Original Article

Patient-reported impact of symptoms in lung cancer (PRISM-LC)

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Background: Individuals with lung cancer (LC) face a variety of symptoms that significantly impact their lives. We use extensive patient input to determine the relative importance and prevalence of these symptoms and identify which demographic features are associated with a higher level of disease burden.

Methods: We performed semi-structured qualitative interviews with participants with LC to identify potentially important symptoms. We then conducted a cross-sectional study, in which participants rated the relative importance of 162 individual symptoms covering 14 symptomatic themes. Participant responses were analyzed by age, sex, disability status, disease duration, LC stage, type of treatment received, and smoking history, among other categories.

Results: Our cross-sectional study had 139 participants with LC. The most prevalent symptomatic themes reported by this population were fatigue (85.5%), impaired sleep and daytime sleepiness (73.5%), and emotional issues (73.0%). The symptomatic themes that had the greatest average impact (on a scale of 0 to 4, with 4 being the most impactful) were social role dissatisfaction (1.67), inability to do activities (1.64), and fatigue (1.60). Disability status had the strongest association with symptomatic theme prevalence. LC stage (stage IV), receipt of therapy, and smoking experience were also associated with higher frequency of symptomatic themes.

Conclusions: Individuals with LC face diverse and disease-specific symptoms that affect their daily lives. Patient insight on the prevalence and relative importance of these symptoms is invaluable to advance meaningful therapeutic interventions.

Keywords: Lung cancer (LC); qualitative research; cross-sectional study; quality of life; patient-reported

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Introduction

Background

Lung cancer (LC) is the leading cause of cancer deaths worldwide (1). Most patients are diagnosed after showing clinical symptoms, at which point the disease has already progressed. Moreover, individuals with LC often experience a wide spectrum of symptoms that affect their physical, cognitive, emotional, and social health, with symptoms such as loss of appetite, fatigue, pain, dyspnea, and psychological distress reducing quality of life (QoL) the most (2-4). Such symptoms have been analyzed in large cross-sectional studies, such as a national study conducted with patients with advanced stage non-small cell LC in 2013 (n=450) (5). In this study, researchers investigated how symptomatic burden relates to (QoL) in those with LC (5). Other studies have looked at how features like disease duration, stage of disease, treatment characteristics, and surgery affect the QoL of patients with LC (2,3,6,7). These studies have examined the interrelationship between QoL and survival, suggesting improved management of fatigue and social support as impactful modalities for patient outcomes (2,3,6,7). Research has also been done to elicit the symptoms that cancer patients find important and to develop and validate patient-reported outcome measures, like the Functional Assessment of Cancer Therapy (FACT-G) scale and the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale, which may be used in oncology clinical trials (8,9). Although previous research has greatly contributed to the understanding of symptom impact on the lives of those with LC and has even led to the generation of useful outcome measures, a clearer understanding of how a patient's disease burden is affected by the many issues and symptoms that occur in LC is needed.

Highlight box

Key findings

- Patient interviews and cross-sectional study examined important symptoms in lung cancer (LC).
- Fatigue, sleep-related problems, & emotional issues were highly prevalent.
- Social dissatisfaction, activity limitations, & fatigue were highly impactful.
- Disability status was associated with higher symptom prevalence.

What is known and what is new?

- Studies on quality of life (QoL) in LC have previously identified numerous areas of health that affect individuals.
- As survival rates in LC increase, we need to understand what issues generate the highest disease burden in LC and how to lessen this burden. This study uses a LC patient-centric approach to elucidate the prevalence & impact of symptoms in all health domains, and correlate these symptoms with participant characteristics.

What is the implication, and what should change now?

- These results conceptualize disease burden and discern patient features that are associated with a higher level of LC symptomatic burden.
- Patient-reported data can improve treatment management and new therapy development.

Rationale and knowledge gap

In addition to the need for medical advances to improve the survival of patients with LC, it is equally imperative to develop meaningful symptom management therapies (2,5-7). Furthermore, as clinical trials are planned for individuals with LC, it is important to better understand the symptoms that are most prevalent and that have the greatest impact on patient lives, from the perspective of the patient. Research that focusses on well-defined groups of patients across multiple stages and types of LC are also of value. Such research is especially useful when future studies look to define particular clinical trial inclusion criteria, study LC disease progression longitudinally, and evaluate how individual or combinations of treatments affect distinct patient groups.

Objective

PRISM-LC aims to increase the understanding of which symptoms are most important to those with LC. Through this research, we leverage data collected from semi-structured participant interviews and a cross-sectional study involving 139 people with LC. Our research begins with qualitative interviews to obtain patients' direct input on symptoms of highest importance. This patient-derived input is then implemented in a cross-sectional study with a larger, diverse population that broadly captures individuals with LC from all stages. The prevalence, relative impact, and population impact (PIP) of the symptoms is determined, and the prevalence of symptomatic themes is correlated with participant demographic and clinical features. This paper adds large-scale patient insight to the existing body of literature regarding LC-specific symptoms, QoL, co-morbidities, and mortality. Moreover, this research suggests that relevant patient-reported outcomes data can add value to treatment management and the development of new

therapies. We present this article in accordance with the STROBE and COREQ reporting checklists (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-831/rc).

Methods

Study participants

Participants for this study were recruited from the University of Rochester Wilmot Cancer Institute (for phase 1 qualitative interviews) and the GO2 Foundation for Lung Cancer, Lung Cancer Registry (www.lungcancerregistry.org; for phase 2 cross-sectional study). All participants were (I) 18 years old or older, (II) had LC, (III) were able to speak, read, and understand English, and (IV) were able to provide informed consent.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All study activities for this research (STUDY00005663: LC-HI) were approved by the University of Rochester Institutional Review Board (RSRB). Informed consent was obtained from all individual participants. Participant interviews were conducted from August 2018–April 2019, and cross-sectional study data were collected from January 2021–February 2021.

Study design

Phase 1: LC qualitative interviews

We conducted 30–60-minute semi-structured, qualitative interviews with adults with LC to identify key symptoms of the disease that affect participants' daily lives. Prior to the commencement of qualitative interviews, potential participants had no relationship or involvement with the study team. They were approached in-person, with permission of the attending physician, during clinic visits at the University of Rochester. During the consent process, potential participants were given information regarding the purpose of the research, the potential benefits and risks of taking part in the study, the names and contact information of the research team, and the voluntary nature of the study. Potential participants were informed that they would be asked questions to pinpoint the symptoms of their disease that have the greatest impact on their daily lives.

During the interviews, we collected standard demographic information (age, sex, race) and asked open-ended questions regarding participants' physical health, mental/emotional health, and social wellness. In addition, we probed common physical burdens like fatigue, difficulty breathing, coughing, difficulty eating, and trouble doing household activities; mental/emotional issues like difficulty concentrating or thinking, fear, and anxiety; and social problems including impaired interactions with family or friends and decreased independence. Interview guides outlining the questions we asked were approved by the RSRB before the study and are included as a supplemental attachment (Appendix 1).

The patient interviews were conducted remotely and privately, with the patient (and sometimes a caregiver) and the researcher present. These interviews were audio-recorded via Zoom, a Health Insurance Portability and Accountability Act (HIPAA) compliant conferencing software. Interviews were conducted by one female clinical research coordinator with an undergraduate degree (C. Zizzi), who had previous experience in collecting, coding, and interpreting qualitative data from participants in other disease populations. The interviews were transcribed, analyzed, and coded to extract direct quotes that identified recurring symptoms, which were then grouped into higher-order symptomatic themes. Two authors, a female clinical research coordinator with an undergraduate degree and the male principal investigator with a doctorate and masters of clinical investigation (C. Zizzi and C. Heatwole), performed the transcript coding and subsequent analysis. Using previously proven qualitative framework methodology involving triangulation and investigator consensus, our analysis identified commonly mentioned symptoms and issues from participants (10-18). Interviews were performed until data saturation was reached (no new symptoms reported by participants); this approach was used to determine sample size (19).

