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Time-dependent Patient-reported Outcomes As Predictors of the Survival of Patients With Lung Cancer

A Prospective Study

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Background: The importance of patient-reported outcomes (PROs) has been increasingly recognized in cancer care. No study has investigated how changes in PROs after completion of cancer treatment affect survival.
Objective: To investigate the predictive value of patient characteristics, including PROs, for cancer survival.
Methods: A total of 86 patients with a confirmed diagnosis of lung cancer were recruited. Data on PROs including sleep disturbance, anxiety, depression, fatigue, nausea, pain, weight loss, cough, good appetite, chest tightness, and ease of breathing were collected through self-reported questionnaires at 5 time points for each patient: before treatment and 6, 12, 24, and 48 weeks after treatment.
Results: Bivariate time-dependent Cox regression revealed the following variables to be significant: small-cell, stage IV lung cancer; pretreatment pneumonia; treatment type; and several PRO variables, including sleep disturbance (hazard ratio [HR] = 1.10, $P < .001$), anxiety (HR = 1.15, $P < .001$), depression (HR = 1.11, $P < .001$), weight loss (HR = 0.71, $P < .001$), chest tightness (HR = 0.83, $P = .029$), and ease of breathing (HR = 0.62, $P < .001$). Multivariable time-dependent Cox regression revealed that only stage IV (HR = 7.33, $P = .029$) and weight loss (HR = 0.76, $P = .006$) were significant variables associated with survival.
Conclusions: Patient-reported weight loss was independently associated with shortened survival in patients with lung cancer.
Implications for Practice: Health care professionals should closely monitor the PROs of patients with lung cancer. In cases of self-reported weight loss, further investigation and appropriate interventions are necessary.
What is Foundational: Patient-reported weight loss has been recognized in our research as a modifiable risk factor in lung cancer survival. PROs have potential predictive value in cancer survival.

Keywords: Lung cancer; Patient-reported outcome; Survival; Time-dependent Cox model

Background

Medical advances have led to improved long-term survival in patients with lung cancer.[1] Nonetheless, symptoms with a high burden, such as fatigue, loss of appetite, shortness of breath, cough, and pain, are nearly universal in patients with lung cancer.[2,3] Unmanaged symptoms can render patients unable to care for themselves and may lead to disorders in physical and psychosocial functioning.[4,5] Studies have shown that patients with lung cancer experience a higher symptom burden than patients with other cancers, which significantly compromises their quality of life (QOL).[3,6]

Accurate assessment of cancer symptoms is crucial for optimal patient care. Inaccurate evaluation of symptoms may lead to incorrect assumptions and subsequent changes in treatment, leading to treatment failure and detriments to patients' QOL. Studies have shown that patients tend to report a higher prevalence of cancer- and treatment-related symptoms than do physicians.[7,8] Therefore, the examination of patient-reported outcomes (PROs) is a comprehensive approach to patient assessment.[9,10] PROs are defined as health status reports directly from patients rather than from medical personnel or other individuals.[11] PROs include disease symptoms (eg, insomnia, fatigue, diarrhea, or pain), disorders in physical functioning (eg, difficulty walking up steps or difficulty opening a jar), symptoms related to mental health (eg, depression, fear, or anxiety), or overall QOL.[12] In patients with lung cancer, worsening of cancer-related symptoms is correlated with a lower response to cancer treatment.[13] PRO data have been increasingly considered as a part of the evaluation of the benefit/risk profile of lung cancer treatment.[14,15]

Research suggests that routine assessment of PROs is associated with a higher likelihood of discussing patient outcomes during consultations as well as improved symptom control, increased supportive care measures, and increased patient satisfaction.[16] In addition, PROs may have prognostic value for the survival of patients with lung cancer. Some studies have found that single-item QOL measures[17] or certain subscales of QOL

