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The Trajectory and Influence Factors of Breast Cancer Patients' Main Chemotherapy-Related Symptoms: A Longitudinal Study

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Abstract

Introduction: Identifying the pattern of change in symptoms is critical to effective symptom management. This study aimed to determine the trajectory of Main Chemotherapy-related Symptoms (MCRS) in breast cancer patients, explore the influencing factors of potential categories of MCRS trajectory.

Methods: Patient-reported Outcomes Measurement System- breast-chemotherapy was used to measure the four highest incidence MCRS (pain, fatigue, anxiety, and depression) weekly in Breast cancer patients. The Growth Mixture Model (GMM) was used to fit the potential categories of the MCRS trajectory. Logistic regression was used to explore the influencing factors of potential categories of MCRS change trajectory.

Results: 239 breast cancer patients completed the study. Fatigue and depression showed an overall upward trend during the chemotherapy cycle, while pain and anxiety showed a downward trend. There are two potential categories of anxiety trajectory, three potential categories of fatigue and pain trajectory, and four potential categories of depression trajectory. Compared with the mild-fatigue group, Patients in the moderate and high fatigue groups were more likely to be less educated, have lower household income, and be treated with anthracyclines. Compared with the mild-pain group, patients in the pain-declining and fluctuating-pain groups were young, live-alone, and treated with paclitaxel. Patients in the anxiety-rising group were younger, had premenopausal menstruation with regular monthly menstruation, and had stage II disease. Patients in the depression-rising and severe depression groups were more likely to be solitary and younger.

Conclusion: The potential classes of major chemotherapy-related symptom trajectories vary in breast cancer patients. As for fatigue management, great attention should be paid to patients with low education, low family income, and anthracycline chemotherapy. For pain management, close attention should be paid to younger, solitary, and paclitaxel chemotherapy patients; For anxiety management, attention should be paid to younger patients with premenopausal menstruation and regular monthly menstruation patients, and those with stage II disease. In managing depression, attention should be paid to younger and solitary patients.

Introduction

In 2020, there will be an estimated 19.3 million new cases and 10 million cancer deaths worldwide [1]. Cancer has become the leading cause of death and an essential obstacle to increasing life expectancy in every country in the world [2]. According to the data from World Health Organization, female breast cancer has surpassed lung cancer as the most diagnosed cancer [1]. Most breast cancer patients require chemotherapy to reduce the relative risk of disease recurrence and death further. During breast cancer chemotherapy, patients may experience various adverse symptoms, among which fatigue, pain, anxiety, and depression are the four most common adverse symptoms, and their incidence is 20%-95% [3–7]. The

single or combined appearance of these four symptoms will significantly affect the level of daily activities and the quality of life during the rehabilitation period, reduce the patient's confidence in completing cancer treatment, thereby harm the quality of life and overall survival rate of breast cancer patients to a certain extent [8–10].

Clarifying the changes of the four symptoms is the basis for formulating appropriate and effective symptom management measures. Previous studies have found that the changes in these four symptoms are different. The overall trend of fatigue and anxiety is a type of "roller coaster" that first rises and then declines [11–14], while the trend of change of pain and depression is roughly a gradual decline [15–17]. Although the results of these studies can roughly reflect the overall trend of changes in symptoms, many studies have found that the development of symptoms may not change according to a single change trend, and there are subgroups of different change trajectories [18]. To identify these potential trajectories of change, the researchers measured these symptoms at multiple time points using the Growth Mixing Model (GMM) to provide a more detailed and complete description of cancer patients' symptom experiences. For example, Donovan's research found two different fatigue change groups [19]. The US research team identified four pain change groups and depression change groups, and two different anxiety change groups [20–22]. Nevertheless, the time range of many studies did not represent the complete chemotherapy process [19, 23]; and the participants of most researches were not for breast cancer patients receiving chemotherapy [20–22, 24, 25], so their findings cannot describe the trajectory change of the four highest incidence symptoms of the breast cancer patient during the chemotherapy period.

Therefore, the purpose of this study is to explore the trajectories of the four highest incidence chemotherapy-related symptoms (fatigue, pain, anxiety, and depression) in breast cancer patients during the whole chemotherapy cycle and analyze the influencing factors of those potential categories of trajectories to provide a reference for the development of targeted intervention strategies.

Methods

Participants

The patient was recruited from three Grade A hospitals in Suzhou City. Patients were eligible to participate if they were: (i)Adult woman (≥18 years) who would receive four-cycle chemotherapy for the first time after breast surgery; (ii)Able to read, write, and understand Chinese; (iii)Agreed to participate and gave written informed consent.