Phase 2: national cross-sectional study of individuals with LC

After completing patient interviews, we executed a large online cross-sectional study of people with LC to investigate the prevalence and relative importance of the previously identified symptoms. Potential participants had no prior contact with the study team; these individuals responded to emails sent out by the GO2 Foundation's Lung Cancer Registry, which comprised 2,256 members as of January 2021. The emails contained a survey link that directed potential participants to the online survey platform. Participants read an information letter containing the details of the research and the research team, completed

an online consent form, and filled out a demographics survey prior to taking the symptom survey. The symptom survey included 162 individual symptoms that represented 14 symptomatic themes. Each symptom question inquired "how much does the following impact your life now?" Participants were provided a six-point Likert-type scale to record their responses. The Likert response options were (I) I don't experience this; (II) I experience this but it does not affect my life; (III) it affects my life a little; (IV) it affects my life moderately; (V) it affects my life very much; (VI) it affects my life severely. At the end, individuals were asked to list any other relevant symptoms that were not included in the survey and appraise their impact. The surveys were administered electronically via Research Electronic Data Capture (REDCap), and completion was anonymous and voluntary.

Statistical analyses

We calculated the prevalence for each symptom of inquiry in our survey. In addition, we computed the relative impact of each issue on subjects' QoL by assigning a numerical value to each of the survey responses such that I don't experience this =0; I experience this but it does not affect my life =0; It affects my life a little =1; It affects my life moderately =2; It affects my life very much =3; It affects my life severely =4. The average response value for those who experienced the symptom (options 2–6 on the Likert scale) was determined, and higher values indicate greater symptom impact.

PIP scores were calculated by multiplying the prevalence (expressed as a fraction) by the average impact (a value between 0–4). Thus, a PIP of 4 corresponds to the greatest severity of a symptom among those who experienced it; a PIP of 0 relates to no impact on the people who experienced it. The methods described here have been used in our previously published work (10-18).

We used Fisher's exact tests to compare the prevalence of each symptom across predefined groups categorized by age (above mean *vs.* below mean); sex (male *vs.* female); disability status (on disability *vs.* not on disability); employment status (on disability or not working/not on disability *vs.* employed full-time, part-time, or stay-at-home parent); education level (grade school, high school, technical degree, or none *vs.* college, master's, or doctorate); disease duration since first symptoms noticed (above mean *vs.* below mean); LC stage (I *vs.* II *vs.* III *vs.* IV); reception of surgery for LC (had surgery *vs.* did not have surgery); hospitalization due to LC (hospitalized *vs.* never hospitalized); reception of various treatments for LC, including chemotherapy, targeted therapy, and immunotherapy (has or had one of these treatments *vs.* has not had one of these treatments); place where treatment is/was received (academic/research medical center *vs.* local clinic or local hospital); distance to place of treatment (less than or equal to 50 miles *vs.* more than 50 miles); current remission status (in remission *vs.* not in remission); number of years smoking (has smoked *vs.* has never smoked; above mean *vs.* below mean for those who have smoked); and smoking packs per day and smoking pack-years for those who have smoked (above mean *vs.* below mean). To correct for multiple comparisons, the Benjamini-Hochberg procedure was used with a false discovery rate of 0.25 and 350 test statistics. The 350 P values were sorted from smallest to largest. Then, the largest value of i such that $P(i) \leq 0.05\ i/350$ was determined. The null hypotheses associated with the P values P(1), …, P(i) were rejected, resulting in 45 "discoveries."

Results

Phase 1: *LC qualitative interviews*

Out of a total of 29 adults with LC from University of Rochester clinics who were provided information about this study, 15 individuals participated in interviews. Of the individuals who elected not to be interviewed, 12 did not respond to a follow-up communication, one later stated that they were not interested, and one was not available due to poor health. During qualitative interviews, the 15 individuals who did participate provided 653 direct quotes identifying 282 distinct symptoms. Following analysis using proven qualitative framework methodology, 162 recurring and clinically meaningful symptoms were selected for inclusion in the survey.

The following is a representative example of how a participant quote was coded as a unique symptom: when a participant was asked, "*what type of functional limitations are most important to a patient with lung cancer?*" he/she responded "*I can't walk as far as I used to. I probably would not be able to walk a mile without getting out of breath.*" This quote was coded as "difficulty walking long distances" and classified into the symptomatic theme of "limitations with physical function."

The symptoms identified during qualitative interviews related to 14 symptomatic themes: fatigue, social role dissatisfaction, breathing difficulties, impaired body image,

impaired sleep and daytime sleepiness, difficulty thinking, limitations with physical function, gastrointestinal issues, social role limitations, emotional issues, pain, inability to do activities, communication difficulties, and choking or swallowing issues.

Phase 2: national cross-sectional study of individuals with LC

A total of 160 adults with LC opened and began the online LC cross-sectional survey. Of the 160 adults, 139 participants completed at least one demographic and one symptom question, satisfying our minimum criteria for inclusion in the data analysis of the study. These participants represented 31 U.S. states and were 17.3% male and 82.0% female (0.7% preferred not to answer). The mean participant age was 60.6±11.4 years, with ages ranging from 30 to 86 years. The largest percentage of participants identified as white (94.2%), and the vast majority of people were non-Hispanic/Latino (98.5%). In addition, most participants, 74.1%, had a college degree or higher. Employed individuals (those working full-time, part-time, or as a stay-at-home parent) made up 35.2% of the population. Among those who were unemployed, the largest groups were retired individuals (41.0%) and individuals on disability (20.9%).

The clinical characteristics of the study population were as follows: (I) 65.2% of participants had stage IV LC, (II) 97.9% of participants had non-small cell LC, of which 85.2% had adenocarcinoma, (III) the majority of people (57.3%) were involved in a current treatment with the goal of living longer (as opposed to feeling better or being cured), and (IV) slightly more than half of the individuals (51.4%) were receiving treatment at academic/research institutions.

Full details regarding the demographics, disease characterization, and treatment of the participants are provided in *Table 1*. An outline of our study activities and results is provided in *Figure 1*.

Prevalence of symptomatic themes and symptoms

Among the 14 symptomatic themes included in the cross-sectional study survey, the symptomatic themes with the greatest prevalence (>70%) in those with LC were fatigue (85.5%), impaired sleep and daytime sleepiness (73.5%), emotional issues (73.0%), and limitations with physical function (72.8%). The most prevalent individual symptoms (>80%) were fear of worsening disease (91.7%), tiredness (87.6%), decreased stamina (82.5%), general fatigue (81.0%), and fatigue after physical activity (80.9%).

Average life impact of symptomatic themes and symptoms

Average life impact scores (on a scale of 0–4) were greatest for the following symptomatic themes: social role dissatisfaction (1.67), inability to do activities (1.64), and fatigue (1.60). Average impact scores were highest for the following individual symptoms: difficulty running (2.04), impaired sexual function (1.93), fear of worsening disease (1.86), and anxiety (1.82).

The prevalence and average impact scores for the 14 symptomatic themes are illustrated in *Figure 2*.

PIP of symptomatic themes and symptoms

The themes with the maximum PIP, which is a summary statistic encompassing both prevalence and average impact of symptoms, were fatigue (1.37), emotional issues (1.12), limitations with physical function (1.12), and impaired sleep and daytime sleepiness (1.05). The distinct symptoms with highest PIP were fear of worsening disease (1.71), difficulty running (1.56), anxiety (1.45), and inability to do things previously done (1.38).

Table S1 provides the prevalence, average life impact, and PIP of all 162 symptoms.

Breakdown of symptomatic themes by demographic and clinical category

Symptoms and symptomatic themes significantly differed in prevalence among subgroups, as displayed in *Tables 2-22*. The prevalence of symptomatic themes varied depending on individual's age, educational level, employment status, LC phenotype, and LC treatment level.