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independently predict cancer patient survival, such as physical function,[18] social function, pain,[19] nausea and vomiting, and appetite loss.[20] Notably, most studies have solely used baseline QOL data to predict cancer patient survival.[17,18,20] One study adopted a longitudinal design to examine whether changes in QOL scores from baseline to during chemotherapy serve as a potential prognostic factor for lung cancer patient survival.[19] However, the study findings for the predictive value of PROs for survival should be interpreted with caution because their PRO data were limited to the subscales of the QOL instrument used. Research supplemented with cancer-related symptom-specific measures is warranted to uncover additional factors with prognostic value for survival to improve prediction accuracy. Moreover, research has shown that patients reported dynamic changes in QOL after completion of cancer treatment.[21] To our knowledge, no study has investigated how changes in PROs posttreatment affect survival. In the present study, longitudinal data with time-varying measures of PROs (including QOL and symptom-specific measures) and confounders were used to understand how the link between PROs and survival unfolds over time.

Through control for time-varying covariates, this study investigated the predictive value of patient characteristics, including PROs, for patient survival. The study findings will serve as a basis for a larger scale study to improve the knowledge of the predictive importance of PROs for survival, which may guide care and the decision-making of patients and their families. In addition, the results will inform the need for routine PRO collection in clinical settings for integration into big data approaches.

Methods

Study Design

This longitudinal study examined the relationship between PROs and the survival of patients with lung cancer. It was conducted between January 1, 2012, and October 31, 2017.

Participants

Patients were considered eligible for this study if they were newly diagnosed as having lung cancer, had histopathologically confirmed lung cancer, were >20 years old, and were yet to start cancer treatment. Patients with psychiatric disorders, who were in a critical condition or who had already been receiving cancer treatment, were excluded. Patients were recruited from the inpatient (including hematology-oncology, radiation oncology, thoracic medicine, and thoracic surgery) and outpatient departments (including hematology-oncology, thoracic medicine, and thoracic surgery) of a teaching hospital in Northern Taiwan through convenience sampling. In both inpatient and outpatient settings, attending physicians first explained the study aims to potential participants, and interested patients were then approached by a trained research nurse in the hospital. During the initial contact, the nurse screened patients for eligibility and explained to them the study purpose, potential benefits and risks, and their rights (as research participants). Patients who met the inclusion criteria were enrolled into this study.

Data Collection

After participants' written consent was obtained, a questionnaire for background information collection and questionnaires for PRO data collection were administered at study entry. The same questionnaires were administered 6, 12, 24, and 48 weeks after cancer treatment to continue collecting data on PROs. Data were collected through face-to-face interviews conducted by the research nurse in a private, quiet environment at the hospital. The research nurse was trained by the investigator (W.-P.C.) in standardized question asking. Moreover, the research nurse was trained to modify their interactions with respondents to quickly identify respondent concerns and respond to them, which may have contributed to the low refusal rate. In case the respondent did not want to complete the interview, he/she was able to withdraw from the research at any time with no adverse effects on the services they were receiving from the hospital. Each interview took approximately 30 minutes. The first pretreatment interview was conducted after consent was obtained, and the subsequent interviews were conducted at follow-up at the hospital. The study was approved by the institutional review board of the selected hospital.

Questionnaires

A questionnaire was designed to collect background information, including demographics and disease characteristics, namely patient sex, age, educational background, marital status, religion, Charlson comorbidity index (CCI), cancer diagnosis, cancer stage, pretreatment pleural effusion, pretreatment pneumonia, and treatment type. The CCI is a weighted index that predicts the risk of death within 1 year of hospitalization for patients with specific comorbidities. Nineteen comorbidities are included in the index, with each comorbidity assigned a weight from 1 to 6 based on the estimated 1-year mortality hazard ratio (HR) from a Cox proportional hazard model. These weights are summed to produce the CCI score.[22]