Patients were excluded if they had other malignant tumors or severe organic craniocerebral syndrome and mental illness and withdrew from research for various reasons.

Procedure

Recruit eligible patients in breast surgical wards and obtain their informed consent. These patients completed a demographic and treatment-related questionnaire and completed an assessment of symptom levels of fatigue, pain, anxiety, and depression before starting chemotherapy. Over the subsequent four cycles of chemotherapy, the researchers kept in touch with the participants weekly, either face-to-face or by phone, to assess them for four chemotherapy-related symptoms. Generally, an on-site questionnaire survey is carried out when patients come to the hospital for blood examination, pipeline maintenance, or chemotherapy in the hospital. Due to the COVID-19 epidemic's impact, some patients may reduce their visits to the hospital. In this case, we will contact the patients by phone to collect the symptom assessment content.

Measure

Demographic and treatment-related characteristics

The demographic and *treatment-related characteristics* information questionnaire collected information on age, sex, marital status, residence, mode of residence, menstrual cycle, education, employment status, occupation, religion, per capita monthly household income, payment method for medical expenses, family history for the disease, knowledge of the disease, other diseases, disease stage, metastasis, surgical options, and chemotherapy medications.

Symptom evaluation

Patient Reporting Outcome Measurement Information System (PROMIS) has been widely promoted in recent years. PROMIS is a set of item response theory-based self-reporting tools, allow researchers to use the minimum response to determine a person's symptoms or functions without losing the accuracy and keep in a wide range of comparability between disease groups for breast cancer patients undergoing chemotherapy[26]. Wu et al. [27] revised and constructed new measurement tools based on Sinicizing PROMIS, forming Patient-reported Outcomes Measurement System-Breast-Chemotherapy (PROMS-B-C). PROMS-B-C includes 20 short forms using a 5-point Likert score for pain, fatigue, anxiety, depression, and the like. Each short form can be used alone to assess the patients' symptoms for the past seven days as required. It is a specific patient self-reporting measurement system for breast patients undergoing chemotherapy[27].

PROMS-B-C Fatigue Short Form[28]

Fatigue was assessed using the Chinese version of the 12-item PROMS-Fatigue Short Form. The total scores ranged from 12 (no fatigue) to 60 (severe fatigue). The raw scores were then converted to standardized T scores (mean=50, SD=10). The Chinese version's Cronbach coefficient and half-fold

reliability are 0.91 and 0.92, respectively, indicating good internal consistency. The structure validity was good, and the correlation was correlated with quality of life (P <0.01).

PROMS-B-C Pain Short Form[28]

The Chinese version of the 10-item PROMS-Pain Short Form was used to assess pain. The scores are summed with a minimum score of 10 (no pain) and a maximum score of 50 (severe pain). The raw scores were then converted to standardized T scores (mean=50, SD=10). The Cronbach's α 0.92 demonstrates good internal consistency.

PROMS-B-C Anxiety Short Form[28]

The Chinese version of the 8-item PROMS-B-C Anxiety Short Form was used to assess anxiety. The scores range from 8 (no anxiety) to 40 (severe anxiety). The Cronbach coefficient is 0.96, suggesting good internal consistency.

PROMS-B-C Depression Short Form[28]

The Chinese version of the 8-item PROMS-B-C Depression Short Form was used to assess anxiety. The scores range from 8 (no depression) to 40 (severe depression). The Cronbach coefficient is 0.91, suggesting good internal consistency.

Statistical analysis

In our study, fatigue, pain, anxiety, and depression were evaluated weekly in 4 complete chemotherapy cycles, and each chemotherapy cycle was three weeks, so there was a total of 12 measurement time points. Nevertheless, our study wants to analyze and show clear and distinct trends of symptoms changes, and the number of 12 points may be too much. So, according to the changes of the four symptoms found in previous studies, the first week of each chemotherapy cycle (fatigue and pain) and the average data of each chemotherapy cycle (anxiety and depression) were selected for statistical analysis.

Statistical analysis proceeded in three steps. First, we used repeated-measures analysis of variance to describe the overall trend of symptoms and drew trend charts to show the development of symptoms throughout the chemotherapy cycle. Second, Growth Mixture Model (GMM) was used to identify different potential trajectories of four symptoms. GMM is a human-centered hybrid model analysis method. The research focuses on the relationship between individuals. The purpose is to divide individuals into different groups or categories according to individual response patterns so that individuals within a group are more similar than individuals between groups [29]. GMM analysis is an iterative procedure in which