The stage of LC affected the frequency of several symptomatic themes, with the most prominent difference between individuals with stage I and stage IV LC. Those with stage IV were more likely to experience higher prevalence of seven of the 14 symptomatic themes: social role limitations, emotional issues, pain, gastrointestinal issues, impaired body image, fatigue, and social role dissatisfaction.

Participants younger than the mean age of 60.6 years were more likely to report impaired body image and

Table 1 Demographic information from cross-sectional study

Clinical characteristics	Value [n=139 (%)]
Sex	
Male	24 (17.3)
Female	114 (82.0)
Prefer not to answer	1 (0.7)
Age, years	
Mean ± SD	60.6±11.4
Range	30–86
Race	
Asian	2 (1.4)
Black/African American	3 (2.2)
White	130 (94.2)
Other	3 (2.2)
Hispanic or Latino	
Yes	2 (1.5)
No	134 (98.5)
Number of U.S. states represented	31
Location of residence	
Rural	24 (17.3)
Suburb of small city less than 1 million people	27 (19.4)
Suburb of big city more than 1 million people	37 (26.6)
Small city less than 1 million people	32 (23.0)
Big city more than 1 million people	19 (13.7)
Employment status	
Full-time	29 (20.9)
Part-time	13 (9.3)
On disability	29 (20.9)
Not working/not on disability	3 (2.2)
Retired	57 (41.0)
Stay-at-home parent	7 (5.0)
Other	1 (0.7)
Education completed	
Grade school	1 (0.7)
High school	25 (18.0)
Technical degree	10 (7.2)
College	57 (41.0)
Master's or Doctorate	46 (33.1)

Table 1 (*continued*)

Table 1 (*continued*)

Clinical characteristics	Value [n=139 (%)]
Months since first symptoms were noticed	
Mean ± SD	49.2±55.2
Range	0–480
Months since receiving diagnosis	
Mean ± SD	49.3±53.4
Range	1–480
Lung cancer stage	
I	20 (14.5)
II	6 (4.3)
III	20 (14.5)
IV	90 (65.2)
I don't know	2 (1.5)
Ever had surgery to treat lung cancer	
Yes	66 (47.8)
No	72 (52.2)
Lung cancer spread to another location	
Yes	96 (69.6)
No	40 (29.0)
I don't know	2 (1.4)
Lung cancer type	
Non-small cell lung cancer	135 (97.9)
Other	1 (0.7)
I don't know	2 (1.4)
Type of non-small cell lung cancer	
Adenocarcinoma	115 (85.2)
Squamous cell carcinoma	9 (6.7)
Adenosquamous carcinoma	3 (2.2)
Other	1 (0.7)
I don't know	7 (5.2)
Received chemotherapy (e.g., Carboplatin, Cisplatin, Pemetrexed, Paclitaxel, Docetaxel, Nab-paclitaxel, Gemcitabine, Etoposide)	
Yes	79 (56.8)
No	60 (43.2)

Table 1 (*continued*)

Table 1 (*continued*)

Clinical characteristics	Value [n=139 (%)]
Received targeted therapy (e.g., Erlotinib, Osimertinib, Alectinib, Lorlatinib, Crizotinib, Dabrafenib + Trametinib)	
Yes	57 (41.0)
No	80 (57.6)
I don't know	2 (1.4)
Received immunotherapy, (e.g., Pembrolizumab, Nivolumab, Ipilimumab)	
Yes	47 (34.3)
No	90 (65.7)
Goal of current treatment	
To cure	16 (11.6)
To live longer	79 (57.3)
To feel better	1 (0.7)
Other	1 (0.7)
I am not receiving treatment	38 (27.5)
I don't know	3 (2.2)
Place of oncology treatment	
Academic/research medical center	71 (51.4)
Local hospital	31 (22.5)
Local clinic	27 (19.6)
Other	9 (6.5)
Distance to place of oncology treatment	
Less than 20 miles	83 (61.0)
20 to 50 miles	30 (22.1)
More than 50 miles	23 (16.9)
Currently in remission	
Yes	65 (47.1)
No	60 (43.5)
I don't know	13 (9.4)
Hospitalized due to lung cancer	
Yes	91 (66.0)
No	46 (33.3)
I don't know	1 (0.7)
Ever smoked	
Yes	70 (50.7)
No	68 (49.3)
Total years smoked for all (smokers and non-smokers), years	
Mean ± SD	14.0±15.7
Range	0.0–47.0
Total years smoked for smokers only, years	
Mean ± SD	26.5±11.7
Range	2.0–47.0
Packs smoked per day for all (smokers and non-smokers), packs/day	
Mean ± SD	0.6±0.7
Range	0.0–2.0
Packs smoked per day for smokers only, packs/day	
Mean ± SD	1.1±0.5
Range	0.1–2.0
Smoking pack-years for all (smokers and non-smokers)	
Mean ± SD	15.8±20.4
Range	0.0–80.0
Smoking pack-years for smokers only	
Mean ± SD	30.9±18.5
Range	1.0–80.0

Demographic and clinical characteristics of LC sample cohort, given as number of respondents and percentage of respondents in each category. Percents are normalized for the number of respondents to each demographic question (omitted responses not included). SD, standard deviation; LC, lung cancer.

emotional issues. Participants with an education level below a college degree and/or who were on disability also showed higher frequency of several symptoms. Participants with lower education levels indicated a higher prevalence of breathing difficulties and pain, and participants who were on disability showed higher prevalence of nine symptomatic themes: inability to do activities, emotional issues, impaired sleep and daytime sleepiness, breathing difficulties, communication difficulties, social role limitations, impaired body image, pain, and gastrointestinal issues.

Those who were currently being treated for LC were more likely to express higher frequency of five symptomatic themes: impaired body image, emotional issues, social role dissatisfaction, social role limitations, and fatigue. Gastrointestinal issues and difficulty thinking were more prevalent among chemotherapy recipients. Impaired body

