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Original Article

The high burden of symptoms associated with cognitive impairment in lung cancer patients: A latent class analysis

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ABSTRACT

Objective: To explore the association between the pain-fatigue-sleep disturbance-depression symptom cluster (SC) and cancer-related cognitive impairment (CRCI) in patients having lung cancer and to identify other factors influencing CRCI.

Methods: A cross-sectional study was conducted to investigate 378 patients having lung cancer in China from October 2021 to July 2022. The perceived cognitive impairment scale and the general anxiety disorder-7 were used to assess patients' cognitive impairment and anxiety, respectively. The pain-fatigue-sleep disturbance-depression SC was assessed with the brief fatigue inventory, the brief pain inventory, the Patient Health Questionnaire-9, and the Athens Insomnia Scale. Latent class analysis by Mplus.7.4 was used to identify latent classes of the SC. We adjusted for covariates in the multivariable logistic regression model to examine the relationship between the pain-fatigue-sleep disturbance-depression SC and CRCI.

Results: Among patients having lung cancer, two SC classes were identified: high and low symptom burden groups. In the crude model, compared to the low symptom burden group, the high symptom group had greater odds of developing CRCI (odds ratio: 10.065, 95% confidence interval: 4.138–24.478). After adjusting for covariates, in model 1, the high symptom group still had greater odds of developing CRCI (odds ratio: 5.531, 95% confidence interval: 2.133–14.336). Additionally, a diagnosis of over 6 months, anxiety, leisure activity, and a high platelet-to-lymphocyte ratio were found to be influencing factors of CRCI (all $P < 0.05$).

Conclusions: Our study revealed that a high symptom burden is a significant risk factor for CRCI, which may provide a new perspective for managing CRCI in lung patients having cancer.

1. Introduction

Cancer-related cognitive impairment (CRCI) refers to the memory loss, decreased attention, and reduced processing that patients having cancer experience due to cancer and its treatment.[1] CRCI affects up to 10 million patients having cancer, resulting in low treatment compliance, poor quality of life, and adverse effects on patients' mental health.[2] However, 75% of the research on CRCI focuses on patients having breast cancer.[3]

According to a newly published report from China in 2022, with 828,100 new cases, lung cancer ranks first in number and incidence among all cancers in the Chinese population.[4] Insufficient studies have focused on the cognitive function of patients having lung cancer. Previous studies have only investigated a small sample of patients having lung cancer and were limited to chemotherapy patients.[5,6] A recently published study on CRCI in patients having lung cancer used only two questions to assess patients' cognitive function,[7] which may have led to an inaccurate assessment of CRCI.[8]

Influencing factors for CRCI include cancer treatments, symptoms, age, and lifestyle habits.[7,9] There is a possibility that psychoneurological symptoms (e.g., depression, fatigue, sleep disturbance, pain, anxiety) rather than chemotherapy can lead to CRCI.[10] Therefore, assessing psychoneurological symptoms is vital to determine CRCI. Moreover, symptoms in patients having cancer do not appear independently but as a symptom cluster (SC), which refers to "two or more concurrent symptoms that are related to each other".[11,12] Additionally, the symptoms within a SC can interact with each other. Thus, SC may multiply the

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patient's symptom burden. In recent years, there has been increasing interest in SCs due to the effectiveness of holistic interventions for SCs compared to interventions for a single symptom, which can better reduce the patient's symptom burden and medical staff's workload.

SCs can also influence patients' cognitive function, according to the symptoms experience model of Armstrong.[13] Therefore, exploring the effect of a SC on CRCI in patients having lung cancer can provide a new perspective for managing CRCI through intervening in SCs. To date, very few studies have explored the relationship between SCs and CRCI in patients having cancer. Only Hooke[14] investigated patients having lymphocytic leukemia and found that a severe SC was associated with worse cognitive function. While the occurrence rates of symptoms vary, pain (39.4%–66.4%), fatigue (25%–99%), depression (8%–58%), and sleep disturbance (17%–70%) often occur at the same time in patients having cancer and have been shown to be a SC[15–17] that seriously affects patients having cancer. Compared with other cancer types, patients having lung cancer experience heavier symptom burdens.[18] The aim of this study is to explore the relationship between the pain-fatigue-sleep disturbance-depression SC and CRCI in patients having lung cancer and to identify other factors that influence CRCI to provide a reference for identifying and managing CRCI in the future.

2. Methods

2.1. Study participants

Convenience sampling was used in this cross-sectional study to investigate 378 patients having lung cancer in the Oncology Department and the Respiratory Department of a tertiary hospital from October 2021 to July 2022 in Guangzhou, China. This study is a part of a team scientific project and the project is still ongoing.

The inclusion criteria were as follows: (1) at least 18 years old, (2) diagnosed with primary lung cancer, and (3) informed and able to participate in this study. The exclusion criteria were as follows: (1) brain metastasis, (2) history of neurological disease, psychiatric diseases, or psychotic episodes, and (3) other types of tumors.

2.2. Sample size calculation

According to the requirements for logistic regression analysis, the sample size should be at least 10 times the number of independent variables.[19] In our study, there were 22 independent variables, and considering 10% invalid questionnaires, the minimum required sample size was 245 (22*10/0.9).