the analyses began with a one-class model, and then successive models extracted additional classes. At each successive model, several statistical fit parameters were inspected (i.e., log-likelihood [LL], Akaike information criterion [AIC], and Bayesian information criterion [BIC]), with lower values indicating a better fitting model. Entropy is used to evaluate the accuracy of classification (ranging from 0 to 1). Entropy value≥0.80 indicates that the classification accuracy rate exceeds 90%, and the closer to 1, the more accurate the classification. Bootstrapped Likelihood Ratio Test (BLRT) and Vuong-Lo- Mendell-Rubin Likelihood Ratio Test (VLMR) are also used for model comparison and selection [29, 30]. Mplus (Version 7.4) was used to develop the growth mixture models. Finally, to test the potential of the demographic and treatment-related variables in predicting the latent members of the four symptoms with different changes, we calculated the univariate and multivariate logistic regression analysis with the symptom latent members as the outcome indicators. For the multivariate logistic regression, only statistically significant measures in the univariate analyses were used as influencing factors of class membership.

Result

Demographic and treatment-related characteristics

A total of 239 patients participated in the study, 188 of whom completed all the investigations. All of them were female, and their mean age was 53.79 (SD 10.44). Demographic and treatment-related characteristics of the patients are shown in Table 1.

Table 1

Demographic and treatment-related characteristics of participants(n=239)

Characteristics of participants	N (%)
Age	53.79±10.44
Sex	
Male	0(0.0%)
Female	239(100.0%)
Marital Status	
Married	205(85.8%)
Unmarried	13(5.4%)
Divorced	14(5.9%)
Widowed	7(2.9%)
Residence	
Rural	76(31.8%)
Urban	163(68.2%)
Mode of residence	
Living alone	31(12.9%)
Living with spouse or children	208(87.1%)
Menstrual Cycle	
Not menopausal, with regular monthly periods	76(34.4%)
Not menopausal, with irregular monthly periods	35(15.8%)
Menopausal	102(46.2%)
Uterine removed	8(3.6%)
Education	
Primary school	29(12.1%)
Junior high school	96(40.2%)
Senior high school/Technical secondary school	69(28.9%)
Bachelor’s degree and above	26(10.9%)
Employment status	
On the job	21(8.8%)
On sick leave	82(34.3%)

Unemployed	31(13.0%)
Retired	105(43.9%)
Occupation	
Farmer	38(15.9%)
Worker	29(12.1%)
Cadre	11(4.6%)
Teacher	31(12.9%)
Student	0(0.0%)
Self-employed	46(19.2%)
Others	84(35.3%)
Religion	
Yes	43(17.9%)
No	196(82.1%)
Per capita monthly household income	
≤3000 RMB	14(5.9%)
3001-6000 RMB	138(57.7%)
6001-9000 RMB	77(32.2%)
>9000 RMB	10(4.2%)
Payment method for medical expenses	
Self-funded	26(10.9%)
Publicly-funded	0(0.0%)
Medical insurance	213(89.0%)
Family history of the disease	
Yes	52(21.8%)
No	187(78.2%)
Knowledge of the disease	
Fully aware	10(4.2%)
Partially aware	189(79.1%)
Unaware	40(16.7%)

Other diseases	
Diabetes	16(6.7%)
Hypertension	49(20.5%)
Heart Disease	11(4.6%)
Others	16(6.7%)
None	147(61.5%)
Disease stage	
	0(0.0%)
	101(42.3%)
	138(57.7%)
	0(0.0%)
Lymph node metastasis	
Yes	130(54.4%)
No	109(45.6%)
Unknown	0(0.0%)
Surgical options	
Breast-conserving surgery	49(20.5%)
Simple mastectomy	67(28.0%)
Modified radical mastectomy	110(46.0%)
Extended radical mastectomy	13(5.5%)
Chemotherapy medications	
Anthracycline	65(27.2%)
Taxanes	78(32.6%)
Anthracycline and Taxanes	96(40.2%)

Overall Trend Analysis

The overall trend of fatigue and depression levels throughout the chemotherapy cycle is gradually increasing. In contrast, the level of pain and anxiety symptoms gradually decreased with the progress of chemotherapy（Figure 1）.

GMM Analysis

Fatigue

Using GMM to analyze fatigue data, the BIC value of the 3-class model was the smallest, and BLRT and VLMR were statistically significant, so the 3-class model was selected (Table 2). As shown in Figure 2, most patients were classified into the moderate-fatigue group (n=174, 73.0%). The proportion of the mild-fatigue group was 14.2% (n=34), and patients of this group had the lowest fatigue level and maintained a similar level throughout the chemotherapy cycle. The severe fatigue group was the least (n=31,12.8%), but these patients experienced more severe fatigue in the whole chemotherapy cycle, and the fatigue level increased with the progress of chemotherapy. The changing trend was gradually increased in the first three chemotherapy cycles and decreased in the fourth chemotherapy cycle.