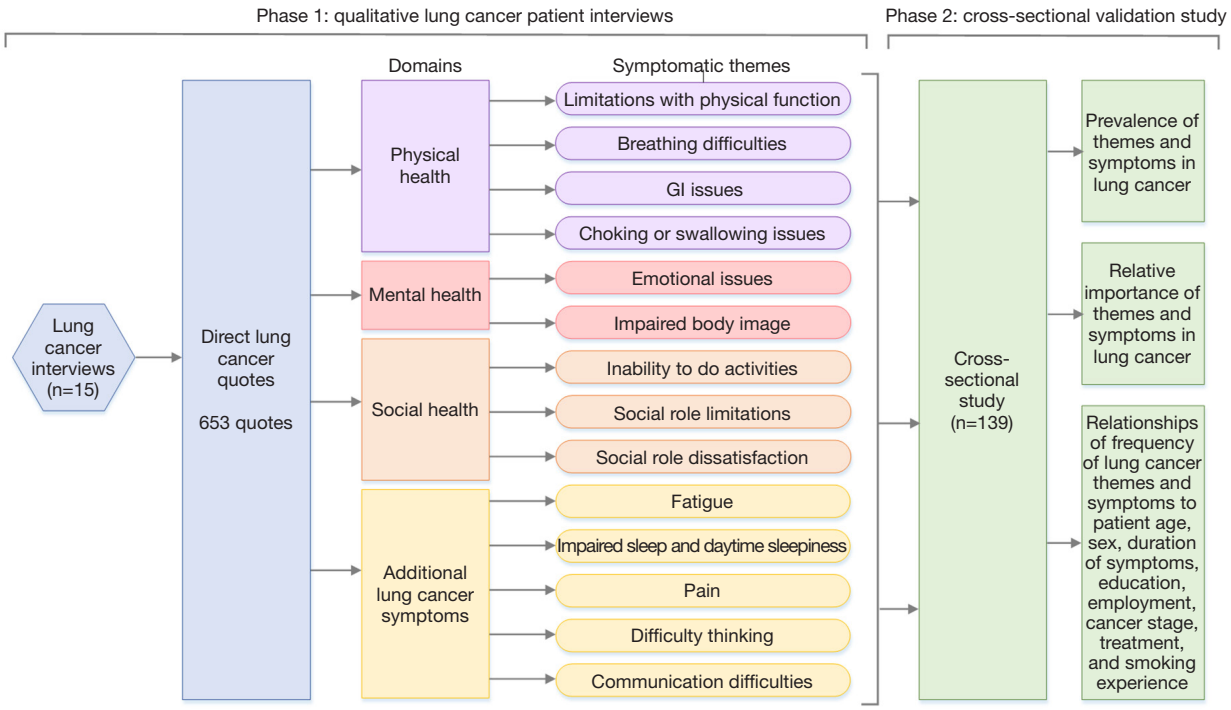

Figure 1 Overview of study activities. Study activities (qualitative interviews and cross-sectional study) to identify symptoms of importance to individuals with LC. GI, gastrointestinal; LC, lung cancer.

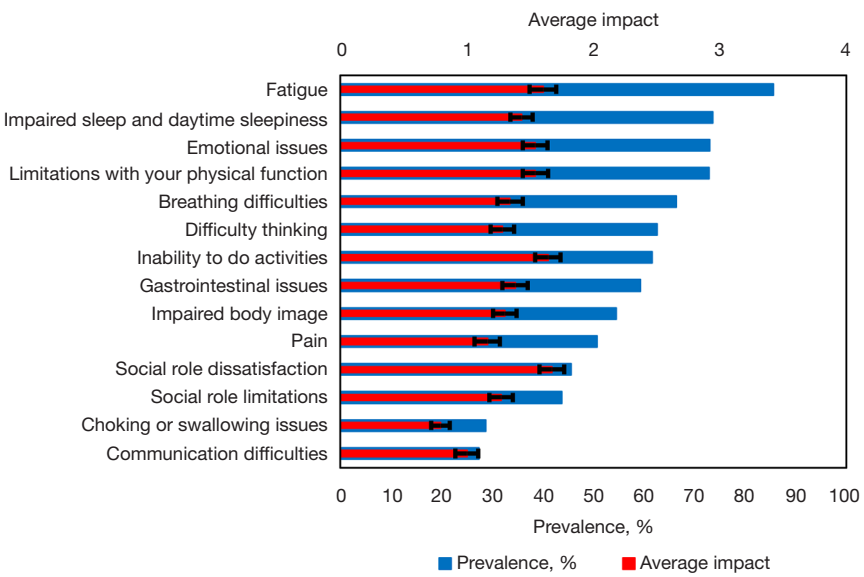

Figure 2 Prevalence and average impact of symptomatic themes. Prevalence (blue bars) values are on the lower x-axis (ranging between 0–100%), and average impact values (red bars) are on the upper x-axis (ranging between 0–4). Error bars on impact values are ±1 standard error.

Table 2 Overall prevalence and average impact of symptomatic themes

Theme	Overall prevalence (%) in full sample	Average impact (0–4) in full sample
Fatigue	85.5	1.60
Social role dissatisfaction	45.5	1.67
Breathing difficulties	66.4	1.34
Impaired body image	54.5	1.30
Impaired sleep and daytime sleepiness	73.5	1.43
Difficulty thinking	62.5	1.28
Limitations with your physical function	72.8	1.54
Gastrointestinal issues	59.3	1.38
Social role limitations	43.7	1.27
Emotional issues	73.0	1.54
Pain	50.7	1.16
Inability to do activities	61.6	1.64
Communication difficulties	27.4	1.00
Choking or swallowing issues	28.7	0.79

Prevalence (%) and average impact (0–4) of symptomatic themes evaluated in the full cross-sectional study sample (n=139).

image and emotional issues were more prevalent among targeted therapy recipients.

A history of smoking and the number of pack-years smoked was related to the prevalence of symptomatic themes. Compared to those who claimed no smoking, participants who smoked showed a higher prevalence of limitations with physical function and choking or swallowing issues. In addition, individuals who smoked above the mean number of pack-years (32.2 pack-years) displayed higher prevalence of breathing difficulties.

The report of impaired body image and social role limitations had the most widespread association with patient clinical state and other markers of disease burden. Specifically, impaired body image was linked with age, disability status, LC stage, surgery to treat LC, receiving targeted therapy, currently getting treatment, and remission status. Similarly, social role limitations was associated with disability status, employment status, LC stage, surgery to treat LC, currently getting treatment, and remission status.

There were no statistically significant differences in symptom prevalence on the basis of sex, disease duration, place of oncology treatment, or distance to place of oncology treatment.

Table 3 Results of subgroup analysis by sex

Theme	Prevalence (%)		P value
	Male	Female	
Fatigue	79.2	86.7	0.35
Social role dissatisfaction	43.5	45.5	1.0
Breathing difficulties	66.7	66.1	1.0
Impaired body image	54.2	55.1	1.0
Impaired sleep and daytime sleepiness	75.0	73.0	1.0
Difficulty thinking	54.2	64.0	0.49
Limitations with physical function	70.8	73.0	0.81
GI issues	45.8	61.8	0.17
Social role limitations	33.3	45.5	0.36
Emotional issues	66.7	74.1	0.46
Pain	58.3	48.7	0.50
Inability to do activities	62.5	61.1	1.0
Communication difficulties	29.2	27.0	0.81
Choking or swallowing issues	20.8	30.3	0.46

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by sex. GI, gastrointestinal.

Table 4 Results of subgroup analysis by age

Theme	Prevalence (%)		P value
	Below mean age (≤60.6 years)	Above mean age (>60.6 years)	
Fatigue	91.9	80.3	0.087
Social role dissatisfaction	54.1	45.9	0.083
Breathing difficulties	62.3	69.7	0.37
Impaired body image	70.5	41.1	0.0009*
Impaired sleep and daytime sleepiness	77.1	70.7	0.44
Difficulty thinking	70.5	56.0	0.11
Limitations with physical function	73.8	72.0	0.85
GI issues	62.3	56.8	0.60
Social role limitations	50.8	37.8	0.16
Emotional issues	85.5	62.7	0.0035*
Pain	56.5	46.0	0.23
Inability to do activities	64.5	59.2	0.60
Communication difficulties	31.2	24.3	0.44
Choking or swallowing issues	24.6	32.0	0.45

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by age. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 5 Results of subgroup analysis by disability status

Theme	Prevalence (%)		P value
	Not on disability (working full-time, working part-time, not working/not on disability, retired, student, stay-at-home parent, other)	On disability	
Fatigue	83.5	93.1	0.25
Social role dissatisfaction	40.6	64.3	0.033
Breathing difficulties	61.5	85.7	0.015*
Impaired body image	49.1	75.0	0.019*
Impaired sleep and daytime sleepiness	68.5	92.9	0.0081*
Difficulty thinking	58.3	78.6	0.052
Limitations with physical function	69.4	85.7	0.099
GI issues	54.2	78.6	0.030*
Social role limitations	38.3	64.3	0.018*
Emotional issues	67.6	93.1	0.0047*
Pain	45.4	71.4	0.019*
Inability to do activities	55.1	86.2	0.0023*
Communication difficulties	22.4	46.4	0.017*
Choking or swallowing issues	27.8	32.1	0.65

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by disability status. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 6 Results of subgroup analysis by employment status