To collect the PRO data of the patients, we administered the Pittsburgh Sleep Quality Index-Taiwanese version (PSQI-T), Hospital Anxiety and Depression Scale-Taiwanese version (HADS-T), Brief Fatigue Inventory-Taiwanese version (BFI-T), and Taiwanese version of the Functional Assessment of Cancer Therapy-Lung (FACT-L) cancer. The details of these scales are as follows:

1. The PSQI-T is a self-reported questionnaire containing 19 items related to patients' sleep quality in the past month. The items are divided into 7 dimensions, each scored on a scale of 0 to 3, with the total score ranging from 0 to 21. A higher score indicates more severe sleep problems. The Cronbach's α for the original scale is 0.83, and its test-retest reliability is 0.85.[23] The Cronbach's α of the PSQI-T is 0.90, and its test-retest reliability between 20 and 28 days is 0.91.[24]
2. The HADS-T comprises anxiety and depression subscales of 7 items each. The total score for each self-assessment subscale ranges from 0 to 21. A higher score indicates a higher degree of anxiety or depression. The Cronbach's α is 0.84 for the original anxiety subscale and 0.76 for the original depression subscale.[25] In this study, the Cronbach's α for the HADS-T was 0.71 for the anxiety subscale and 0.83 for the depression subscale.
3. The BFI-T contains 9 items and is divided into 2 parts. The first part assesses the effect of cancer and cancer therapy on patient fatigue, and the second part measures the effect of fatigue symptoms on patient QOL. The Cronbach's α is 0.96 for the original scale[26] and 0.89 for the BFI-T. The test-retest reliability (r) is 0.80.[27]
4. The FACT-L was developed by Cella et al[28,29] at Northwestern University in the United States. The FACT-L comprises the 27-item Functional Assessment of Cancer Therapy-General (FACT-G) and 9-item Lung Cancer Subscale. The FACT-G encompasses 4 aspects: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well-being (7 items), and the Lung Cancer Subscale consists of 9 additional concerns of patients with lung cancer (weight loss, shortness of breath, clarity of thought, cough, appetite, chest tightness, ease of breathing, and regret of smoking), wherein 2 questions are not scored (hair loss and clarity of thought). The 35 items in the FACT-L

are measured on a 5-point Likert scale ranging from absolutely not (0) to very much (4). Negatively worded items are reverse scored before the score is summed. The scores are then summed, with higher scores indicating higher QOL. The Chinese version of the FACT-L has been validated (Cronbach's $\alpha = 0.82$).[30]

Data Analysis

The HRs of patient survival were estimated using Cox regression with simultaneous adjustment for time-varying covariates, demographic characteristics, disease characteristics, and PROs.

Independent variables were analyzed using time-dependent Cox regression with adjustment for time-dependent covariates. The basic pretreatment independent variables selected for this study were sex, age, educational background, marital status, religion, CCI, cancer diagnosis, cancer stage, pretreatment pleural effusion, pretreatment pneumonia, and treatment type. The time-varying PRO variables were sleep disturbance, anxiety, depression, fatigue, nausea, pain, weight loss, cough, appetite, chest tightness, and ease of breathing. Data were analyzed in 2 stages. First, we analyzed all independent variables using bivariate Cox regression; subsequently, we analyzed all significant variables using multivariable Cox regression to identify the main predictors of survival. Each participant was tracked from the day of pathological diagnosis to death. Data analysis was conducted using SPSS for Windows 21.0 (SPSS, Chicago, IL).

