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Predicting postoperative fatigue in surgically treated lung cancer patients – a longitudinal five-month follow-up study.

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ABSTRACT

Objectives: Despite the negative influence of fatigue on quality of life in patients who undergo lung cancer surgery, little is known about the possible predictors of postoperative fatigue. The aim of this study was to examine demographic and clinical characteristics that might predict postoperative fatigue five months after lung cancer surgery.

Design: A prospective longitudinal follow up study comprising pre- and postoperative questionnaires, including Lee Fatigue Scale, and sociodemographic and clinical data.

Setting: Three university hospitals in Norway (e.g., Oslo University Hospital, St. Olav University Hospital, Haukeland University Hospital).

Participants: In total, 196 surgically treated patients who answered the questionnaires both preoperatively and at five-month follow-up with valid fatigue scores.

Results: Bivariate analyses showed that preoperative fatigue was associated with comorbidities and the symptoms of shortness of breath, cough, depression, anxiety, sleep disturbance, and pain. Only cough was directly associated with preoperative fatigue in a regression model. Comorbidities and the symptoms of shortness of breath, cough, depression, and sleep disturbance were associated with postoperative fatigue in the bivariate analyses, but only shortness of breath was associated with postoperative fatigue in the regression model. We did not find any significant correlations between fatigue and any treatment variable.

Conclusion: Clinicians should pay special attention to lung symptoms and be aware that these may lead to long-term postoperative fatigue. Further research should examine whether interventions reducing lung symptoms, such as shortness of breath and coughing, may prevent development of fatigue in patients undergoing lung cancer surgery.

Key words: Fatigue, Lung Cancer, Neoplasm, Quality of Life, Surgery

Strengths and limitations of this study

- A rather large sample of surgically treated lung cancer patients were included in the study
- Patients' fatigue was measured both preoperatively and after surgery
- Several clinical, treatment and medical variables as well as symptoms that might be related to fatigue was assed
- There was a five-month gap between the two measurement points. During this time, other factors might have influenced patients' fatigue experience.
- There were limited information on symptom management interventions such as physiotherapy and rehabilitation

1. Introduction

Lung cancer (LC) is presently one of the most common malignancies, and it is estimated that 20% of cancer-related deaths are caused by LC,[1]. Only 20% of patients diagnosed with non-small-cell lung cancer meet the criteria for surgery due to their late stage at diagnosis; for these patients, surgery may be curative,[2]. In Norway during 2014, five-year LC survival was generally 19% in women and 13% in men,[1]. In surgically treated patients, the five-year survival ranges from 50% to 70%, depending on the tumor stage at surgery.

Fatigue is common among cancer patients. An estimated 75–90% of LC patients report fatigue after cancer treatment,[3,4]. Fatigue has been described as a complex, multidimensional symptom and has been defined as a sense of exhaustion, lack of energy, or tiredness distinct from sleepiness, sadness, or weakness,[5]. Cancer-related fatigue is related to cancer or its treatment, and interferes with usual functioning,[3]. Fatigue has a negative impact on patients' health-related quality of life (HRQOL),[6], their ability to receive treatment, and their long-term prognosis. Although there are limited data on LC and fatigue in patients who have undergone surgery, it has been shown that fatigue has a negative impact on

HRQOL in LC survivors,[7]. One study showed that fatigue was a significant predictor of survival at each time point assessed,[8]. In another study on symptom severity after thoracotomy, fatigue was reported as the most common and severe symptom at every time point,[7].

Several studies have reported interrelations between fatigue, cough, and dyspnea,[8–11]. Fatigue is also strongly related to symptoms of depression and anxiety,[12,13]. Associations between fatigue and sex, pain, insomnia, and dyspnea have also been reported,[12,14]. Studies on fatigue in populations with lung cancer in different stages have also shown strong correlations between fatigue and sleep disturbance,[6,15–17]. Sarna et al.,[12] found that symptom severity in surgical patients was related to the extent of their comorbid condition. Other studies of LC patients have also shown correlations between comorbidities and fatigue,[6], as well as strong correlations between pulmonary diseases such as COPD and asthma, and fatigue,[3,18]. Fatigue has a negative impact on both LC patients and survivors in general,[19]; however, to our knowledge, there have been no studies to date specifically investigating fatigue in surgically treated LC patients.