2.3. Measures

2.3.1. Demographic and clinical characteristics

The questionnaire included age, sex, education, work, marital status, and monthly income. The work of patients having lung cancer was identified according to classifications developed by Nucci.[20]

Clinical characteristics were obtained from the patient's medical records regarding their current admission, including pathological type and cancer stage of lung cancer, Nutritional Risk Screening 2002 scores (with a score $\geq$3 indicative of having nutritional risk[21]), body mass index, and so on. Some laboratory results of patients' current admission were also collected from patients' medical records. The four relevant indicators of the inflammatory status of patients were calculated accordingly[22]: lymphocyte–monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and PNI = lymphocyte count (10^9/L) $\times$ 5 + serum albumin (g/L).

2.3.2. Cognitive function

The Perceived Cognitive Impairment scale (CogPCI) is a subscale of the widely used functional assessment of cancer therapy–cognitive scale (version 3). The functional assessment of cancer therapy–cognitive scale was developed by Wanger,[23] who recommended using the CogPCI scales to assess cancer patients' cognitive difficulties. The CogPCI consists of 20 items ranging from 0 ("Never") to 4 ("Several times a day"), and the total score ranges from 0 to 72 points (two items are not scored). A score less than 54 is indicative of cognitive impairment and can well distinguish between CRCI and non-CRCI.[24,25] The Cronbach's α coefficient of the CogPCI in this study was 0.947.

2.3.3. The pain-fatigue-sleep disturbance-depression SC

The pain-fatigue-sleep disturbance-depression SC consists of four symptoms, which we measured using the following four instruments.

The brief pain inventory (BPI): The BPI includes two dimensions, pain severity, and distress. Each item ranges from 0 (no pain) to 10 (pain as bad as the patient can imagine), with an average score of 0, 1–4, 5–6, and 7–10 representing no, mild, moderate, and severe pain, respectively.[26] We assessed pain using the 4-item severity subscale of the BPI. The Cronbach's alpha coefficient in this study was 0.927.

The brief fatigue inventory (BFI): The BFI includes two dimensions, fatigue severity and fatigue interference, with a high internal consistency for both components. The items can be categorized into scores of 0, 1–3, 4–6, and 7–10, representing none, mild, moderate, and severe fatigue, respectively.[27] We assessed fatigue using the 3-item severity subscale of the BFI with a Cronbach's alpha coefficient of 0.951 in this study.

The Athens insomnia scale (AIS): The AIS was used to assess sleep disturbance. There are eight items, ranging from 0 to 3. The AIS has total scores of 0–4, 4–6, and >6, indicating no insomnia, suspicion of insomnia, and insomnia.[28] The Cronbach's alpha coefficient in this study was 0.849.

The Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 was used to assess patients' depression. The total score ranges from 0 to 27, with scores of 0–5, 6–10, 11–15, and 16–20 indicating mild, moderate, moderately severe, and severe depressive symptoms, respectively.[29] In this study, the Cronbach's alpha coefficient was 0.782.

2.3.4. Anxiety

The general anxiety disorder-7 (GAD-7) is based on the diagnostic criteria of the DSM-IV to assess the anxiety of patients.[30] There are 7 items scored from 0 (not at all) to 3 (nearly every day), and the total score ranges from 0 to 21. Patients with a score below 10 are regarded as having anxiety.[31] The Cronbach's alpha coefficient in this study was 0.787.

2.3.5. Leisure activity

Leisure activity (LA) was classified into 3 categories according to the Cognitive Reserve Index questionnaire.[20] Therefore, we asked whether patients having lung cancer had a habit of performing LAs. The question was as follows: Did you have a habit of engaging in LAs in the past year (multiple choice): (1) did not have a habit; (2) had a habit of engaging in cognitive activities, such as reading, reading newspapers, watching TV, playing music, and so on; (3) had a habit of engaging in physical activities, such as exercise and dancing; (4) had a habit of engaging in social activities, such as traveling and participating in community activities. In the analysis, patients were divided into two groups based on their responses: those with and those without LAs.

2.4. Data collection

After obtaining informed consent from patients, questionnaires were administered to patients by four uniformly trained investigators. For those who could not complete the questionnaire independently, the researcher read the questions and recorded the patients' responses. The questionnaires were collected at the time of the patients' current admission and before starting this treatment.

Since the patients' inflammatory biomarkers may have been affected by the current treatment, special care was taken to obtain hematological tests and clinical characteristics from the patients' medical records by selecting the relevant results at the time of the patients' current admission and one day before their current treatment.

2.5. Covariates

Some covariates were included, such as suspected risk factors for cognitive function and potential confounding factors according to previous studies[32–34]. The covariates in this study included age, sex, work, income, marital status, education, smoking status, drinking status, time since diagnosis, treatment, cancer stage, LA, pathological type of cancer, body mass index, LMR, NLR, PLR, PNI, operation history, anxiety, and nutrition status.

2.6. Data analysis

We used the statistical software IBM SPSS Statistics version 25.0 to describe and analyze statistics. Continuous variables are presented as the mean ± standard deviation or median (interquartile range) according to the distribution characteristics of the data. Student's t test or the Mann–Whitney U test was used to compare the differences in the participants' sociodemographic and clinical characteristics. By drawing the receiver operating characteristic curve for CRCI and the four inflammatory indicators (PNI, PLR, LMR, NLR), the Youden index was calculated to determine the best cutoff point. Categorical variables are described as frequencies and percentages and analyzed by the chi-squared test or Fisher's exact test. Multiple imputation was used to fill in the missing values in the clinical characteristics of the patients.