Theme	Prevalence (%)		P value
	Employed full-time, part-time, or stay-at-home parent	On disability or not working/ not on disability	
Fatigue	83.7	87.5	0.78
Social role dissatisfaction	36.7	64.5	0.022*
Breathing difficulties	51.0	80.7	0.0094*
Impaired body image	57.1	71.0	0.24
Impaired sleep and daytime sleepiness	65.3	90.3	0.016*
Difficulty thinking	69.4	74.2	0.80
Limitations with physical function	61.2	80.7	0.086
GI issues	53.1	71.0	0.16
Social role limitations	34.7	61.3	0.023*
Emotional issues	81.6	90.6	0.35
Pain	44.9	64.5	0.11
Inability to do activities	51.0	81.3	0.0091*
Communication difficulties	22.5	41.9	0.082
Choking or swallowing issues	18.4	29.0	0.29

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by employment status. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 7 Results of subgroup analysis by education level

Theme	Prevalence (%)		P value
	Higher (College, Master's or Doctorate)	Lower (Grade school, High school, Technical degree, none)	
Fatigue	83.5	91.4	0.40
Social role dissatisfaction	43.6	51.5	0.55
Breathing difficulties	59.2	88.2	0.0016*
Impaired body image	55.5	51.5	0.84
Impaired sleep and daytime sleepiness	68.9	87.9	0.041
Difficulty thinking	59.2	72.7	0.22
Limitations with physical function	69.9	81.8	0.26
GI issues	59.8	57.6	0.84
Social role limitations	43.6	44.1	1.0
Emotional issues	72.6	74.3	1.0
Pain	44.6	68.6	0.018*
Inability to do activities	57.3	74.3	0.11
Communication difficulties	24.8	35.3	0.27
Choking or swallowing issues	24.5	41.2	0.080

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by education level. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 8 Results of subgroup analysis by months since first noticing symptoms

Theme	Prevalence (%)		P value
	Below mean (≤49.2 months)	Above mean (>49.2 months)	
Fatigue	86.5	84.6	0.79
Social role dissatisfaction	45.5	44.4	1.0
Breathing difficulties	67.4	63.2	0.68
Impaired body image	56.2	58.3	0.84
Impaired sleep and daytime sleepiness	77.5	67.6	0.27
Difficulty thinking	60.7	73.0	0.22
Limitations with physical function	71.9	73.0	1.0
GI issues	55.1	66.7	0.32
Social role limitations	43.8	44.4	1.0
Emotional issues	77.8	73.0	0.65
Pain	53.9	46.0	0.44
Inability to do activities	60.0	63.2	0.84
Communication difficulties	22.5	38.9	0.077
Choking or swallowing issues	28.1	24.3	0.83

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by months since first noticing symptoms. GI, gastrointestinal.

Table 9 Results of subgroup analysis by stage of lung cancer

Theme	Prevalence (%)				P value (I *vs.* II)	P value (I *vs.* III)	P value (I *vs.* IV)	P value (II *vs.* III)	P value (II *vs.* IV)	P value (III *vs.* IV)
	I	II	III	IV						
Fatigue	70.0	83.3	80.0	91.0	1.0	0.72	0.021*	1.0	0.46	0.23
Social role dissatisfaction	25.0	40.0	36.8	52.9	0.60	0.50	0.028*	1.0	0.67	0.31
Breathing difficulties	60.0	100.0	70.0	65.9	0.13	0.74	0.61	0.28	0.17	0.80
Impaired body image	31.6	40.0	35.0	65.5	1.0	1.0	0.0093*	1.0	0.35	0.021*
Impaired sleep and daytime sleepiness	65.0	66.7	65.0	80.5	1.0	1.0	0.15	1.0	0.60	0.15
Difficulty thinking	66.7	50.0	55.0	66.7	0.65	1.0	0.20	1.0	1.0	0.44
Limitations with physical function	66.7	60.0	75.0	75.9	1.0	0.50	0.17	1.0	0.63	1.0
GI issues	30.0	60.0	60.0	66.7	0.31	0.11	0.0045*	1.0	1.0	0.61
Social role limitations	5.0	40.0	31.6	54.6	0.091	0.044	<0.0001*	1.0	0.66	0.081
Emotional issues	45.0	60.0	65.0	82.0	0.64	0.34	0.0013*	1.0	0.24	0.13
Pain	35.0	60.0	55.0	54.6	0.36	0.34	0.0013*	1.0	1.0	1.0
Inability to do activities	50.0	83.3	60.0	64.0	0.20	0.75	0.14	0.38	0.66	0.80
Communication difficulties	20.0	40.0	30.0	28.4	0.56	0.72	0.31	1.0	0.63	1.0
Choking or swallowing issues	55.0	40.0	30.0	22.7	0.64	0.20	0.58	1.0	0.59	0.56

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by stage of lung cancer. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 10 Results of subgroup analysis by surgery to treat cancer

Theme	Ever had surgery to treat cancer?		
	Prevalence (%)		P value
	Yes	No	
Fatigue	80.3	90.1	0.15
Social role dissatisfaction	40.6	49.3	0.38
Breathing difficulties	72.7	60.0	0.15
Impaired body image	42.4	66.2	0.0090*
Impaired sleep and daytime sleepiness	69.7	76.8	0.44
Difficulty thinking	57.6	66.7	0.29
Limitations with physical function	66.7	78.3	0.18
GI issues	48.5	69.1	0.022*
Social role limitations	33.9	53.6	0.025*
Emotional issues	66.7	80.0	0.084
Pain	43.9	56.5	0.17
Inability to do activities	56.1	66.2	0.29
Communication difficulties	25.0	28.6	0.70
Choking or swallowing issues	33.9	22.9	0.18

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by surgery to treat cancer. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 11 Results of subgroup analysis by reception of chemotherapy

Theme	Received chemotherapy? (e.g., Carboplatin, Cisplatin, Pemetrexed, Paclitaxel, Docetaxel, Nab-paclitaxel, Gemcitabine, Etoposide)		
	Prevalence (%)		P value
	Yes	No	
Fatigue	89.7	80.0	0.14
Social role dissatisfaction	50.7	39.0	0.22
Breathing difficulties	71.4	60.0	0.20
Impaired body image	54.7	54.2	1.0
Impaired sleep and daytime sleepiness	75.0	71.7	0.70
Difficulty thinking	71.1	51.7	0.032*
Limitations with physical function	80.3	63.3	0.034*
GI issues	68.0	48.3	0.023*
Social role limitations	52.0	33.3	0.037*
Emotional issues	75.3	70.0	0.56
Pain	55.8	44.1	0.23
Inability to do activities	66.7	55.0	0.22
Communication difficulties	32.0	21.7	0.24
Choking or swallowing issues	29.0	28.3	1.0

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by reception of chemotherapy. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 12 Results of subgroup analysis by reception of targeted therapy

Theme	Received targeted therapy? (e.g., Erlotinib, Osimertinib, Alectinib, Lorlatinib, Crizotinib, Dabrafenib + Trametinib)		
	Prevalence (%)		P value
	Yes	No	
Fatigue	93.0	79.8	0.048*
Social role dissatisfaction	48.2	42.1	0.60
Breathing difficulties	57.1	73.4	0.064
Impaired body image	67.3	45.5	0.014*
Impaired sleep and daytime sleepiness	72.7	74.7	0.84
Difficulty thinking	60.0	63.3	0.72
Limitations with physical function	67.3	76.0	0.33
GI issues	67.3	46.2	0.15
Social role limitations	47.3	39.7	0.48
Emotional issues	83.9	64.6	0.018*
Pain	49.1	51.9	0.86
Inability to do activities	58.9	62.5	0.72
Communication difficulties	21.4	31.2	0.24
Choking or swallowing issues	21.4	34.6	0.12

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by reception of chemotherapy. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 13 Results of subgroup analysis by reception of immunotherapy