Thus, our aim was to examine the relationships between fatigue and disease characteristics, treatment, and other symptoms. We hypothesized that fatigue levels at five-month follow-up would be significantly related to: (1) clinical variables (preoperative comorbidities, forced expiratory volume in one second [FEV1], and forced vital capacity [FVC]); (2) preoperative symptoms (shortness of breath, coughing, depression, anxiety, pain, and sleep disturbance); and (3) treatment and medical variables (surgery type, cancer stage, and adjuvant therapy).

2. Material and methods

This study is part of a larger, longitudinal investigation of symptoms in LC patients who were eligible for surgery,[20–22] for which data were collected prior to surgery and

prospectively at four time points up to one year after surgery. Here, we analyzed the data collected prior to surgery and at the five-month follow-up to gain insight into patients' experiences with fatigue before surgery and after the immediate postoperative period.

2.1. Patients and settings

Patients were included if they were 18 years or older, scheduled for primary LC surgery, and could understand, read, and write Norwegian. Patients with a benign or metastatic disease, whose surgery was canceled, or who had cognitive impairment, were excluded. We recruited patients from three university hospitals in Norway: Oslo University Hospital, St. Olav University Hospital, and Haukeland University Hospital.

2.2. Study procedures

Hospital research staff approached patients and explained the study purpose: 91% of the participants were recruited in the hospital 1–3 days before surgery, and the remainder in outpatient clinics prior to surgery. The patients completed several self-report questionnaires with information on sociodemographic and clinical characteristics, and symptoms both prior to surgery and at a five-month follow-up. Data on type of tumor, cancer stage, surgery type, and lung function were collected from the patients' medical records. FEV1 and FVC were measured preoperatively using a spirometer. Five months after surgery, patients received questionnaires by regular mail, along with a postage-paid return envelope.

2.3. Instruments and assessment

2.3.1. Sociodemographic, clinical, symptom, and fatigue characteristics

Patients provided information on their sex, marital status, living situation, level of education, and employment status. Information on age, smoking status, FEV1, tumor histology, cancer stage, type of surgery, pre- and postoperative treatment, postoperative

complications, and TNM classification were collected from patients' medical records; the TNM classification is a system for cancer staging based on tumor (T), node (N), and metastasis (M).

2.3.2. Comorbidities

Comorbidities were measured using the Self-administered Comorbidity Questionnaire-19 (SCQ-19),[23] on which scores can range from 0 to 57, with a higher score indicating a more severe comorbidity profile. The SCQ includes 16 comorbidities and three optional conditions. Patients indicated whether or not they had the comorbid condition (yes/no); if they had the condition they were asked if they received treatment for it; and finally if it limited their activities. The SCQ-19 has well-established validity and reliability and has been used to assess comorbidity in Norwegian oncology patients,[23]. Only the number of comorbidities was used in the present study.

2.3.3. Fatigue

The Lee Fatigue Scale (LFS),[5] was used to measure fatigue at baseline and five-month follow-up. The LFS consists of 18 items designed to assess fatigue (13 items) and energy (5 items). We used only the 13 fatigue items in this study. Patients were asked to rate each item on a 0–10 scale, with a higher score indicating greater fatigue severity. A fatigue score was calculated using the mean of the 13 items at each measurement. The LFS has well-established validity and reliability,[24,25]. Fatigue scores at baseline were defined as preoperative fatigue and at five-month follow-up as postoperative fatigue.