Latent class analysis (LCA) in Mplus 7.4 was used to explore different classes of the pain-fatigue-sleep disturbance-depression SC in patients having lung cancer according to the grade of these four symptoms. Currently, the fit indices of LCA models are the Akaike information criterion (AIC), Bayesian information criterion (BIC), sample size-adjusted Bayesian information criterion (aBIC), information entropy index (Entropy), Lo-Mendell-Rubin likelihood ratio test (LMR), Bootstrap likelihood ratio test (BLRT), and so on. Generally, the smaller the AIC, BIC, and aBIC values are, the better the fit of the model. Entropy is used to evaluate the classification accuracy, ranging from 0 to 1, with closer to 1 indicating a more accurate classification. The LMR and BLRT were used to compare the fit differences between the k-1 and k-category models, and the k-category model outperformed the k-1 category model when the P values reached a significant level ($P < 0.05$).[35,36] Another key point of determining the best model that fits the population is the size of the smallest class. In practical applications, the indices may be not consistent with each other. The final number of categories should be determined by taking into account the actual meaning of the classification and the number of samples included in one class (50 samples per class should be guaranteed to ensure the accuracy of the model).[37] GraphPad Prism software was used to draw the conditional probability plot.

Multivariable logistic regression was performed to explore the association between the pain-fatigue-sleep disturbance-depression SC and CRCI. GraphPad Prism software was used to draw forest plots to visualize the odds ratios (ORs) and 95% confidence intervals (95% CIs). In this study, two models were constructed: the crude model, with no adjustments for any covariates, and model 1, which adjusted for the covariates. Statistical significance for the two-tailed tests was $P < 0.05$.

2.7. Ethical considerations

This study was approved by the Medical Ethics Committee of Nan Fang Hospital of Southern Medical University (IRB. NFEC-2020-281). All participants provided written informed consent.

3. Results

3.1. Participant characteristics

In total, 378 patients having lung cancer participated in this study (response rate: 96.92%), and 12 questionnaires were excluded because of incomplete information. The detection rate of CRCI was 11.64%. There were 44 patients in the CRCI group with an average age of 62.16 ± 10.24 years and 334 patients in the non-CRCI group with an average age of 58.67 ± 10.39 years. Most patients in our study were male (68.52%), married (94.18%), and had a primary school education or less (41.27%).

As shown in Table 1, age ($P = 0.037$), education ($P = 0.028$), LA ($P < 0.001$), time since diagnosis ($P = 0.028$), nutrition risk ($P = 0.015$), anxiety ($P < 0.001$), PNI ($P = 0.031$), LMR ($P = 0.022$), PLR ($P = 0.035$), and NLR ($P = 0.049$) were significantly different between the two groups. However, no significant between-group differences were found for sex, marital status, or work (all $P > 0.05$). See Table 1.

3.2. Latent classes of the pain-fatigue-sleep disturbance-depression SC

Compared with the 3-class model, the 4-class has larger AIC, BIC, and aBIC and smaller Entropy, and it did not have a statistically significant LMR ($P = 0.5663$) (Table 2). Therefore, the 3-class model is better than the 4-class model. What stands out in Table 2 was that the LMR of the 3-class model was not statistically significant ($P = 0.0544$), which indicated that the 3-class model was not better than the 2-class model. Moreover, the 3-class model had a class with a sample size of 36 patients, which may lead to the inaccuracy of the model. Thus the 2-class model outperforms than the 3-class model. Meanwhile, the 2-class model had statistically significant LMR ($P < 0.001$) and BLRT ($P < 0.001$) and smaller AIC, BIC, and aBIC than the 1-class model. For the above reasons, two subgroups of the pain-fatigue-sleep disturbance-depression SC were identified via LCA.

Based on the characteristics of the four symptoms, 44.18% ($n = 167$) of the patients were labeled the "high symptom burden" group, and 55.82% ($n = 211$) of the patients were labeled the "low symptom burden" group. Fig. 1 demonstrates the conditional probabilities of the two subgroups corresponding to the four different symptoms when patients have moderate symptoms. For example, patients in the high symptom burden group tend to have moderate pain, fatigue, insomnia, and depression with probabilities of 15.33%, 26.34%, 69.57%, and 15.20%, respectively.

3.3. Association between the pain-fatigue-sleep disturbance-depression SC and CRCI

By drawing receiver operating characteristic curves of PNI, NLR, LMR, and PLR for CRCI, the cutoff points were determined to be 49.78, 4.03, 2.96, and 183.88, respectively. Then, the four indicators were transformed into categorical variables for further statistical analysis and clinical application. The AUC, sensitivity, specificity, and Youden index are shown in Table 3.

We built two models (Table 4). In the crude model, compared to the low symptom burden group, the high symptom burden group had higher odds of developing CRCI (OR: 10.065, 95% CI: 4.138–24.478). After adjusting for the covariates, in model 1, compared to the low symptom burden group, the high symptom burden group had higher odds of developing CRCI (OR: 5.531, 95% CI: 2.133–14.336). Meanwhile, Fig. 2 shows that in model 1, being diagnosed for more than 6 months, anxiety and high PLR are risk factors for CRCI by multivariate analysis, while LA was a protective factor Specific results of multivariate logistic regression are shown in Supplementary Table A1.

4. Discussion

Our study identified two classes of the pain-fatigue-sleep disturbance-depression SCs in patients having lung cancer, nearly half of whom experienced a high symptom burden. Furthermore, the high symptom

Table 1
Sociodemographic characteristics of lung cancer patients ($n = 378$).