Table 2

Summary of model fitting information

(a) Fitting results of six alternative potential class models for fatigue trajectory in breast cancer patients undergoing chemotherapy

GMM	LL	AIC	BIC	ABIC	entropy	BLRT *p*	VLMR *p*
1C	-667.22	1352.44	1371.87	1343.55			
2C	-657.47	1338.94	1364.84	1327.08	0.79	0.10	0.11
3C	**-647.05**	**1324.10**	**1356.48**	**1303.27**	**0.84**	**<0.00**	**0.10**
4C	-642.44	1320.87	1359.73	1309.08	0.81	0.08	0.25
5C	-654.52	1307.03	1369.37	1346.28	0.74	0.34	0.50
6C	-659.46	1314.92	1366.73	1387.20	0.65	0.56	0.46

(b) Fitting results of six alternative potential class models for pain trajectory in breast cancer patients undergoing chemotherapy

GMM	LL	AIC	BIC	ABIC	entropy	BLRT *p*	VLMR *p*
1C	-520.87	1059.75	1079.72	1051.38			
2C	-510.67	999.56	1056.25	1001.02	0.80	0.12	0.56
3C	**-481.48**	**987.96**	**1026.25**	**979.02**	**0.91**	**0.00**	**0.01**
4C	-475.61	992.21	1027.16	979.48	0.86	0.05	0.34
5C	-466.98	997.96	1044.57	999.44	0.77	0.07	0.45
6C	-463.46	1004.93	1428.19	1001.67	0.72	0.13	0.55

(c) Fitting results of six alternative potential class models for anxiety trajectory in breast cancer patients undergoing chemotherapy

GMM	LL	AIC	BIC	ABIC	entropy	BLRT *p*	VLMR *p*
1C	-502.42	1026.83	1051.25	1016.61			
2C	**-451.46**	**932.92**	**966.21**	**918.92**	**0.90**	**0.00**	**0.00**
3C	-426.47	990.94	987.11	973.27	0.84	0.04	0.43
4C	-420.11	980.22	997.27	984.84	0.81	0.07	0.48
5C	-513.61	1081.21	1041.14	1056.11	0.77	0.60	0.56
6C	-599.40	1160.81	1129.61	1131.99	0.73	0.71	0.59

(d) Fitting results of six alternative potential class models for depression trajectory in breast cancer patients undergoing chemotherapy

GMM	LL	AIC	BIC	ABIC	entropy	BLRT *p*	VLMR *p*
1C	-744.16	1508.32	1529.91	1498.44			
2C	-716.71	1459.42	1487.49	1446.57	0.71	0.31	0.238
3C	-693.21	1418.41	1452.95	1402.59	0.79	0.10	0.263
4C	**-681.33**	**1440.67**	**1441.69**	**1380.89**	**0.83**	**0.01**	**0.281**
5C	-669.04	1465.27	1496.21	1502.25	0.79	0.10	0.56
6C	-661.07	1472.13	1526.10	1547.42	0.73	0.20	0.60

Notes: GMM=Growth mixture model; LL=log likelihood test; AIC=Akaike Information Criteria; BIC=Bayesian Information Criterion; ABIC=Adjusted Bayesian Information Criterion; BLRT=bootstrapped

likelihood ratio test; VLMR=Vuong-Lo-MendelleRubin test.

Pain

Using GMM to analyze fatigue data, A 3-class model was selected because its BIC was the smallest and the entropy value was the largest. In addition, LL and AIC were smaller among the six analyzed groups, and BLRT and VLMR were statistically significant (Table 2). As shown in Figure 2, most patients were classified into the mild-pain group (n = 119, 49.9%). The trend of mild pain and pain-declining groups both decreased. The pain change trend of patients in the fluctuating-pain group (n = 43,17.9%) was first to decline and then to rise, and they had the highest pain level at the end of chemotherapy.

Anxiety

Using GMM to analyze anxiety data, A 2-class model was selected because its BIC was the smallest and the most considerable entropy value. In addition, AIC and ABIC were smaller among the six analyzed groups, and BLRT and VLMR were statistically significant (Table 2). The anxiety change trajectory is shown in Figure 2. The largest group of the patients was classified into the anxiety-declining group (n = 183, 76.5%). Furthermore, the trend of this group was declining. By contrast, the other group's trajectory increased during the whole cycle (n = 56, 23.5%).