Theme	Received immunotherapy? (e.g., Pembrolizumab, Nivolumab, Ipilimumab)		
	Prevalence (%)		P value
	Yes	No	
Fatigue	84.8	85.6	1.0
Social role dissatisfaction	55.6	39.1	0.096
Breathing difficulties	73.9	61.8	0.18
Impaired body image	60.0	51.1	0.36
Impaired sleep and daytime sleepiness	80.0	70.8	0.30
Difficulty thinking	66.7	59.6	0.46
Limitations with physical function	84.4	66.3	0.040*
GI issues	60.0	59.1	1.0
Social role limitations	55.6	37.5	0.064
Emotional issues	71.7	74.2	0.84
Pain	63	43.2	0.045*
Inability to do activities	71.7	55.6	0.094
Communication difficulties	31.1	25.0	0.54
Choking or swallowing issues	28.9	28.1	1.0

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by reception of targeted therapy. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 14 Results of subgroup analysis by current treatment

Theme	Currently getting treatment?		P value
	Prevalence (%)		
	Yes	No	
Fatigue	90.1	73.0	0.026*
Social role dissatisfaction	53.1	25.0	0.0057*
Breathing difficulties	65.0	70.3	0.68
Impaired body image	65.0	27.0	<0.0001*
Impaired sleep and daytime sleepiness	75.8	67.6	0.38
Difficulty thinking	65.7	54.1	0.24
Limitations with physical function	73.7	70.3	0.67
GI issues	63.3	48.7	0.17
Social role limitations	50.5	26.3	0.012*
Emotional issues	79.8	55.3	0.0053*
Pain	51.0	50.0	1.0
Inability to do activities	62.0	60.5	1.0
Communication difficulties	26.5	29.7	0.83
Choking or swallowing issues	27.6	31.6	0.68

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by current treatment. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 15 Results of subgroup analysis by place of treatment

Theme	Prevalence (%)		P value
	Academic/research medical center	Local clinic or local hospital or other	
Fatigue	84.5	86.6	0.81
Social role dissatisfaction	37.7	53.9	0.082
Breathing difficulties	62.0	71.2	0.28
Impaired body image	55.7	53.1	0.86
Impaired sleep and daytime sleepiness	70.4	76.9	0.44
Difficulty thinking	54.9	70.8	0.076
Limitations with physical function	69.0	76.9	0.34
GI issues	55.7	63.1	0.48
Social role limitations	36.2	51.5	0.084
Emotional issues	74.3	71.6	0.85
Pain	47.1	54.6	0.40
Inability to do activities	54.9	68.7	0.12
Communication difficulties	26.1	28.8	0.85
Choking or swallowing issues	27.1	30.0	0.71

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by place of treatment. GI, gastrointestinal.

Table 16 Results of subgroup analysis by distance to place of treatment

Theme	Prevalence (%)		P value
	Less than or equal to 50 miles	More than 50 miles	
Fatigue	84.8	95.7	0.31
Social role dissatisfaction	46.4	45.5	1.0
Breathing difficulties	64.9	73.9	0.47
Impaired body image	56.9	50.0	0.64
Impaired sleep and daytime sleepiness	73.6	78.3	0.80
Difficulty thinking	60.0	78.3	0.15
Limitations with physical function	71.8	82.6	0.43
GI issues	57.3	72.7	0.24
Social role limitations	42.7	50.0	0.64
Emotional issues	36.5	77.3	0.80
Pain	51.4	45.5	0.65
Inability to do activities	63.4	56.5	0.64
Communication difficulties	25.2	38.1	0.28
Choking or swallowing issues	27.9	31.8	0.80

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by place of treatment. GI, gastrointestinal.

Table 17 Results of subgroup analysis by hospitalization due to lung cancer

Theme	Hospitalized due to lung cancer?		
	Prevalence (%)		P value
	Yes	No	
Fatigue	87.8	80.4	0.31
Social role dissatisfaction	44.3	47.7	0.72
Breathing difficulties	74.2	52.2	0.013*
Impaired body image	52.9	57.8	0.71
Impaired sleep and daytime sleepiness	78.4	63.0	0.067
Difficulty thinking	67.1	54.4	0.19
Limitations with physical function	77.3	65.2	0.15
GI issues	59.1	60.0	1.0
Social role limitations	42.7	45.5	0.85
Emotional issues	74.4	71.1	0.68
Pain	57.8	36.4	0.027*
Inability to do activities	67.8	50.0	0.062
Communication difficulties	30.7	20.0	0.22
Choking or swallowing issues	30.3	24.4	0.55

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by place of treatment. *, $P<0.05$, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 18 Results of subgroup analysis by remission status

Theme	Currently in remission?		P value
	Prevalence (%)		
	Yes	No	
Fatigue	81.3	91.7	0.12
Social role dissatisfaction	37.7	52.5	0.14
Breathing difficulties	64.1	74.6	0.24
Impaired body image	45.2	66.1	0.028*
Impaired sleep and daytime sleepiness	73.0	78.0	0.54
Difficulty thinking	61.9	66.1	0.71
Limitations with physical function	68.3	78.0	0.31
GI issues	56.5	66.1	0.35
Social role limitations	35.5	55.9	0.029*
Emotional issues	66.7	83.3	0.039
Pain	52.4	50.9	1.0
Inability to do activities	59.4	66.7	0.46
Communication difficulties	25.8	28.8	0.84
Choking or swallowing issues	30.2	30.5	1.0

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by place of treatment. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 19 Results of subgroup analysis by smoking history

Theme	Prevalence (%)		P value
	0 years	Greater than 0 years	
Fatigue	79.0	91.4	0.050*
Social role dissatisfaction	37.1	50.8	0.16
Breathing difficulties	56.5	72.5	0.068
Impaired body image	50.0	59.7	0.29
Impaired sleep and daytime sleepiness	69.4	76.5	0.43
Difficulty thinking	58.1	64.7	0.47
Limitations with physical function	61.3	82.4	0.010*
GI issues	64.5	54.4	0.29
Social role limitations	40.3	44.1	0.72
Emotional issues	72.6	74.3	0.85
Pain	45.9	54.3	0.38
Inability to do activities	51.6	68.6	0.052
Communication difficulties	21.0	32.4	0.17
Choking or swallowing issues	17.7	36.2	0.020*

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by place of treatment. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Table 20 Results of subgroup analysis by number of years smoking

Theme	Prevalence (%)		P value
	Below mean (≤26.5 years)	Above mean (>26.5 years)	
Fatigue	88.4	94.1	0.67
Social role dissatisfaction	43.8	54.6	0.46
Breathing difficulties	63.6	82.4	0.10
Impaired body image	59.4	57.6	1.0
Impaired sleep and daytime sleepiness	72.7	78.8	0.77
Difficulty thinking	57.6	72.7	0.30
Limitations with physical function	72.7	90.9	0.11
GI issues	48.5	57.6	0.62
Social role limitations	36.4	48.5	0.46
Emotional issues	73.5	73.5	1.0
Pain	55.9	52.9	1.0
Inability to do activities	58.8	76.5	0.19
Communication difficulties	27.3	36.4	0.598
Choking or swallowing issues	36.4	35.3	1.0

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by place of treatment. GI, gastrointestinal.

Table 21 Results of subgroup analysis by smoking packs per day

Theme	Prevalence (%)		P value
	Below mean (≤1.1 packs)	Above mean (>1.1 packs)	
Fatigue	91.5	90.5	1.0
Social role dissatisfaction	46.7	55.0	0.60
Breathing difficulties	69.6	81.0	0.39
Impaired body image	63.6	47.6	0.28
Impaired sleep and daytime sleepiness	85.7	71.1	0.23
Difficulty thinking	64.4	66.7	1.0
Limitations with physical function	77.8	90.5	0.31
GI issues	51.1	57.1	0.79
Social role limitations	40.0	47.6	0.60
Emotional issues	70.2	81.0	0.55
Pain	51.1	61.9	0.44
Inability to do activities	70.2	61.9	0.58
Communication difficulties	36.2	21.1	0.26
Choking or swallowing issues	36.2	35.0	1.0

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by place of treatment. GI, gastrointestinal.