Variates	CRCI ($n = 44$), n (%)	Non-CRCI ($n = 334$), n (%)	$t/Z/\chi^2$	P value
Age, mean (SD), years	62.16 ± 10.24	58.67 ± 10.39	−2.096*	0.037
Gender			0.550	0.458
Male	28 (63.64%)	231 (69.16%)		
Female	16 (36.36%)	103 (30.84%)		
Marital status			1.781	0.344
Married	43 (97.73%)	308 (92.22%)		
Others	1 (2.27%)	26 (7.78%)		
Education			9.071*	0.028
Primary school or less	22 (50.00%)	134 (40.12%)		
Junior high school	17 (38.64%)	89 (26.65%)		
High school or technical school	2 (4.55%)	57 (17.07%)		
Bachelor's degree or higher	3 (6.82%)	54 (16.17%)		
Work			3.006	0.224
unskilled, manual work	23 (52.27%)	158 (47.31%)		
skilled manual work	16 (36.36%)	101 (30.24%)		
skilled non-manual or technical work	5 (11.36%)	75 (22.46%)		
Income (yuan per month)			2.649	0.266
< 3000	12 (27.27%)	72 (21.56%)		
3000-5000	16 (36.36%)	165 (49.40%)		
≥ 5000	16 (36.36%)	97 (29.04%)		
Smoke			0.537	0.464
Yes	21 (47.73%)	179 (53.59%)		
No	23 (57.27%)	155 (46.41%)		
Drink			2.141	0.143
Yes	12 (27.27%)	129 (38.62%)		
No	32 (72.73%)	205 (61.38%)		
BMI[a]			3.443	0.168
Normal	30 (75.00%)	198 (60.37%)		
Underweight	3 (7.50%)	28 (8.54%)		
Overweight	7 (17.50%)	102 (31.10%)		
Leisure activity			26.191***	<0.001
Yes	10 (22.73%)	211 (63.17%)		
No	34 (77.27%)	123 (36.83%)		
Treatment			1.893	0.388
Without treatment	6 (13.63%)	68 (20.36%)		
Chemotherapy	29 (65.91%)	81 (24.25%)		
Non-chemotherapy	9 (20.45%)	185 (55.39%)		
Variates	CRCI, n (%)	Non-CRCI, n (%)	$t/Z/\chi^2$	P value
Time since diagnosis			9.103*	0.028
< 1 month	5 (11.36%)	85 (25.45%)		
1–3 months	9 (20.45%)	73 (21.86%)		
3–6 months	4 (9.10%)	52 (15.57%)		
≥6 months	26 (59.09%)	124 (37.13%)		
Operation			2.488	0.115
Yes	14 (31.82%)	71 (21.26%)		
No	30 (68.18%)	263 (78.74%)		
Cancer stage			0.829	0.687
II	2 (4.55%)	27 (8.08%)		
III	8 (18.18%)	73 (21.86%)		
IV	34 (77.27%)	234 (70.06%)		
Pathological Type			0.258	0.612
Non-small-cell lung cancer	40 (90.91%)	295 (88.32%)		
Small-cell lung cancer	4 (9.09%)	39 (11.68%)		
Nutrition risk			5.958*	0.015
Yes	9 (20.45%)	29 (8.68%)		
No	35 (79.55%)	305 (91.32%)		
Anxious			31.178***	<0.001
Yes	11 (25.00%)	12 (3.59%)		
No	33 (75.00%)	322 (96.41%)		
PNI[a], median (IQR)	48.40 (44.80, 52.41)	50.50 (46.16, 54.06)	−2.152*	0.031
LMR, median (IQR)	2.21 (1.80, 2.93)	2.60 (1.96, 2.65)	−2.288*	0.022
NLR, median (IQR)	3.40 (2.21, 7.01)	2.77 (1.97, 4.29)	−1.970*	0.049
PLR[a], median (IQR)	199.20 (137.71, 252.48)	169.09 (122.98, 230.08)	−2.108*	0.035

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

[a] Indicates that there are missing values for the BMI (10 missing values), PNI (2 missing values), PLR (2 missing values). We have filled them using the multiple imputation.

Table 2
Fit indices of the latent class analysis of the pain-fatigue-sleep disturbance-depression SC in lung cancer patients (n = 378).

Class	AIC	BIC	aBIC	Entropy	LMR	BLRT	Number of subgroups
1	3186.854	3230.138	3195.237				
2	2915.682	3006.185	2933.211	0.763	0.0000	0.0000	211/167
3	2480.951	2614.446	2503.422	0.799	0.0544	0.0000	174/36/125
4	2486.479	2665.743	2516.654	0.787	0.5663	0.0000	42/99/36/158
5	2881.007	3113.166	2925.972	0.806	0.1250	0.6667	18/73/18/120/149

aBIC, sample size-adjusted Bayesian information criterion; AIC, Akaike information criterion; BIC, Bayesian information criterion; BLRT, Bootstrap likelihood ratio test; Entropy, classification accuracy; LCA, latent class analysis; LMR, Lo-Mendell-Rubin likelihood ratio test.

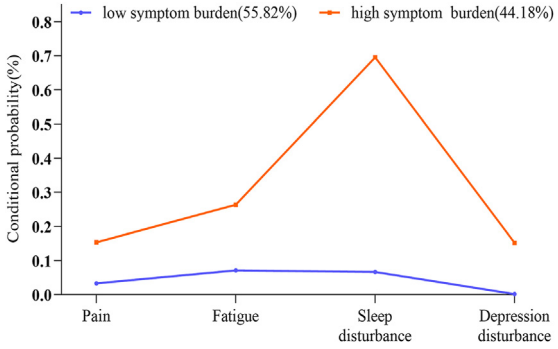

Fig. 1. Conditional probability distribution of potential categories of pain-fatigue-sleep disturbance-depression SC in lung cancer patients (N = 378).

burden remains a risk factor for CRCI even after adjusting for some confounding factors.