Results

Basic Pretreatment Variables and PROs

In total, 101 patients were approached for study enrollment from January 1, 2012, to January 1, 2015. Fourteen patients refused to participate in the study and 1 patient felt physical discomfort during the initial contact; thus, she was not enrolled into the study. Finally, 86 patients with lung cancer who were yet

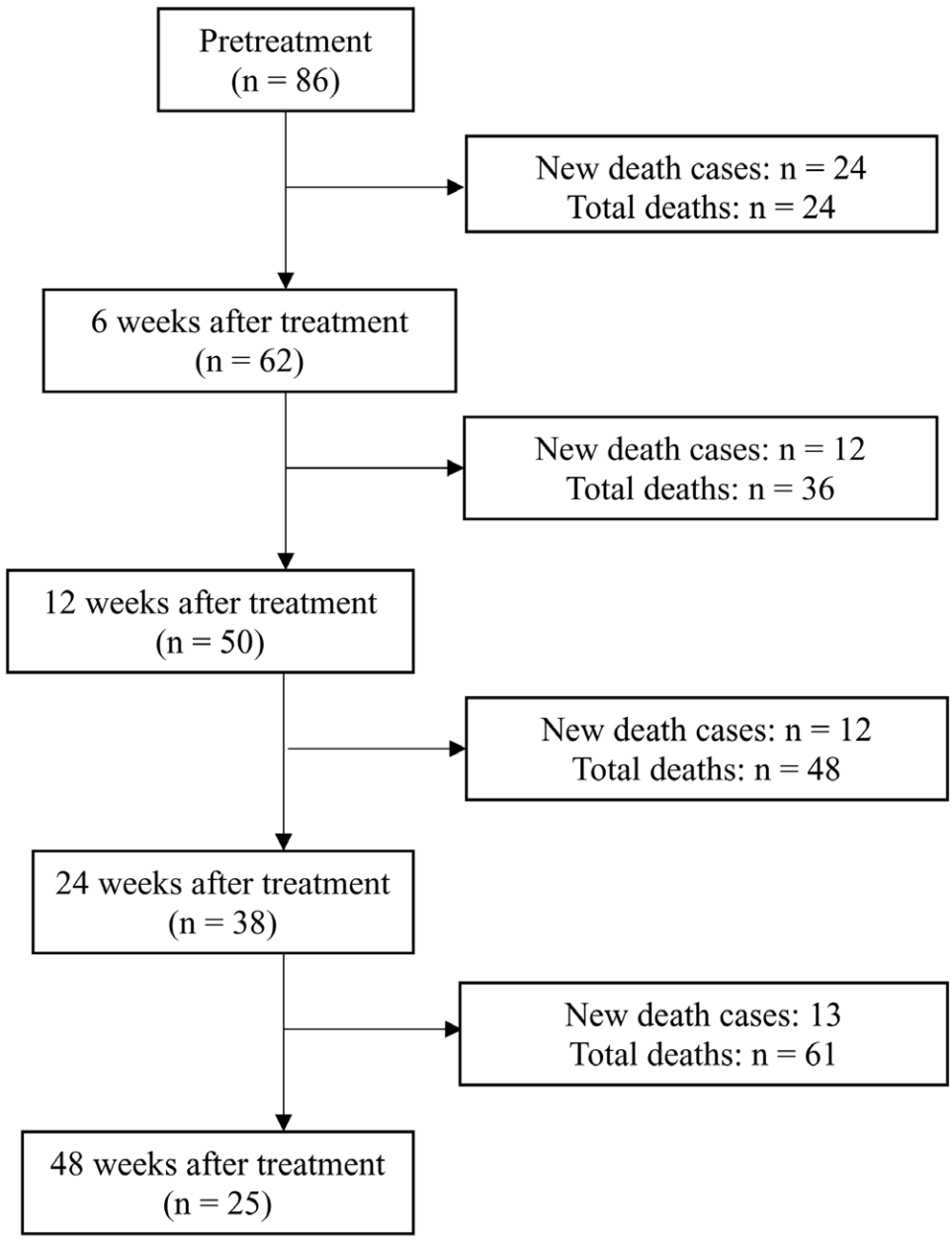

Figure. Patient death occurring during data collection.

Table 1.