Depression

Using GMM to analyze depression data, A 4-class model was selected because BIC and ABIC were the smallest, and the entropy value was the largest. In addition, LL and AIC were smaller among the six analyzed groups, and BLRT was statistically significant (Table 2). The depression change trajectory, as shown in Figure 2, the largest group of the patients was classified into the mild-depression group (n=160, 67.2%). The depression level of this group of patients was low and remained stable throughout the cycle. The next largest class was the depression-declining group (n=37, 15.6%), and their trajectory was slowly decreasing. Both the depression-rising group (n=11, 4.7%) and the severe-depression group (n=30, 12.5%) showed a gradual increase, and the depression level of patients in the severe depression group was the highest.

Differences in Demographic Characteristics

Fatigue

As shown in Table 3, compared with the mild-fatigue group, patients in the moderate- fatigue group had a lower income (<6000 RMB/month), a lower educational level (primary and secondary education) and

received anthracycline chemotherapy. Compared between the mild-fatigue and severe-fatigue groups, education levels and family per capita income are no longer significant. However, the chemotherapy scheme included anthracycline is the only predictor of severe degree of fatigue group. The risk of severe fatigue trajectory in patients using anthracycline was 10.63 times higher than those using taxanes.

Pain

Compared with the mild pain group, the older the patients were, the less likely they developed the pain trajectory into the pain-declining group. The solitary patients were more likely to develop into the pain-declining group. Patients treated with anthracyclines were less likely to develop a fluctuating-pain trajectory (Table 3).

Anxiety

Compared with the anxiety-declining group, the older the patients were, the less likely they developed into the anxiety-rising group. On the contrary, the anxiety trajectory of pre-menopausal patients with regular monthly menstruation is more likely to develop into increased anxiety; regression analysis also confirmed that the disease stage has a predictive effect, and patients diagnosed with stage II breast cancer have lower anxiety levels (Table 3).

Depression

Compared with the mild-depression group, the change trajectory of depression in the solitary patients was more likely to develop into the depression-rising group. In addition, the older the patients were, the less likely they were to develop into severe depression (Table 3).

Table 3

Multinational logistic regression of predictors of four symptoms

Trajectories	Predictors	OR	95%CI for OR	P
Moderate-fatigue group	Education			
	Primary school	1.08	0.39-2.99	0.01
	Junior high school	1.76	0.13-0.81	0.04
	Per capita monthly household income			
	≤3000 RMB	11.34	1.32-13.95	0.00
	3001-6000 RMB	10.45	1.24-14.67	0.01
	Chemotherapy medications			
	Anthracycline	1.78	0.52-1.94	0.02
Severe-fatigue group	Chemotherapy medications			
	Anthracycline	10.63	1.34-20.16	0.01
Pain-declining group	Age	0.79	0.69-1.69	0.04
	Mode of residence			
	Living alone	8.48	0.61-118.72	0.02
Fluctuating-pain group	Chemotherapy medications			
	Anthracycline	0.01	0.00-0.20	0.02
Anxiety-rising group	Age	0.91	0.63-156.69	0.03
	Menstrual Cycle			
	Not menopausal, with regular monthly periods	1.44	1.08-311.30	0.04
	Disease stage			
	□	0.32	0.15-16.49	0.04
Depression-rising group	Mode of residence			
	Living alone	10.04	0.56-1734.73	0.04
Severe-depression group	Age	0.86	0.76-0.96	0.01

Discussion

We measured fatigue, pain, anxiety, and depression symptoms and selected data to depict their trajectories during the entire chemotherapy cycle. The analysis results of fatigue symptoms were consistent with previous studies [31, 32], and the fatigue level gradually rose throughout the chemotherapy cycle. At present, similar studies that used the GMM to fit the trajectory of fatigue changes in breast cancer patients were still minimal. Junghaenel[33] reflected the daily changes in fatigue during 1-2 cycles of chemotherapy for breast cancer patients undergoing chemotherapy. This study showed that the proportion of patients in the severe fatigue group was 50%, which was higher than the result in our study (14.2%). The possible reason was that there was a two-week chemotherapy program in his study, which caused some patients to receive chemotherapy every 14 days, and the patients' fatigue symptoms might not be well alleviated before receiving the subsequent chemotherapy. However, our study's chemotherapy program was three-week, and patients had a longer recovery time, which made the overall fatigue level relatively low. Four nonmodifiable demographic characteristics—namely less education, lower per capita monthly household income, and anthracycline drugs—were associated with more severe fatigue. Consistent with previous studies [23, 34], lower-income patients had more server fatigue, and the possible reason was the economic limitation. Chemotherapy was a long-term treatment process, and the cost of long-term treatment had a more significant impact on the family economy of these patients. Financial stress and anxiety could cause more severe fatigue. In addition, due to economic restrictions, patients with lower income were more likely to choose domestic chemotherapy drugs. Compared with imported chemotherapy drugs with higher prices, the side effects of domestic drugs were more fantastic, so the fatigue symptoms of these patients were more serious. In our study, patients with lower education levels also suffered high-level fatigue. This might be due to the lack of knowledge of related diseases in these patients, mistakenly thinking that this symptom was a sign of disease recurrence or insufficient reporting of fatigue to medical staff due to fear of affecting routine treatment after the report, and thus unable to receive some practical help to manage fatigue.