4.1. Severe pain-fatigue-sleep disturbance-depression SC have a negative impact on CRCI

Although various studies have explored the effect of a single symptom on CRCI, few have examined SCs. Hooke[14] investigated children with lymphocytic leukemia and found that a severe fatigue-sleep disturbances-pain-nausea-depression SC was associated with worse cognitive function. Compared with other cancer types, patients having lung cancer experience heavier symptom burdens.[18] To our knowledge, this is the first study to explore the relationship between SC and CRCI in patients having lung cancer. We found a negative impact of severe pain-fatigue-sleep disturbance-depression SC on CRCI. Despite the diversity of studies on SC, Wang X[38] reviewed the current state of research on cancer SC subgroups in China and other countries via bibliometric methods and found that 44% of studies explored the pain-fatigue-sleep disturbance-depression SC. Studies have shown that this SC is the most severe and troubling SC for patients having cancer.

The mechanisms of how SCs or a single symptom affects CRCI are unclear. On the one hand, extensive research has shown that inflammation directly or indirectly affecting CRCI through neural–immune interactions is one of the core mechanisms of CRCI.[39] The elevation of circulating proinflammatory factors in patients with cancer may be related to CRCI.[40] Some inflammatory cytokines, including interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor α, have been studied in recent years.[40,41] On the other hand, previous studies have shown that systemic inflammation is the biological basis of SCs as well,[42] and some cytokines, including interleukin (IL)-6, C-reactive protein (CRP), and tumor necrosis factor α, have been studied before. However, the cytokines mentioned above are not routinely tested for, and the results are not readily available.

In contrast, the NLR, LMR, PLR, and PNI, calculated through routine laboratory tests of patients' peripheral blood, can reflect systemic inflammation and be associated with patient prognosis.[22] A recent study found that serum biomarkers such as the NLR are associated with the fatigue-psychological SC in patients with colorectal cancer.[43] Therefore, we explored the four inflammation indicators and determined their cutoff points. We found that high PLR is a risk factor for CRCI in patients having lung cancer, which is consistent with Kimberly's study in patients having breast cancer.[44] Peripheral proinflammatory cytokines can cross the blood–brain barrier and trigger the release of local cytokines. Those cytokines will deregulate neurotransmitters, increase oxidative stress, and decrease neurogenesis and neuroplasticity, which can lead to CRCI.[45] An implication of this is that the pain-fatigue-sleep disturbance-depression SC and CRCI may share common inflammatory mechanisms.

4.2. Other risk factors for CRCI

In addition, our study showed that a diagnosis of more than 6 months and having anxiety may be risk factors for CRCI, while LA was a protective factor. Compared with those diagnosed less than a month, lung cancer patients diagnosed for more than 6 months were more prone to CRCI, which may be related to the toxicity accumulation of treatment or the progression of cancer. However, this needs to be verified by longitudinal studies in the future. Anxiety may affect the spontaneous functional activities of the thalamus and hippocampus, which are closely related to cognitive function.[46]

Another significant protective factor of CRCI is LA, which was reported among older adults in the community.[47,48] Few studies have examined the relationship between LAs and cognitive function in patients having cancer, and most studies have been conducted in community populations. Engaging in LAs in an enriched environment can increase brain-derived neurotrophic assessment and promote synaptogenesis.[49] LAs include cognitive activities, social activities, and physical activities. In our study, 41.53% of lung cancer patients did not engage in leisure activities, which may be explained by the low exercise compliance of lung cancer patients due to the disease and surgery. Cole[50] found that 58.1% of patients having cancer chose to reduce their exercise after diagnosis. Further, a cancer diagnosis threatens the social life of cancer

Table 3
The cutoff points of four inflammatory indicators.

Item	Cutoff point	AUC (95% CI)	Sensitivity	Specificity	Youden index
PNI[a]	49.78	0.600 (0.513–0.686)	0.71	0.54	0.25
PLR[a]	183.88	0.598 (0.510–0.685)	0.64	0.59	0.23
NLR	4.03	0.591 (0.492–0.691)	0.48	0.73	0.21
LMR	2.96	0.606 (0.521–0.691)	0.82	0.39	0.21

LMR, lymphocyte–monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.
[a] Indicates that there are missing values for the PNI (2 missing values), PLR (2 missing values). We have filled them using the multiple imputation.

Table 4
Association between CRCI and pain-fatigue-sleep disturbance-depression SC in lung cancer patients ($n = 378$).

Variates	OR (95% CI)	*P value*
Crude model		
Pain-fatigue-sleep disturbance-depression SC		
Low symptom burden	Ref	
High symptom burden	10.065 (4.138, 24.478)	0.001
Model 1		
Pain-fatigue-sleep disturbance-depression SC		
Low symptom burden	Ref	
High symptom burden	5.531 (2.133, 14.336)	<0.001

Crude model: with no adjustments for any covariates; Model 1: adjusted for covariates age, sex, smoking, drinking, diagnosed time, treatment, cancer stage, LA, work, income, education, cancer pathological type, marital status, BMI, LMR, NLR, PLR, PNI, operation history, anxiety, and nutrition status. And there are missing values for the BMI (10 missing values), PNI (2 missing values), PLR (2 missing values). We have filled them using the multiple imputation.
Abbreviation: SC (symptom cluster).