2.3.4. Shortness of breath and cough

The European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire – Lung Cancer Module (EORTC QLQ-LC13),[26] was used to measure shortness of breath and cough. Patients were asked to rate their severity on each shortness of breath and cough item using a four-point Likert scale where 1 = not at all; 2 = a little; 3 =

quite a bit; and 4 = very much. The EORTC QLQ-LC13 has been validated in Norwegian LC patients,[27,28].

2.3.5. Depression

The Center for Epidemiologic Studies – Depression Scale (CES-D),[29] was used to measure depression symptoms. The scale has 20 items related to depression and patients were asked to report how they felt during the past week. Each item was rated on a four-point Likert scale and scores ranged from 0 to 60, with a higher score indicating a higher level of depression. A total depression score was calculated as the mean of all the sub scores. Acceptable reliability and validity have been reported in a previous study,[30].

2.3.6. Anxiety

The State-Trait Anxiety Inventory (STAI, Y-2),[31] was used to measure anxiety. The STAI includes 20 items related to anxiety rated on a four-point Likert scale. Scores range from 20 to 80, with a higher score indicating a higher level of anxiety. The STAI has been validated in LC patients,[32].

2.3.7. Sleep disturbance

The General Sleep Disturbance Scale (GSDS),[33] was used to measure sleep disturbance. The GSDS consists of 21 items related to sleep disturbance. Each item is rated on a numeric rating scale ranging from 0 (never) to 7 (every day). A sleep disturbance score was calculated from the mean of all scale items. Higher scores indicate more severe sleep disturbance. The GSDS has been validated in cancer patients,[24].

2.3.8. Pain

The Brief-Pain Inventory (BPI),[34] was used to measure pain interference. The BPI is a multidimensional questionnaire measuring pain intensity (four items), pain interference (seven items), pain relief (one item), and pain location (body map). Only pain interference was used in the present study. The seven interference items (general activity, normal work,

walking ability, mood, relationships with other people, sleep, and enjoyment of life) were combined into a single interference item. The measurement scale ranges from 0 to 10, with higher scores indicating more pain interfering with daily living. The BPI has been validated in Norwegian cancer patients,[35].

2.4. Ethics

The Regional Ethics Committee for the South-East 2010/1508, and the Institutional Review Boards (Personvernombudet) at each hospital approved the study. Each participant received written information about the study and signed informed consent.

2.5. Statistical analyses

Descriptive statistics were used to describe the sociodemographic, clinical, and treatment characteristics of the patient sample. Differences between sexes were analyzed using a chi-squared test for categorical variables and an independent Student's *t* test for the continuous variables. One-way ANOVA was used to explore differences within groups on levels of pre- and postoperative fatigue. Patients with more than 20% of missing items on the LFS were excluded from analyses. The bivariate relationships between symptoms and fatigue at baseline were assessed using Pearson correlation analyses. Variables with significant correlation coefficients on bivariate analyses were included in a hierarchical linear analyses.

Two stepwise multivariate regression analyses were performed. In the first analysis, preoperative fatigue was the dependent variable. In the second analysis, postoperative fatigue was the dependent variable. In both analyses, age and sex were entered in step one. Clinical variables including comorbidities, FEV1, and FVC were entered in step two. Finally, the symptom variables of shortness of breath, cough, depression, anxiety, sleep disturbance, and pain interference were entered in step three. For the second regression analysis, the model

Table 1
Demographic, clinical, and treatment characteristics of the patients (N=196).

	Total	Men	Women	Statistics	p-value
Sociodemographics					
Age in years (mean, SD)	196	66.7 (8.2)	64.1 (7.9)	t 2.28 (194)	**0.024**
		% (n)	% (n)	χ (df)	
Cohabitation (living with someone)	147	84.0 (89)	(69.0) 58	5.95 (1)	**0.015**

also included a fourth step in which preoperative fatigue was included as an independent variable.

The entry of variables in different model steps was carried out according to theoretical and logical considerations. For all analyses, $p<0.05$ was considered statistically significant. Post hoc statistical power was calculated for hierarchical multiple regression: with an effect size (f^2) for set B (five-month follow-up) at 0.15 (medium),[36], 11 predictors in set A and 12 in set B, a probability level of 0.05, and a sample size of 196, the observed power for the addition of set B was 0.95,[37]. Data were analyzed using SPSS (IBM Corporation, Armonk, NY, USA) version 24.0.