In our study, although the potential change trajectory of pain was not distinguished as in previous studies [35–37], the overall change trend results were consistent with it. The overall pain level of breast cancer patients showed a downward trend during the investigation period. Compared with this study, the study of the American research team [38, 39] included more breast cancer pain patients, and the results identified more potential categories. This difference indicates that a larger sample size often helps GMM analyze more potential trajectories and better fit the trajectory. A small sample size may contain several potential change categories, but due to the limitation of the sample size, some latent category models may be recognized. However, the fit is not ideal, or the method cannot be recognized, thus simplifying the trajectory category of the observation result. By analyzing the influencing factors of pain, we confirmed that the pain would be heavier in younger patients and those living alone. The possible reason was that these patients needed to use their arms to finish more work and daily activities due to social responsibility and lack of family help, so the pain relief was poor. In addition, chemotherapy drugs could also affect the patient's pain trajectory change. Taxane acute pain syndrome (TAPS) caused by Taxanes may bring severe pain after receiving chemotherapy and last for 5-7 days [40, 41]. Therefore, patients receiving such drugs would experience an upward trend in pain during the chemotherapy cycle.

Although the overall trend of anxiety was decreasing, we identified a group of patients with increasing anxiety through GMM analysis. Nevertheless, this group of patients did not appear in the study of the American research team [42, 43]. The possible reason was different of participation. Unlike our study, which were all breast cancer patients undergoing chemotherapy, the research's participants of the American research team were breast cancer patients after breast cancer surgery, who received several different follow-up treatments, including chemotherapy. Moreover, the analysis of influencing factors found that young patients and those who were not menopausal and had regular monthly menstrual periods had higher anxiety levels. The populations corresponding to these two factors are the same. Young patients who have not experienced menopause need to take on more social and family responsibilities, coupled with the physical disability caused by surgery, making it more difficult for them. Unlike previous studies, our study also found a predictive indicator of disease stage. The patients in the anxiety-declining group had earlier disease stages than most patients in the anxiety-rising group. For the patients without professional knowledge, later stages would bring more negative thoughts on their illness and recovery and increase their thinking of survival and future uncertainty, thereby aggravating anxiety.

The potential categories identified for depression were the most, with four different potential trajectories consistent with previous studies [44, 45]. Furthermore, it has been proved that most breast cancer patients have a lower level of depression. In addition, this study, and the research of the American research team [22] also identified a group with a relatively small number of people. Research by the American team showed that the depression level of this group decreased first and then rose, while our research showed a gradual increase. The possible reason for this difference was that the research participants of the two studies were not homogeneous. However, the number of patients in these groups was relatively small in these two studies, and other large-sample studies were needed to confirm the existence and trajectory. Consistent with anxiety symptoms, age was one of the influencing factors of depression. Insufficient social support, physical disability, and physiological distress could lead to a higher level of depression in younger patients, so this kind of patient deserves more attention [46, 47]. In addition, lifestyle was also a decisive influencing factor. Compared with patients with low depression levels, the depression levels of patients living alone gradually increased during the chemotherapy. Without family members, living alone made it impossible for patients to obtain support and help from family and society effectively. Moreover, as the chemotherapy cycle continues, this situation will continue to increase.

The present study had some limitations. Although this study's sample size was enough, more extensive, independent samples may confirm these preliminary findings and identify additional latent classes and significant influencing factors. Also, our study participants were all post-operate breast cancer receiving chemotherapy, but it did not include patients receiving neoadjuvant chemotherapy, and this part of the population deserves more attention for future research. Finally, the generalizability of the study findings is limited to only female patients with breast cancer included.

Conclusion

The overall change trends of the main chemotherapy-related symptoms of breast cancer patients are different, with fatigue and depression manifested as an upward trend; pain and anxiety indicated as a downward trend. The potential categories of the above symptoms are different. Anxiety indicated two potential categories of symptoms trajectories, fatigue and pain indicated three potential categories, and depression indicated four. Breast cancer patients with different characteristics showed different symptom trajectories. Therefore, when performing symptom management on breast cancer patients undergoing four cycles of chemotherapy, these factors should be considered. Close attention should be paid to patients with low education, low family income, and anthracycline treatment in fatigue management. As for pain management, close attention should be paid to younger patients, living-alone, and paclitaxel treatment. Close attention should be paid to younger, non-menopausal with monthly menstrual regularity and stage II patients while managing anxiety. As for depression management, close attention should be paid to the younger and living-alone patients.