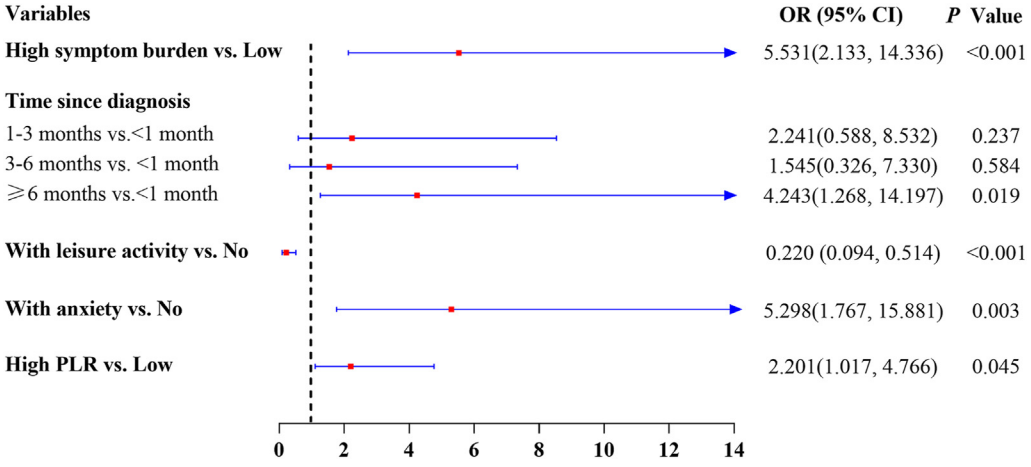

Fig. 2. Odds Ratios forest plot of multivariable logistic regression (N = 378).

patients, a group that faces stigma, discrimination, and exclusion; they may internalize stigma and develop feelings of guilt and shame, which can lead to avoidance of establishing new relationships, social isolation, reduced interest in life, and loneliness, resulting in a reduction in social and cognitive activities.[51]

4.3. Clinical implications

Lung cancer is a disease that affects a large number of people. As treatments other than chemotherapy can affect patients' cognitive function, our study included patients who received different treatments (including no treatment), rather than solely focusing on patients undergoing chemotherapy, as previous studies have done. Overall, our findings imply that the pain-fatigue-sleep disturbance-depression SC is associated with CRCI, which shows that the assessment of psychoneurological symptoms is important. Non-pharmacological interventions for SCs have been discussed. For example, acupoint massage and mindfulness-based stress reduction are effective in managing SCs based on the results of network meta-analysis and probability ranking.[52] An implication of this is that by assessing the SC early, clinicians can identify patients who are more likely to develop CRCI, and intervention in the SC may achieve timely and efficient management of CRCI. It also suggests that medical staff and caregivers should pay attention to the psychological status of patients having lung cancer and encourage them to maintain their hobbies and participate in social and physical activities, which are conducive to protecting their cognitive function.

4.4. Limitations

There are also limitations in this study. First, since the study is a cross-sectional study, it cannot infer causality and observe the changes in CRCI in patients having lung cancer. Future longitudinal studies can be conducted to understand the predictive significance of the pain-fatigue-sleep disturbance-depression SC for CRCI, explore the trends of CRCI in patients having lung cancer and determine the optimal timing of interventions. Second, the participants in this study come from one hospital, so the generalizability of the results in this study is limited. In addition, only patient self-report instruments were used. Future studies may combine subjective and objective instruments to jointly evaluate patients' CRCI and explore the mediating role of SCs between the inflammation and cognitive function of individuals, to better understand the mechanism of CRCI.

5. Conclusions

This study identified two classes of pain-fatigue-sleep disturbance-depression SCs, in which a high symptom burden is a risk factor for CRCI. Additionally, other factors, such as anxiety, a diagnosis made more than 6 months prior, LA, and high PLR, may also be of vital significance for CRCI. This study provides a new perspective on the clinical management of CRCI in patients. However, future large-scale prospective studies are needed to validate the findings of this study.

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CRediT author statement

Jiahui Luo and Ruiqi Liu: collected the questionnaire, performed the data analysis, drafted the manuscript. **Yuanyuan Luo and Qinghong**

Fang: collected the questionnaire. **Suting Liu and Zhihui Yang**: manuscript revision. **Jingxia Miao**: recruiting participants. **Lili Zhang**: study design. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have.

Declaration of competing interest

The authors declare no conflict of interest.

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Ethics statement

This study was approved by the Medical Ethics Committee of Nan Fang Hospital of Southern Medical University (IRB. NFEC-2020-281). Informed consent was obtained from all study participants.

Data availability statement

The data used in our study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2023.100200.