Basic Pretreatment Variables and Self-reported Outcomes of Patients With Lung Cancer (N = 86)

Variable	N (%)
Sex	
Men	65 (75.6)
Women	21 (24.4)
Educational background	
Junior high school and below	59 (68.6)
Senior high school and vocational high school	18 (20.9)
Junior college and above	9 (10.5)
Marital status	
Married	71 (82.6)
Single	4 (4.7)
Divorced, separated, or widowed	11 (12.8)
Religion	
None	33 (38.4)
Buddhism or Taoism	51 (59.3)
Christianity	2 (2.3)
Cancer diagnosis	
Squamous cell carcinoma	23 (26.7)
Adenocarcinoma	47 (54.7)
Small-cell cancer	16 (18.6)
Cancer stage	
I or II	7 (8.1)
III	21 (24.4)
IV	58 (67.4)
Pretreatment pleural effusion	
No	65 (75.6)
Yes	21 (24.4)
Pretreatment pneumonia	
No	62 (72.1)
Yes	24 (27.9)
Type of treatment	
Chemotherapy	49 (57.0)
Surgery	8 (9.3)
Targeted oral therapy	23 (26.7)
Symptom management	6 (7.0)
Variable	**Mean ± SD**
Age	66.36 ± 11.14
CCI score	0.95 ± 1.27
Sleep disturbance	7.78 ± 3.38
Anxiety	4.92 ± 3.07
Depression	7.91 ± 3.93
Fatigue	3.44 ± 2.23
Nausea	3.69 ± 0.76
Pain	2.84 ± 1.35
Weight loss	1.72 ± 1.52
Cough	2.20 ± 1.18
Good appetite	1.65 ± 1.25
Chest tightness	2.69 ± 1.14
Ease of breathing	2.34 ± 0.95

Abbreviations: CCI, Charlson comorbidity index.

Table 2.

Summary of Cox Regression Analysis Results for the Risk of Death Based on Patient-reported Outcomes (N = 86)

	Bivariate		Multivariate	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex				
Men	1			
Women	1.00 (0.59-1.70)	.988		
Age	1.01 (0.99-1.03)	.454		
Educational background				
Junior high school and below	1			
Senior high school and vocational high school	0.65 (0.36-1.17)	.151		
Junior college and above	0.60 (0.27-1.32)	.200		
Marital status				
Married	1			
Single	1.09 (0.40-3.03)	.862		
Divorced, separated, or widowed	0.94 (0.48-1.83)	.846		
Religion				
None	1			
Buddhism or Taoism	1.21 (0.75-1.97)	.437		
Christianity	0.27 (0.04-1.98)	.197		
CCI score	1.03 (0.88-1.20)	.758		
Cancer diagnosis				
Squamous cell carcinoma	1		1	
Adenocarcinoma	0.80 (0.46-1.37)	.415	1.09 (0.54-2.17)	.814
Small-cell cancer	2.07 (1.05-4.09)	.037[a]	1.99 (0.89-4.42)	.093
Cancer stage				
I or II	1		1	
III	4.57 (1.05-19.89)	.043[a]	4.05 (0.65-25.23)	.134
IV	5.53 (1.33-22.96)	.018[a]	7.33 (1.23-43.82)	.029[a]
Pretreatment pleural effusion				
No	1			
Yes	0.89 (0.53-1.49)	.665		
Pretreatment pneumonia				
No	1		1	
Yes	2.04 (1.22-3.43)	.007[b]	1.74 (0.98-3.09)	.057
Type of treatment				
Chemotherapy	1		1	
Surgery	0.41 (0.15-1.16)	.093	1.25 (0.35-4.54)	.732
Targeted oral therapy	0.73 (0.43-1.25)	.255	0.71 (0.36-1.40)	.317
Symptom management	3.54 (1.46-8.59)	.005[b]	1.52 (0.56-4.10)	.413
PROs				
Sleep disturbance	1.10 (1.04-1.17)	<.001[c]	1.05 (0.97-1.13)	.253
Anxiety	1.15 (1.07-1.24)	<.001[c]	1.04 (0.94-1.16)	.421
Depression	1.11 (1.06-1.16)	<.001[c]	1.01 (0.94-1.09)	.794
Fatigue	1.08 (1.00-1.17)	.066		
Nausea[d]	0.90 (0.72-1.12)	.339		
Pain[d]	0.90 (0.78-1.05)	.198		
Weight loss[d]	0.71 (0.61-0.82)	<.001[c]	0.76 (0.63-0.93)	.006[b]
Cough[d]	0.85 (0.71-1.03)	.107		
Good appetite	0.96 (0.86-1.07)	.432		
Chest tightness[d]	0.83 (0.70-0.98)	.029[a]	1.05 (0.84-1.31)	.685
Ease of breathing	0.62 (0.50-0.76)	<.001[c]	0.79 (0.56-1.12)	.190