Abbreviations

MCRS: Main Chemotherapy-related Symptoms; GMM: Growth Mixture Model; PROMIS: Patient Reporting Outcome Measurement Information System; PROMS-B-C: Patient-reported Outcomes Measurement System-Breast-Chemo- therapy; LL: log-likelihood; AIC: Akaike information criterion; BIC: Bayesian information criterion; BLRT: Bootstrapped Likelihood Ratio Test; VLMR: Vuong- Lo-Mendell-Rubin Likelihood Ratio Test.

Declarations

Ethics approval and consent to participate

This study acquired ethical approval from the Medical Ethics Committee of Soochow University (No. SUDA20210126H01). All participants signed the informed consent form.

Consent for publication

All participants have read the final manuscript and agreed to publish the data included in this manuscript.

Availability of data and materials

The authors have full control of all primary data and agree to allow the journal to review the data if requested.

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Competing interests

The authors declare that they have no conflicts of interest.

Authors' contributions

Y.S.Q. and L.T. contributed to study concepts and study design. Y.S.Q., N.Z., Y.M., E.W.X., Z.K.B., J.Q., and J.H.C contributed to data acquisition. Y.S.Q. and N.Z. contributed to data analysis and interpretation. L.L. and Q.M.H. contributed to the quality control of data and algorithms. Y.S.Q. wrote the original draft, L.T. reviewed and edited the manuscript. All authors reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

