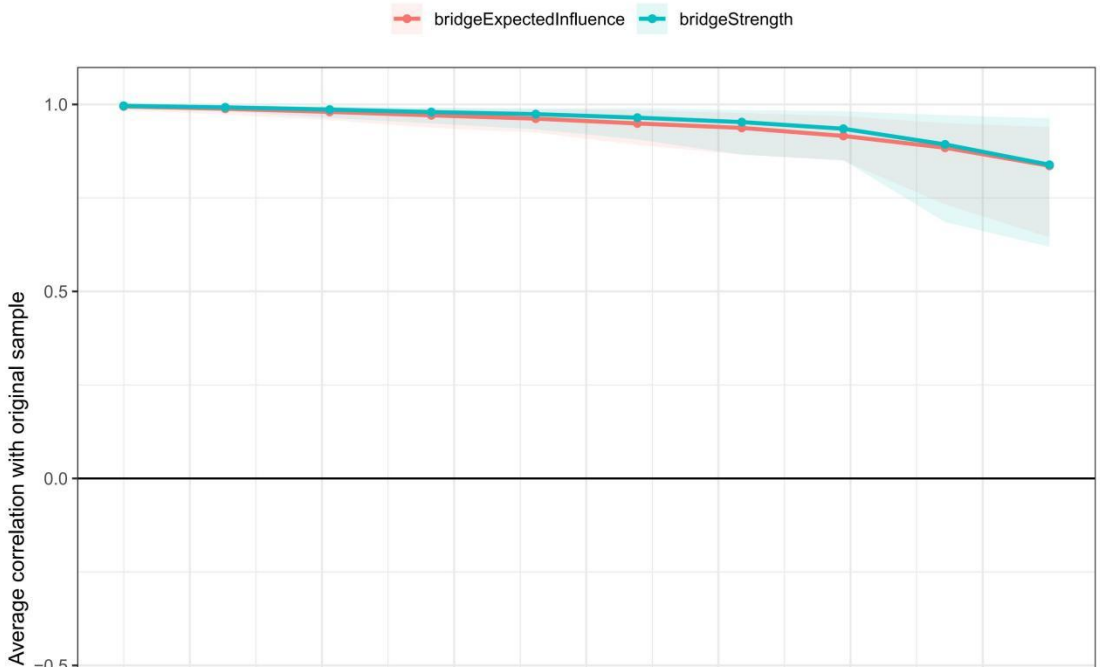

Figure S1 Network stability: bridge expected influence and bridge strength.

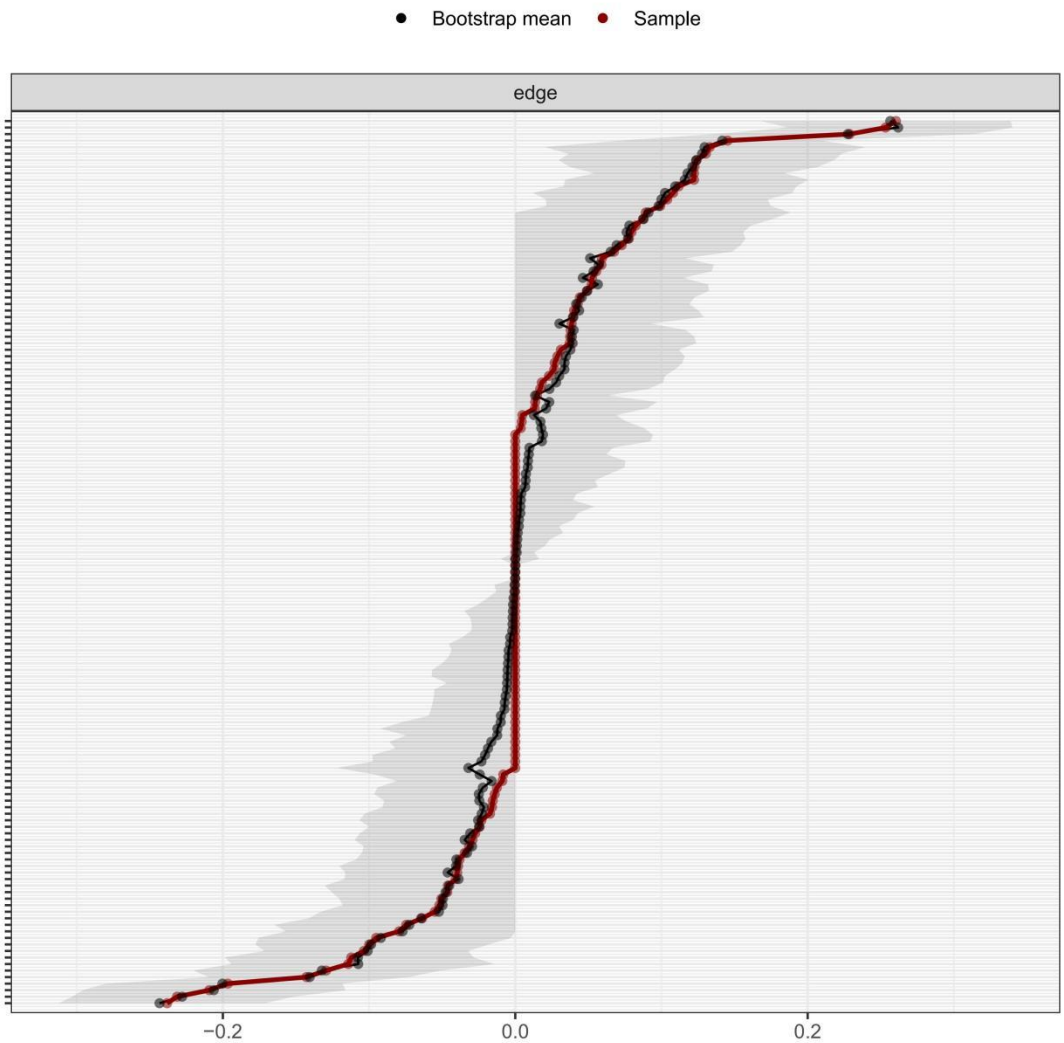

Figure S2 Bootstrapped confidence intervals of edge weights.