Table 22 Results of subgroup analysis by smoking pack-years

Theme	Prevalence (%)		P value
	Below mean (≤32.2 pack-years)	Above mean (>32.2 pack-years)	
Fatigue	86.8	96.7	0.22
Social role dissatisfaction	47.2	51.7	0.81
Breathing difficulties	62.3	86.7	0.029*
Impaired body image	62.9	53.3	0.46
Impaired sleep and daytime sleepiness	69.4	83.3	0.25
Difficulty thinking	61.1	70.0	0.60
Limitations with physical function	75.0	90.0	0.20
GI issues	44.4	63.3	0.14
Social role limitations	37.1	48.4	0.46
Emotional issues	67.6	80.7	0.28
Pain	46.0	64.5	0.15
Inability to do activities	62.2	74.2	0.31
Communication difficulties	29.7	34.5	0.79
Choking or swallowing issues	40.5	30.0	0.45

Prevalence (%) and P values of symptomatic themes evaluated in cross-sectional study subgroup analysis by place of treatment. *, P<0.05, statistical significance by the Benjamini-Hochberg method. GI, gastrointestinal.

Discussion

Key findings

This research represents one of the largest and most clinically diverse studies of disease burden in LC, with participants representing all four stages of disease progression. Using semi-structured patient interviews and a national cross-sectional study with people with LC, we discovered and analyzed the prevalence, relevance, and importance of numerous areas of disease burden in LC. Our research reveals which symptoms and themes are the most common (fatigue, sleep-related problems, and emotional issues) and impactful (social dissatisfaction, activity limitations, and fatigue) for those living with LC. Our research also shows which demographic and clinical subgroups (those on disability, those who are unemployed, those currently receiving treatment, and those in the later stages of LC) experience higher disease burden due to LC.

Strengths and limitations

Our results should be interpreted in the context that our sample cohorts are not completely representative of the general population of people with LC. In particular, potential interview participants were referred by partnering oncologists at one tertiary medical center. Physicians were specifically requested to refer a broad and diverse sample (in terms of demographic, clinical, and treatment features); however, all interviewees received care at the same center. In contrast, participants in our cross-sectional validation study represented a more geographically diverse population.

In our cross-sectional study, participants were predominantly female (82.0%), white (94.2%), non-Hispanic/Latino (98.5%), and of high education background (74.1%). While these demographic features are not atypical of registry studies, they likely do not represent the demographic profile of all individuals affected with LC, specifically in terms of sex, race, ethnicity, and educational attainment (20). Our sample was also marginally younger (with a mean age just over 60) than what has been reported in the greater population of patients with LC (21).

Participants in our research may also not have accurately represented the broader LC population in terms of smoking history. In our cross-sectional study cohort, only a little over 50% reported having ever smoked. This is in contrast to a case-control study conducted in Montreal in 2018,

where ~95% of cases with LC had smoked (n=1,203) (22). Although this percentage is on the high end from studies in the literature, reports by the Centers for Disease Control and Prevention (CDC) and American Cancer Society, nevertheless, indicate that ~75–80% of those with LC have a smoking history (23,24). The discrepancy in our study participants' smoking experience may be explained by a few factors. It is possible that our participants underreported their smoking history. It is also known that the Lung Cancer Registry through which participants were recruited comprises a disproportionately large number of individuals with a known target or oncogenic driver, and the majority of these people have no smoking history.

Of note, while participants were offered the opportunity to have a paper survey mailed to them, this study was promoted and conducted using email and an online survey platform. For this reason, individuals with limited or no access to the internet are likely underrepresented in our study. Furthermore, those with the highest degree of disease burden may not have been capable of participating and may not be represented by these results. Nevertheless, we believe that our sample adequately represents the individuals with LC that are likely to participate in future clinical studies of LC.

Comparison with similar researches

Many of the findings from our research were confirmatory with those reported in prior studies. For example, we found fatigue, impaired sleep and daytime sleepiness, and limitations with physical function to be among the most prevalent symptomatic themes in our study cohort, and inability to do activities and fatigue to be among the most impactful symptomatic themes. Using the Lung Cancer Symptom Scale, Iyer *et al.* showed that persistent cough, fatigue, and shortness of breath were the most prevalent symptoms in a U.S. sample of LC patients (5); Iyer *et al.* also showed that fatigue, loss of appetite, respiratory problems, cough, pain, and blood in sputum were the most frequent symptoms and that loss of appetite, fatigue, pain, and shortness of breath were most impactful in a sample of LC patients from France and Germany (25). Similarly, Gift *et al.* demonstrated that fatigue, nausea, weakness, loss of appetite, weight loss, and vomiting were the most frequent patient-reported symptoms that impaired daily functioning in patients who were recently diagnosed with LC, across 24 hospitals and clinics (26). Montazeri *et al.* presented findings that were congruent to those by Iyer *et al.* and Gift *et al.* in a population-based study with 129 patients in Scotland (6).

In our study, emotional issues was also a highly prevalent symptomatic theme, and social role dissatisfaction was highly impactful. Prior studies largely focus on the physical burden and toxicities of LC, but a few studies like those by Tishelman *et al.* and by Ostlund *et al.* demonstrate that self-perception and emotional functioning play a significant role in LC patients' QoL (27,28).

Interestingly, individuals with LC in our interviews and cross-sectional study placed an emphasis on several functional limitations, like difficulty running, impaired sexual function, and inability to do things previously done as greatly affecting their lives. Indeed, in a study by Leppert, more than 90% of patients with advanced LC complained of limitations in performing occupational roles or pursuing hobbies (29). Such symptoms that decrease daily function are often under-recognized by physicians who treat LC patients and by researchers searching for symptomatic targets and treatments for these individuals. Our research suggests that increased attention on and addressing the functional effects of LC may help alleviate burden.

Explanation of findings

We found that the prevalence of many symptoms differed considerably between subgroups of individuals, most notably based on age, education level, employment or disability status, LC phenotype, and LC treatment. Participants who were younger than the mean age had higher incidences of impaired body image and emotional issues, which may stem from the fact that younger people are at a different emotional and social stage in their lives, and may be more socially active and conscious (30,31). This finding is in agreement with prior work in the general population showing greater body image dissatisfaction during youth and middle-age, and higher prevalence of any mental illness in adults occurring below the age of 50 (30,31). While these symptoms may not be the direct consequence of the pathophysiology of LC, they may be exacerbated by the disease.

The patient characteristics that had the strongest association with the prevalence of symptomatic themes were related to disability status, with those who were on disability experiencing a greater frequency of symptoms in many of the physical, emotional, and social categories. Employment and disability likely have a multifaceted relationship with disease burden. Frequent and severe symptoms may discourage individuals, particularly those with physical jobs,

from working. Individuals who are not employed may also be less likely to seek valuable medical care, due to financial hindrances, leading to a higher disease burden and lack of therapeutic options for symptom management.

The data from this study show an increase in the prevalence of several symptomatic themes as individuals progress from stage I through stage IV LC. This is particularly apparent with fatigue; pain; gastrointestinal problems; and mental, emotional, and social issues, which are much higher in those whose LC has progressed to stage IV, as is corroborated by existing literature (32,33).

The prevalence of multiple symptomatic themes increased in association with a patient receiving chemotherapy or targeted therapy (but not necessarily immunotherapy). A higher prevalence of difficulty thinking and gastrointestinal issues was seen among those receiving chemotherapy. Our research cannot determine if this increase in prevalence was a result of the disease itself or the side effects from chemotherapy; however, it is likely that both factors contributed (34,35). A higher prevalence of impaired body image and emotional issues was displayed in those on targeted therapy. This, again, may be because of the disease itself or because of the younger demographic profile of targeted therapy recipients, as these individuals typically have biologically distinct, oncogene-driven cancer (36,37). A higher prevalence of physical symptoms, namely breathing difficulties and pain, was seen in people with LC who had been hospitalized due to their disease. This provides insight into two potentially treatable factors associated with hospitalization in this population.