3. Results

3.1. Sample characteristics

A total of 264 patients consented to participate in the study. Among these, 196 patients who answered the questionnaire both preoperatively and at five-month follow-up and had valid fatigue scores were included in the study. Sample characteristics are shown in Table 1. Most of the sample had adenocarcinoma stage 1A or 1B, received no preoperative treatment and had a lobectomy.

The mean preoperative fatigue scores were 2.49 (SD=2.02) for men and 2.47 (SD=1.96) for women. At the five-month follow-up, the postoperative fatigue scores were 3.0 (SD=2.1) for men and 2.9 (SD=2.1) for women. There were no significant differences in fatigue level preoperatively between those who completed or did not complete the postoperative fatigue scale.

Work status					
Full or part time	58	27.6 (29)	34.9 (29)	.80 (2)	0.25
Sick leave or disability	47	22.9 (24)	27.7 (23)		
Retired	83	49.5 (52)	37.3 (31)		
Education					
≤12 years	158	81.1(86)	86.7 (72)	1.07 (1)	0.30
≥13 years	31	18.9 (20)	13.3 (11)		
Clinical variables		Mean (SD)	Mean (SD)	t (df)	
Comorbidities (SCQ)	193	3.72 (3.3)	4.67 (4.0)	–1.74 (161.4)	0.08
FEV1 (expected %)	190	76.7 (19.2)	80.4 (22.8)	–1.20 (188)	0.23
FVC (expected %)	183	91.2 (15.00)	102.4 (19.4)	t –4.30(149.8)	**<.001**
Symptoms					
Fatigue (LFS) baseline	196	2.50 (2.0)	2.48 (2.0)	t –0.07 (194)	0.94
Fatigue (LFS) 5-month follow-up	196	3.0 (2.2)	2.9 (2.1)	t 0.32 (194)	0.75
Shortness of breath (EORTC)	194	2.24 (0.8)	2.00 (0.7)	t –2.28 (192)	**0.023**
Cough (EORTC)	193	1.96 (0.7)	1.98 (0.8)	t –0.11 (191)	0.92
Depression (CES-D)	190	10.49 (8.8)	12.92 (8.8)	t –1.89 (188)	0.06
Anxiety (STAI)	192	51.22 (3.1)	50.80 (2.9)	t 0.96 (190)	0.34
Sleep disturbance (GSDS)	191	2.26 (1.05)	2.32 (1.00)	t –0.36 (189)	0.72
		% (n)	% (n)	χ (df)	p-value
Pain (BPI) yes	171	40.0 (38)	51.3 (39)	2.18 (1)	0.14
Pathology and treatment					
Tumor type					
Adenocarcinoma	106	45.0 (50)	65.9 (56)	24.00 (4)	**<.001**
Squamous cell	66	45.0 (50)	12.9 (11)		
Small cell	5	1.8 (2)	3.5 (3)		
Carcinoid	6	1.8 (2)	4.7 (4)		
Other	18	6.3 (7)	12.9 (11)		
Stage of cancer disease					
IA	58	25.2 (27)	41.3 (31)	9.12 (4)	0.06
IB	59	35.5 (38)	28.0 (21)		
II	35	24.3 (26)	12.0 (9)		
IIIA	31	14.0 (15)	18.7 (14)		
IIIB-IV	1	0.9 (1)	–		
Preoperative treatment					
None	192	97.3 (108)	98.8 (84)	1.58 (3)	0.66
Radiation	1	0.9 (1)	–		
Chemotherapy	1	0.9 (1)	–		
Combination	2	0.9 (1)	1.2 (1)		
Type of surgery					
Lobectomy	133	67.6 (75)	68.2 (58)	1.26 (4)	0.87
Bilobectomy	15	6.3 (7)	9.4 (8)		
Pneumonectomy	18	9.0 (10)	9.4 (8)		
Wedge resection	18	9.9 (11)	8.2 (7)		
Thoracoscopic	12	7.2 (8)	4.7 (4)		
Postoperative complications					
Reoperation	9	3.6 (4)	5.9 (5)	0.57 (1)	0.45
Pneumonia	50	27 (30)	23.8 (20)	0.26 (1)	0.61
Posttreatment					
Radiation therapy	16	9.9 (11)	5.9 (5)	1.04 (1)	0.31
Chemotherapy	57	30.6 (34)	27.1 (23)	0.30 (1)	0.59
Physiotherapy	58	24.3 (26)	38.1 (32)	4.24 (1)	**0.04**
Rehabilitation	24	7.5 (8)	19.3 (16)	5.90 (1)	**0.015**