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; FACT-L, Functional Assessment of Cancer Therapy-Lung; HR, hazard ratio; PROs, patient-reported outcomes; QOL, quality of life.

[a]$P < .05$.

[b]$P < .01$.

[c]$P < .001$.

[d]As measured using the FACT-L and reverse scored before summing so that higher scores indicate higher QOL.

to start treatment were recruited. At the data collection points of 6, 12, 24, and 48 weeks after cancer treatment, 62, 50, 38, and 25 participants survived, respectively. Data were collected for all living patients at each time point; no data were missing (Figure). No refusal or withdrawal was noted.

The mean age of the participants was 66.36 ± 11.14 years, and the majority of the participants were men (75.6%), had completed only junior high school or a lower level of education (68.6%), were married (82.6%), and were Buddhists or Taoists (59.3%). More than half of the participants were diagnosed as having adenocarcinoma (54.7%), most had stage IV lung cancer (67.4%), and many exhibited no pretreatment pleural effusion or pneumonia (75.6%). Most were treated with chemotherapy (57.0%). The mean CCI was 0.95 ± 1.27. Regarding PROs, the mean PSQI-T score was 7.78 ± 3.38, the mean Hospital Anxiety and Depression Scale for Anxiety – Taiwan version score was 4.92 ± 3.07, the mean Hospital Anxiety and Depression Scale for Depression – Taiwan version score was 7.91 ± 3.93, and the mean BFI-T severity score was 3.44 ± 2.23. In the FACT-L, the mean scores of nausea, pain, weight loss, cough, appetite, chest tightness, and ease of breathing were 3.69 ± 0.76, 2.74 ± 1.35, 1.72 ± 1.52, 2.20 ± 1.18, 1.65 ± 1.25, 2.69 ± 1.14, and 2.34 ± 0.95, respectively (Table 1).

Predictors of Mortality in Patients With Lung Cancer

Table 2 presents the significant variables identified in bivariate analysis: cancer diagnosis, cancer stage, pretreatment pneumonia, treatment type, sleep disturbance, anxiety, depression, weight loss, chest tightness, and ease of breathing. We analyzed the predictive power of these 10 variables as well as their interrelationships to identify risk factors for mortality. Multivariable analysis revealed that stage IV cancer (HR = 7.33, $P = .029$) and patient-reported weight loss (HR = 0.76, $P = .006$) were significant mortality risk factors. The death risk associated with stage IV lung cancer was 7.33 times that associated with stage I or II lung cancer. The death risk was 0.76 times lower among patients who did not report substantial weight loss than in those who did.

Discussion

To our knowledge, this is the first study to investigate the association between changes in PROs after cancer treatment and survival periods among patients with lung cancer through consideration of time-varying covariates. The results of this study indicated that cancer diagnosis, cancer stage, pretreatment pneumonia, and treatment type as well as sleep disturbance, anxiety, depression, weight loss, chest tightness, and ease of breathing were significant predictors of survival in the patients with lung cancer. In the adjusted time-dependent Cox regression model, we discovered that only cancer stage and patient-reported weight loss were significant predictors of mortality among the patients with lung cancer.