Participants in our study who had a history of smoking demonstrated a greater prevalence of limitations with physical function and choking or swallowing issues, and those who smoked more than the mean number of pack-years showed a higher prevalence of breathing problems. This finding is supported by the literature, which demonstrates that smoking increases the likelihood of LC and that it is also associated with greater disease severity and higher probability of treatment failure (38,39).

Implications and actions needed

The data presented here provide a basis for conceptualizing disease burden experienced by people with LC and discerning patient characteristics that are associated with a higher level of disease burden. Future studies should consider exploring if there are additional differences in patient symptomatic profiles based on clinical state and the scores of psychometrically validated patient-reported measures of physical and mental health. In total, the data obtained from this research may allow clinicians to better understand and address the important and potentially treatable symptoms that occur in LC. Furthermore, this research may be used by researchers looking to identify impactful therapeutic targets for future interventional studies.

Conclusions

This study systematically identifies the symptoms that are most common and have the greatest impact on the lives of individuals with LC. This data provides a fundamental basis for understanding the disease burden experienced by individuals with LC and identifies patient characteristics that are associated with a higher level of disease burden. The findings have the potential to better equip clinicians who care for those with LC to acknowledge important and potentially treatable symptoms associated with this disease. This study contributes patient-reported data that are critical to direct novel therapeutic development efforts for the most relevant symptom management targets to achieve improvement in patient outcomes and QoL.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study (STUDY00005663: LC-HI) was approved by University of Rochester Institutional Review Board (RSRB), and informed consent was obtained from all individual participants.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Polanski J, Jankowska-Polanska B, Rosinczuk J, et al. Quality of life of patients with lung cancer. Onco Targets Ther 2016;9:1023-8.
3. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. Psychooncology 2001;10:19-28.
4. Ramirez RA, Lu J, Thomas KEH. Quality of life for non-small cell lung cancer patients in the age of immunotherapy. Transl Lung Cancer Res 2018;7:S149-52.
5. Iyer S, Roughley A, Rider A, et al. The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. Support Care Cancer 2014;22:181-7.
6. Montazeri A, Milroy R, Hole D, et al. Quality of life in lung cancer patients: as an important prognostic factor. Lung Cancer 2001;31:233-40.
7. Ganz PA, Lee JJ, Siau J. Quality of life assessment. An independent prognostic variable for survival in lung cancer. Cancer 1991;67:3131-5.
8. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570-9.
9. Cella DF, Bonomi AE, Lloyd SR, et al. Reliability and validity of the functional assessment of cancer therapy—lung (FACT-L) quality of life instrument. Lung Cancer 1995;12:199-220.
10. Guber RD, Kokkinis AD, Schindler AB, et al. Patient-identified impact of symptoms in spinal and bulbar muscular atrophy. Muscle Nerve 2018;57:40-4.
11. Glidden AM, Luebbe EA, Elson MJ, et al. Patient-reported impact of symptoms in Huntington disease: PRISM-HD. Neurology 2020;94:e2045-53.
12. Hamel J, Johnson N, Tawil R, et al. Patient-Reported Symptoms in Facioscapulohumeral Muscular Dystrophy (PRISM-FSHD). Neurology 2019;93:e1180-92.
13. Heatwole C, Bode R, Johnson N, et al. Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1). Neurology 2012;79:348-57.
14. Heatwole C, Johnson N, Bode R, et al. Patient-Reported

Impact of Symptoms in Myotonic Dystrophy Type 2 (PRISM-2). Neurology 2015;85:2136-46.
15. Mongiovi P, Dilek N, Garland C, et al. Patient Reported Impact of Symptoms in Spinal Muscular Atrophy (PRISM-SMA). Neurology 2018;91:e1206-14.
16. Johnson NE, Heatwole CR, Dilek N, et al. Quality-of-life in Charcot–Marie–Tooth disease: The patient's perspective. Neuromuscul Disord 2014;24:1018-23.
17. Johnson NE, Quinn C, Eastwood E, et al. Patient-identified disease burden in facioscapulohumeral muscular dystrophy. Muscle Nerve 2012;46:951-3.
18. Johnson NE, Heatwole CR, Ferguson M, et al. Patient identification of the symptomatic impact of charcot-marie-tooth disease type 1A. J Clin Neuromuscul Dis 2013;15:19-23.
19. Green J, Thorogood N. Qualitative methods for health research. 4th ed. London: Sage; 2004.
20. Spitzer S. Biases in health expectancies due to educational differences in survey participation of older Europeans: It's worth weighting for. Eur J Health Econ 2020;21:573-605.
21. American Cancer Society. Cancer Facts and Figures 2022.
22. Remen T, Pintos J, Abrahamowicz M, et al. Risk of lung cancer in relation to various metrics of smoking history: a case-control study in Montreal. BMC Cancer 2018;18:1275.
23. Morbidity and Mortality Weekly Report. Centers for Disease Control and Prevention 2008 November 14.
24. Lung Cancer Risks for People Who Don't Smoke. 2020; Available online: https://www.cancer.org/latest-news/why-lung-cancer-strikes-nonsmokers.html. Accessed May 15, 2022.
25. Iyer S, Taylor-Stokes G, Roughley A. Symptom burden and quality of life in advanced non-small cell lung cancer patients in France and Germany. Lung Cancer 2013;81:288-93.
26. Gift AG, Jablonski A, Stommel M, et al. Symptom clusters in elderly patients with lung cancer. Oncol Nurs Forum 2004;31:202-12.
27. Tishelman C, Degner LF, Mueller B. Measuring symptom distress in patients with lung cancer. A pilot study of experienced intensity and importance of symptoms. Cancer Nurs 2000;23:82-90.
28. Ostlund U, Wennman-Larsen A, Gustavsson P, et al. What symptom and functional dimensions can be predictors for global ratings of overall quality of life in lung cancer patients? Support Care Cancer 2007;15:1199-205.
29. Leppert W, Turska A, Majkowicz M, et al. Quality of life in patients with advanced lung cancer at home palliative care and at the in-patient palliative care unit. Am J Hosp Palliat Care 2012;29:379-87.
30. Government Equalities Office. Body confidence: Findings from the British Social Attitudes Survey October 2014.
31. Mental Illness. Available online: https://www.nimh.nih.gov/health/statistics/mental-illness. Accessed Mar 13, 2022.
32. Potter J, Higginson IJ. Pain experienced by lung cancer patients: a review of prevalence, causes and pathophysiology. Lung Cancer 2004;43:247-57.
33. Jim HSL, Eisel SL, Hoogland AI, et al. Use of a Cancer Registry to Evaluate Patient-Reported Outcomes of Immune Checkpoint Inhibitors. Cancers (Basel) 2020;13:103.
34. Kovalchuk A, Kolb B. Chemo brain: From discerning mechanisms to lifting the brain fog—An aging connection. Cell Cycle 2017;16:1345-9.
35. Boussios S, Pentheroudakis G, Katsanos K, et al. Systemic treatment-induced gastrointestinal toxicity: incidence, clinical presentation and management. Ann Gastroenterol 2012;25:106-18.
36. Tan AC, Tan DSW. Targeted Therapies for Lung Cancer Patients With Oncogenic Driver Molecular Alterations. J Clin Oncol 2022;40:611-25.
37. Yuan M, Huang LL, Chen JH, et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Signal Transduct Target Ther 2019;4:61.
38. U.S. Department of Health and Human Services. The Health Consequences of Smoking - 50 Years of Progress: A report of the Surgeon General. 2014.
39. Guo NL, Tosun K, Horn K. Impact and interactions between smoking and traditional prognostic factors in lung cancer progression. Lung Cancer 2009;66:386-92.

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