Abbreviations: SCQ, Self-administered Comorbidity Questionnaire; FEV1, forced expiratory volume in one second; FVC, Forced vital Capacity; EORTC, European Organization for Research and Treatment of Cancer; CES-D, Center for Epidemiologic Studies – Depression Scale; STAI, State-Trait Anxiety Inventory; GSDS, General Sleep Disturbance Scale; BPI, Brief Pain Inventory; LFS, Lee Fatigue Inventory.

Notes: Fatigue, range 0–10, higher score indicating greater fatigue severity; shortness of breath and cough range 1–4, higher score indicating more shortness of breath and cough; depression, range 0–60, higher score indicating more depression; pain, range 0–10, higher score indicating more pain; comorbidity, range 0–57, higher score indicating more comorbidity; anxiety, range 20–80, higher score indicating more anxiety; sleep disturbance, range 0–7, higher score indicating more severe sleep disturbance.

Bold numbers represent significant relationships.

3.2. Bivariate analyses

The bivariate analyses between the symptom variables are shown in Table 2. Medical and treatment characteristics including cancer stage, tumor type, type of surgery, and postoperative treatment such as radiation therapy, chemotherapy, physiotherapy, and rehabilitation were not significantly correlated with either preoperative or postoperative fatigue and, thus, were not included in the final model. Sociodemographic variables including work, education, and cohabitation were excluded before the final analyses for the same reason.

Table 2
Correlation matrix for symptoms at baseline, and fatigue baseline and 5-month follow-up (N=196).

	1	2	3	4	5	6	7	8	9	10	11	12	13
1 Age	1												
2 Gender	–.16*	1											
3 FEV1	.06	.09	1										
4 FVC	.02	.31*	.65*	1									
5 Fatigue (LFS) baseline	–.23*	–.01	–.19*	–.14	1								
6 Fatigue (LFS) 5-month follow-up	–.16*	–.02	–.22*	–.17*	.52*	1							
7 Comorbidities (SCQ)	.04	.13	–.23*	–.12	.29*	.31*	1						
8 Shortness of breath (EORTC)	–.03	–.16*	–.25*	–.24*	.35*	.62*	.31*	1					
9 Cough (EORTC)	–.04	.01	–.14	–.15*	.33*	.33*	–.04	.17*	1				
10 Depression (CES-D)	–.15*	.14	–.07	–.03	.47*	.31*	.17*	.17*	.12	1			
11 Anxiety (STAI)	.06	–.07	.08	–.00	–.24*	–.12	–.08	–.01	–.1	–.28*	1		
12 Sleep disturbance (GSDS)	–.22*	.03	–.09	–.08	.50*	.41*	.18*	.26*	.14	.57*	–.22*	1	
13 Pain (BPI)	.1	–.11	.09	.1	–.25*	–.23*	–.18*	–.15	–.02	–.08	.18*	–.23*	1

* Correlation is significant at the 0.05 level (2-tailed).
Abbreviations: SCQ, Self-administered Comorbidity Questionnaire; FEV1, Forced expiratory volume in one second; FVC, Forced vital Capacity; EORTC, European Organization for Research and Treatment of Cancer; CES-D, Center for Epidemiologic Studies – Depression Scale; STAI, State-Trait Anxiety Inventory; GSDS, General Sleep Disturbance Scale; BPI, Brief Pain Inventory; LFS, Lee Fatigue Inventory.