References

1. He S, Lim C, Dhillon HM, Shaw J. Australian oncology health professionals' knowledge, perceptions, and clinical practice related to cancer-related cognitive impairment and utility of a factsheet. *Support Care Cancer*. 2022. https://doi.org/10.1007/s00520-022-06868-z.
2. Brautigam L, Hill NL. Promoting cognitive health in older adult cancer survivors. *J Gerontol Nurs*. 2022;48(1):2–4. https://doi.org/10.3928/00989134-20211206-01.
3. Gates P, Krishnasamy M, Wilson C, et al. Cancer-related cognitive impairment in patients with newly diagnosed aggressive lymphoma undergoing standard chemotherapy: a longitudinal feasibility study. *Support Care Cancer*. 2022. https://doi.org/10.1007/s00520-022-07153-9.
4. Zheng R, Zhang S, Zeng H, et al. Cancer incidence and mortality in China, 2016. *Journal of the National Cancer Center*. 2022;2(1):1–9. https://doi.org/10.1016/j.jncc.2022.02.002.
5. Liu S, Yin N, Ma R, et al. Abnormal topological characteristics of brain white matter network relate to cognitive and emotional deficits of non-small cell lung cancer (NSCLC) patients prior to chemotherapy. *Int J Neurosci*. 2020:1–10. https://doi.org/10.1080/00207454.2020.1813130.
6. Eggen AC, Richard NM, Bosma I, et al. Factors associated with cognitive impairment and cognitive concerns in patients with metastatic non-small cell lung cancer. *Neurooncol Pract*. 2022;9(1):50–58. https://doi.org/10.1093/nop/npab056.
7. Takemura N, Ho MH, Cheung D, Lin CC. Factors associated with perceived cognitive impairment in patients with advanced lung cancer: a cross-sectional analysis. *Support Care Cancer*. 2022;30(11):9607–9614. https://doi.org/10.1007/s00520-022-07377-9.
8. Bray VJ, Dhillon HM, Vardy JL. Systematic review of self-reported cognitive function in cancer patients following chemotherapy treatment. *J Cancer Surviv*. 2018;12(4):537–559. https://doi.org/10.1007/s11764-018-0692-x.
9. Cerulla Torrente N, Navarro Pastor J, de la Osa Chaparro N. Systematic review of cognitive sequelae of non-central nervous system cancer and cancer therapy. *J Cancer Surviv*. 2020;14(4):464–482. https://doi.org/10.1007/s11764-020-00870-2.
10. Kim HJ, Jung SO, Kim H, Abraham I. Systematic review of longitudinal studies on chemotherapy-associated subjective cognitive impairment in cancer patients. *Psycho Oncol*. 2020;29(4):617–631. https://doi.org/10.1002/pon.5339.
11. Kim HJ, McGuire DB, Tulman L, Barsevick AM. Symptom clusters: concept analysis and clinical implications for cancer nursing. *Cancer Nurs*. 2005;28(4):270–282. https://doi.org/10.1097/00002820-200507000-00005. quiz 283-4.
12. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum*. 2001;28(3):465–470.
13. Armstrong TS. Symptoms experience: a concept analysis. *Oncol Nurs Forum*. 2003;30(4):601–606. https://doi.org/10.1188/03.ONF.601-606.
14. Hooke MC, Rodgers C, Taylor O, et al. Physical activity, the childhood cancer symptom cluster-leukemia, and cognitive function: a longitudinal mediation analysis. *Cancer Nurs*. 2018;41(6):434–440. https://doi.org/10.1097/NCC.0000000000000634.
15. Lee LJ, Ross A, Griffith K, Jensen RE, Wallen GR. Symptom clusters in breast cancer survivors: a latent class profile analysis. *Oncol Nurs Forum*. 2020;47(1). https://doi.org/10.1188/20.ONF.89-100.
16. Doong SH, Dhruva A, Dunn LB, et al. Associations between cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression in patients prior to breast cancer surgery. *Biol Res Nurs*. 2015;17(3):237–247. https://doi.org/10.1177/1099800414550394.
17. Hammer MJ, Cooper B, Paul SM, et al. Identification of distinct symptom profiles in cancer patients using a pre-specified symptom cluster. *J Pain Symptom Manag*. 2022;64(1):17–27. https://doi.org/10.1016/j.jpainsymman.2022.03.007.
18. Yannitsos D, Barbera L, Al-Rashdan A, Grendarova P. Diagnostic timelines and self-reported symptoms of patients with lung and gastrointestinal cancers undergoing radiation therapy. Retrospective case control study. *Support Care Cancer*. 2022;30(2):1501–1509. https://doi.org/10.1007/s00520-021-06522-0.
19. Hu Y, Wang Z. *Nursing Research*. Beijing: People's Medical Publishing House; 2017.
20. Nucci M, Mapelli D, Mondini S. Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clin Exp Res*. 2012;24(3):218–226. https://doi.org/10.3275/7800.
21. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321–336. https://doi.org/10.1016/s0261-5614(02)00214-5.
22. Yamamoto T, Kawada K, Obama K. Inflammation-related biomarkers for the prediction of prognosis in colorectal cancer patients. *Int J Mol Sci*. 2021;22(15):8002. https://doi.org/10.3390/ijms22158002.
23. Wagner LSJJB. Measuring patient self-reported cognitive function: qualitative findings and initial development of the functional assessment of cancer therapy–cognitive function (FACT-COG) instrument. *Joumal of Supportive Oncology*. 2009;7(6):W32–W39.
24. Dyk KV, Crespi CM, Petersen L, Ganz PA. Identifying cancer-related cognitive impairment using the FACT-cog perceived cognitive impairment. *JNCI Cancer Spectr*. 2020;4(1):pkz099. https://doi.org/10.1093/jncics/pkz099.
25. Root JC, Zhou X, Ahn J, et al. Association of markers of tumor aggressivity and cognition in women with breast cancer before adjuvant treatment: the Thinking and Living with Cancer Study. *Breast Cancer Res Treat*. 2022;194(2):413–422. https://doi.org/10.1007/s10549-022-06623-2.
26. Wang XS, Mendoza TR, Gao SZ, Cleeland CS. The Chinese version of the Brief Pain Inventory (BPI-C): its development and use in a study of cancer pain. *Pain (Amsterdam)*. 1996;67(2-3):407.
27. Wang XS, Hao XS, Wang Y, et al. Validation study of the Chinese version of the brief fatigue inventory (BFI-C). *J Pain Symptom Manag*. 2004;27(4):322–332. https://doi.org/10.1016/j.jpainsymman.2003.09.008.
28. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. *J Psychosom Res*. 2000;48(6):555–560. https://doi.org/10.1016/s0022-3999(00)00095-7.
29. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
30. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–1097. https://doi.org/10.1001/archinte.166.10.1092.
31. So WK, Marsh G, Ling WM, et al. Anxiety, depression and quality of life among Chinese breast cancer patients during adjuvant therapy. *Eur J Oncol Nurs*. 2010;14(1):17–22. https://doi.org/10.1016/j.ejon.2009.07.005.
32. Shen S, Cheng J, Li J, et al. Association of marital status with cognitive function in Chinese hypertensive patients: a cross-sectional study. *BMC Psychiatr*. 2022;22(1):504. https://doi.org/10.1186/s12888-022-04159-9.
33. Wang A, Zhao M, Luo J, Zhang T, Zhang D. Association of dietary vitamin K intake with cognition in the elderly. *Front Nutr*. 2022;9, 900887. https://doi.org/10.3389/fnut.2022.900887.
34. Huang Y, Zhang S, Shen J, et al. Association of plasma uric acid levels with cognitive function among non-hyperuricemia adults: a prospective study. *Clin Nutr*. 2022;41(3):645–652. https://doi.org/10.1016/j.clnu.2021.12.039.
35. Kim S. Determining the number of latent classes in single- and multiphase growth mixture models. *Struct Equ Model: A Multidiscip J*. 2014;21(2):263–279. https://doi.org/10.1080/10705511.2014.882690.
36. Sinha P, Calfee CS, Delucchi KL. Practitioner's guide to latent class analysis: methodological considerations and common pitfalls. *Crit Care Med*. 2021;49(1):e63–e79. https://doi.org/10.1097/CCM.0000000000004710.
37. Wang M, Bi X. *Latent Variable Modeling and Mplus Application Advanced*. Chongqing: Chongqing University Press; 2018.
38. Wang X, Duan B, Xia C, Wang A. Bibliometric analysis of subgroup studies of cancer symptom clusters. *J Nurs*. 2019;5(26):20–24.
39. Oppegaard K, Harris CS, Shin J, et al. Cancer-related cognitive impairment is associated with perturbations in inflammatory pathways. *Cytokine*. 2021;148, 155653. https://doi.org/10.1016/j.cyto.2021.155653.