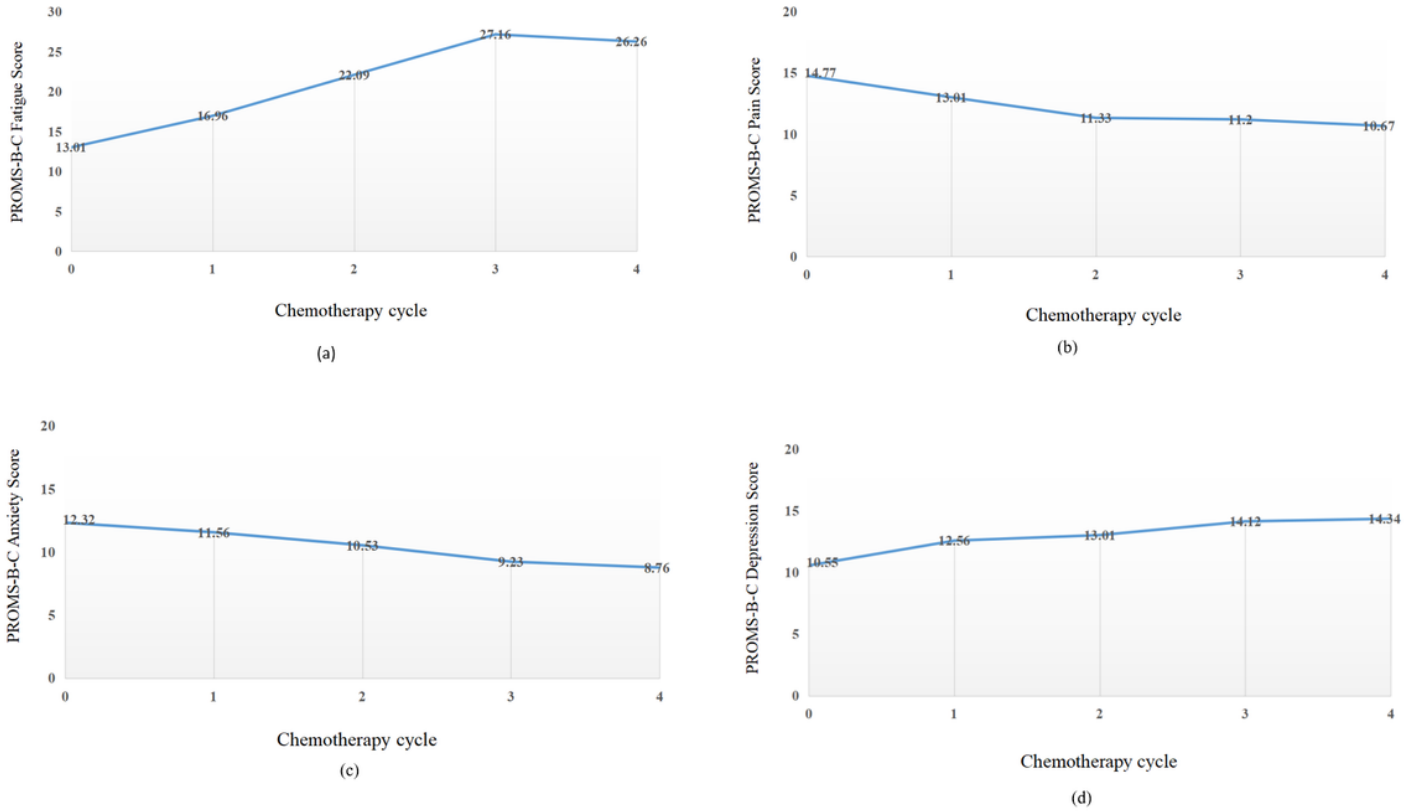

Figure 1

The overall trend of four symptoms (a)The overall trend of fatigue; (b) The overall trend of pain; (c) The overall trend of anxiety; (d) The overall trend of depression

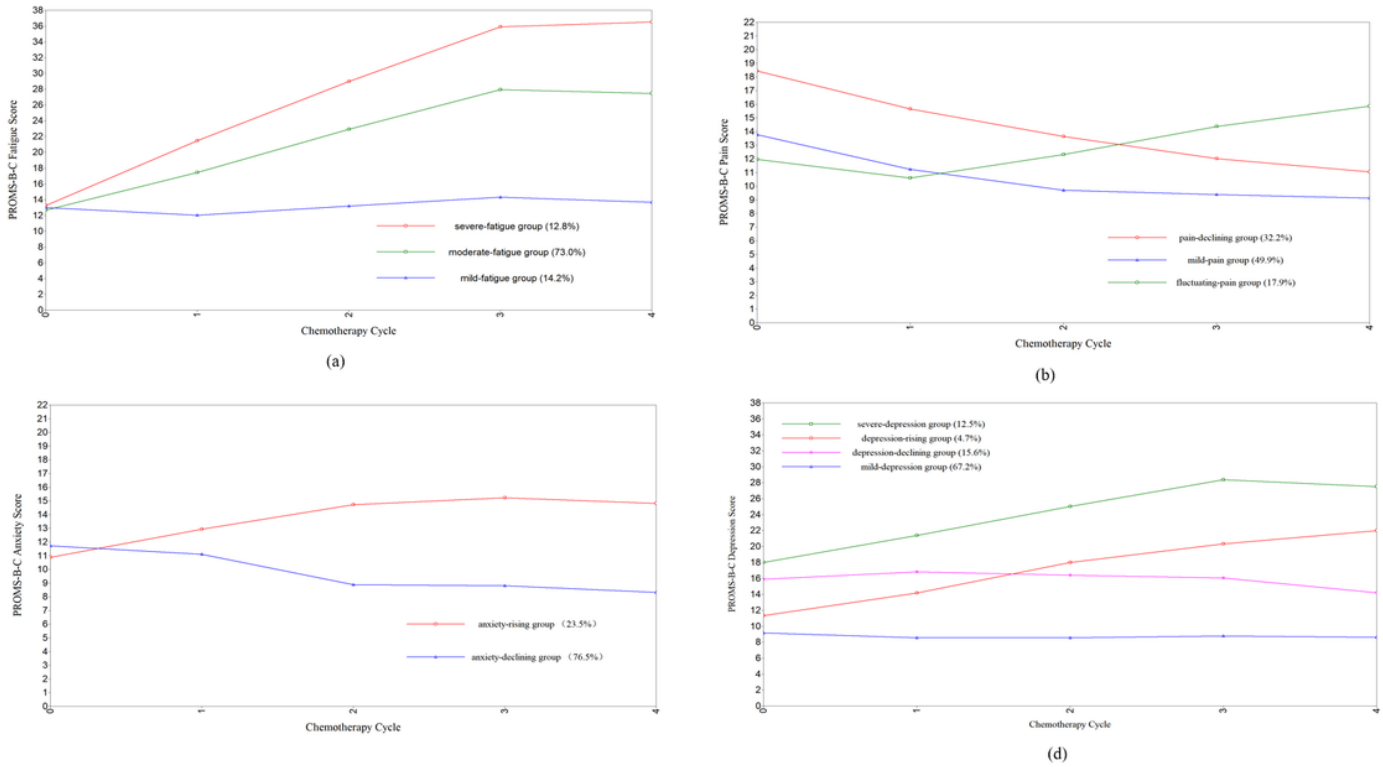

Figure 2

Trajectory Patterns for Four Symptoms (a) Trajectory patterns for Fatigue; (b) trajectory patterns for Pain; (c) trajectory patterns for anxiety; (d) trajectory patterns for Depression.