3.3. Multivariate analyses

Hierarchical multiple regression analyses were used to assess the impact of the selected variables on levels of preoperative and postoperative fatigue (Table 3). Age, sex, and clinical variables were unrelated to preoperative fatigue.

Table 3
Results from the two hierarchical multivariate linear regression analyses with preoperative fatigue and postoperative fatigue (at 5-month follow-up) were used as dependent variables (N=196).

	Preoperative fatigue			Postoperative fatigue		
	Beta	β	p-value	Beta	β	p-value
Sociodemographics						
Age	–0.04	–0.14	0.13	–0.02	–0.07	0.26
Gender	–0.39	–0.10	0.16	0.03	0.01	0.93
Explained variance (R^2)		**5.5%**	**0.01**		2.9%	0.10
Clinical variables						
FEV1	–0.00	–0.05	0.63	–0.00	–0.03	0.71
FVC	–0.01	0.04	0.61	0.00	0.04	0.65
Comorbidity	0.10	0.18	0.008	0.05	0.08	0.19
R^2 change		**10.6%**	**<0.001**		**12.1%**	**<0.001**
Explained variance		16.1			15.0	
Fatigue at baseline						
Fatigue				**0.18**	**0.17**	**0.03**
R^2 change					**16.2%**	**<0.001**
Explained variance					31.2%	
Other symptoms at baseline						
Shortness of breath	0.33	0.13	0.06	**1.27**	**0.46**	**<0.001**
Cough	**0.64**	**0.25**	**<0.001**	**0.50**	**0.18**	**0.004**
Depression	**0.05**	**0.23**	**0.003**	0.01	0.04	0.63
Anxiety	–0.05	–0.07	0.29	0.00	0.00	0.95
Sleep disturbance	**0.02**	**0.20**	**0.01**	0.01	0.11	0.12
Pain	**0.44**	**0.20**	**0.01**	–0.29	–0.07	0.26
R^2 change		**30.5%**	**<0.001**		**23.2%**	**<0.001**
Explained variance		46.6%			54.3%	

Abbreviations: FEV1, Forced expiratory volume in one second; FVC, Forced vital capacity.
Note: Bold numbers represent significant relationships.

At baseline, patients who reported pain scored higher on fatigue (M=2.9, SD=2.05) compared with patients who reported no pain (M=2.03, SD=1.8, t=3.28, p=0.001). Patients who reported pain at baseline also reported higher mean fatigue at five-month follow-up (M=3.54, SD=2.21) compared with those who reported no pain at baseline (M=2.55, SD=2.04, t=3.08, p=0.002). Among the reported symptoms, coughing, depression, sleep disturbance, and pain interference were related to preoperative fatigue after controlling for age, sex, clinical variables, and the other symptoms. The total model explained 46.6% of variance, while 30.5% was explained by the other symptoms.

At five-month follow-up, the only variables that predicted fatigue after controlling for age, sex, clinical variables, preoperative fatigue, and symptoms were shortness of breath and coughing. The total model explained 54.3% of variance, while 23.2% was explained by the other symptoms.

4. Discussion

To our knowledge, this is the first study examining fatigue in surgically treated LC patients, including both preoperative data and data from five-month follow-up. Preoperative fatigue was significantly correlated with comorbidities and all the included symptoms in the bivariate analyses, while postoperative fatigue was significantly correlated with comorbidities and four out of six measured symptoms. However, shortness of breath was the only baseline variable that predicted postoperative fatigue.