40. Janelsins MC, Lei L, Netherby-Winslow C, et al. Relationships between cytokines and cognitive function from pre- to post-chemotherapy in patients with breast cancer. *J Neuroimmunol*. 2022;362, 577769. https://doi.org/10.1016/j.jneuroim.2021.577769.
41. Chen VC, Lin C, Hsiao H, et al. Effects of cancer, chemotherapy, and cytokines on subjective and objective cognitive functioning among patients with breast cancer. *Cancers (Basel)*. 2021;13(11):2576. https://doi.org/10.3390/cancers13112576.
42. George MA, Lustberg MB, Orchard TS. Psychoneurological symptom cluster in breast cancer: the role of inflammation and diet. *Breast Cancer Res Treat*. 2020;184(1):1–9. https://doi.org/10.1007/s10549-020-05808-x.
43. Li N, Lu J, Xia D, et al. Serum biomarkers predict adjuvant chemotherapy-associated symptom clusters in radical resected colorectal cancer patients. *J Gastrointest Oncol*. 2022;13(1):197–209. https://doi.org/10.21037/jgo-21-904.
44. Van der Willik KD, Koppelmans V, Hauptmann M, et al. Inflammation markers and cognitive performance in breast cancer survivors 20 years after completion of chemotherapy: a cohort study. *Breast Cancer Res*. 2018;20(1):135. https://doi.org/10.1186/s13058-018-1062-3.
45. Baratali L, Major K, Rouaud O, Draganski B. Cancer-related cognitive impairment in older adults. *Rev Med Suisse*. 2020;16(714):2172–2175.
46. Allemann-Su YY, Vetter M, Koechlin H, et al. Pre-surgery demographic, clinical, and symptom characteristics associated with different self-reported cognitive processes in patients with breast cancer. *Cancers (Basel)*. 2022;14(13). https://doi.org/10.3390/cancers14133281.
47. Liu X, Ruan Y, Huang L, et al. Cognitive leisure activity and all-cause mortality in older adults: a 4-year community-based cohort. *BMC Geriatr*. 2021;21(1):236. https://doi.org/10.1186/s12877-021-02180-3.
48. Zhu CE, Zhou L, Zhang X. Effects of leisure activities on the cognitive ability of older adults: a latent variable growth model analysis. *Front Psychol*. 2022;13, 838878. https://doi.org/10.3389/fpsyg.2022.838878.
49. Iizuka A, Murayama H, Machida M, et al. Leisure activity variety and brain volume among community-dwelling older adults: analysis of the neuron to environmental impact across generations study data. *Front Aging Neurosci*. 2021;13, 758562. https://doi.org/10.3389/fnagi.2021.758562.
50. Cole SF, Skaczkowski G, Wilson C. The role of illness perceptions and exercise beliefs in exercise engagement during treatment for cancer. *Support Care Cancer*. 2021;29(9):5065–5073. https://doi.org/10.1007/s00520-021-06055-6.
51. Sleight AG, Myers JS, Cook-Wiens G, et al. Loneliness as a risk factor for cancer-related cognitive impairment: a secondary data analysis from the Haze study. *Disabil Rehabil*. 2022:1–4. https://doi.org/10.1080/09638288.2022.2089738.
52. He C, Meng L, Liu H, et al. Effectiveness of non-pharmacological interventions on symptom clusters in cancer patients: a network meta-analysis. *Chinese General Practice*. 2022;19(25):2414–2420. https://doi.org/10.11124/JBISRIR-2016-2476.