Most studies have examined the predictors of cancer patient survival by using objective indicators, such as disease characteristics and biomedical measures, and only a few of them have based their assessments on PROs, which are considered increasingly important for identifying concerns that are often overlooked in routine practice.[9,10] Regarding objective predictors, consistent with previous research,[31,32] our study found that cancer stage was correlated with the survival of the patients with lung cancer. Regarding PROs, many studies have demonstrated that baseline QOL can predict overall survival in patients with lung cancer.[17,18,20] One longitudinal study indicated that physical functioning (at baseline), pain (at baseline and its change from baseline to cycle 1), and social function (change from baseline to cycle 2), as measured using the subscales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version, were prognostic factors for survival.[19] In our study, changes in PROs after cancer treatment were measured using the PSQI, BFI, HADS, and FACT-L; patient-reported weight loss was the only significant PRO predicting survival.

The extent of weight loss in patients with cancer is attributed to multiple factors, including tumor-related symptoms,[33] treatment-related side effects, side effects that impair oral intake,[34] and metabolic changes resulting from inflammation in response to the tumor or treatment.[35,36] Weight loss occurs in as many as half of patients with cancer[37]; a similar prevalence was reported specifically among patients with lung cancer.[38] Numerous studies have demonstrated that objectively measured weight loss is a major predictor of survival in patients with cancer, including breast, head and neck, colorectal, and gastric cancers.[39–41] However, limited information is available regarding the association between patient-reported weight loss and cancer patient survival. Our study filled the research gap by examining the predictive value of patient-reported weight loss for lung cancer patient survival. A previous study demonstrated that a discrepancy exists between the self-reported weight status and the actual body mass index of patients with cancer.[42] More research is required to compare the consequences of actual and self-reported weight loss in patients with cancer, and the results would inform comprehensive weight management interventions and support the predictive value of certain PROs for survival.

A major strength of our study is that PROs were assessed using a multidimensional QOL instrument and multiple questionnaires for symptoms, which would be more informative than using the global/subscale scores of a single QOL instrument. Moreover, through the inclusion of time-varying covariates in analyses, how the link between PROs and survival unfolds over time can be determined. This study has some limitations. First, the sample size was small, and the analysis performed in this study was limited to data from a single hospital. These observations raise concerns of generalizability. Our results require confirmation in larger scale studies. Second, the study results may have been confounded by some unmeasured variables, such as patients' pulmonary function, comorbidities, and lifestyle factors. In the future, researchers should conduct a comprehensive assessment with full adjustment of potential confounders so that the independent predictive power of PROs can be demonstrated. Finally, in the present study, the causative relationships between PROs and survival periods could not be examined due to the observational study design.

The study results have practical value because they improve health care workers' knowledge and awareness of the predictive importance of PROs for lung cancer survival. This is particularly useful for guiding patient assessment and care planning. For example, the subjective perception of weight loss should be assessed in routine follow-up in addition to objectively measured weight change. This is because patient-reported weight loss, which may sometimes indicate muscle mass loss even if the overall weight remains unchanged, has been proven to be an independent predictor of shortened patient survival. Health care workers can perform further investigation into the causes of self-reported weight loss and implement appropriate interventions.

Conclusions

The PROs of sleep disturbance, anxiety, depression, chest tightness, and ease of breathing were associated with survival periods of the studied patients with lung cancer. The adjusted time-varying regression model revealed that patient-reported weight loss was the only PRO that independently influenced patient survival. Our study results indicate that PROs may independently predict cancer patient survival. However, further studies with a large sample size are required to confirm the findings. Health care professionals should closely monitor the PROs of patients with lung cancer; this would provide valuable and complementary information for the survival prediction of patients with lung cancer. Including PROs in big data analysis may maximize the potential of the data to inform health care policy and delivery.

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