4.1. Relationship between postoperative fatigue level and preoperative symptoms

Shortness of breath, coughing, depression, anxiety, sleep disturbance, and pain interference were significantly correlated with level of preoperative fatigue. Except for anxiety and pain interference, the same symptoms were associated with postoperative fatigue in the bivariate analyses at five-month follow-up. Before surgery, cough was significantly

associated with fatigue, while shortness of breath was the symptom predictive of postoperative fatigue. Shortness of breath is a prevalent and disturbing symptom in these patients, which is physiologically based on disease location, damage caused by lung tumors, and history of smoking. Shortness of breath requires intensive effort to breath, thus making patients tired. The constant use of rib and respiratory muscles caused by shortness of breath can exacerbate fatigue,[38]. These patients may benefit from prescribed bronchodilators and non-pharmacological treatment such as physical activity. For some, it may be useful to learn how to manage shortness of breath by controlled breathing techniques and practicing calming techniques during shortness of breath episodes.

Consistent with previous research, we found that fatigue in LC patients undergoing surgery is correlated with their symptoms and might cluster with other symptoms,[2,39]. Cheville et al.,[2] found a cluster of fatigue, cough, and dyspnea in LC survivors lasting for eight years; however, in a later study, the same group found that the cluster did not predict patient outcomes but that fatigue and dyspnea, alone and together, were sufficient to predict important outcomes,[8].

4.2. Relationship between fatigue and patients' disease characteristics and treatment

Although comorbidities did not predict postoperative fatigue in our analyses, there was a bivariate relationship with fatigue both pre- and postoperatively. Others have also reported correlations between comorbidity and fatigue,[6,12]. Respiratory comorbidities and cardiac disease are especially related to fatigue in LC patients,[3,40]. We also found a correlation between fatigue and spirometry results, with lower FEV1 and FVC related to higher levels of fatigue at both measurement times. These variables were related to comorbidity and are an important factor in identifying and screening patients at risk for developing fatigue. Poorer respiratory test outcomes could indicate shortness of breath or respiratory comorbidities, such as COPD, and may lead to distress and exhaustion and contribute to fatigue in these patients.

Surgery type has been established as a predictor of fatigue in LC survivors and surgery has been associated with a greater symptom burden generally,[19]. In the present study, treatment and disease variables did not correlate with postoperative fatigue at five-month follow-up. These findings are inconsistent with other reports in which correlations have been found between fatigue and chemotherapy,[9] and radiotherapy,[11]. However, our findings are consistent with those from a general cancer population on the symptom cluster of pain, fatigue, sleep disturbance, and depression. That group found that symptom experiences were independent of demographic, disease, or treatment effects; their findings suggest that different subgroups of patients may harbor different determinants (e.g., genetic) for experiencing symptoms and suggested etiology that are independent of demographic, disease, or treatment characteristics,[41].

4.3. Limitations

Some study limitations need to be acknowledged. There was a five-month gap between the two measurement points. During this time, other factors might have influenced patients' fatigue experience. Surgery type might also be a predictor of patient fatigue,[19]. In this study, only 6% of patients had video-assisted thoracoscopy; thus, it is not possible to determine whether this influenced postoperative fatigue. Detailed information on symptom management interventions such as physiotherapy and rehabilitation was not collected. However, even if these variables had been included, no detailed information about the type and length of these therapies was available.

5. Conclusions

Based on the findings in the present study, patients should be screened for symptoms before surgery and offered treatment for their symptoms to reduce pre- and postoperative fatigue. Special attention should be given to treating patients' shortness of breath, since this is

a modifiable predictor for which treatments are available. Further research should pay specific attention to the pair of symptoms of shortness of breath and fatigue, and to the effects on fatigue and QOL when shortness of breath is treated.

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Footnotes

Contributors: TR and TO conceptualised the study. TO wrote the protocol manuscript and TR contributed to protocol development. TO had responsibility for data collection. TH and AL conducted the data analyses and drafted the initial report. TO and TR critically reviewed and edited the manuscript. All authors read and approved the final manuscript. Each author contributed to interpreting the analyses and to critically revising the article, and approved the final draft.

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		Reporting Item	Page Number
	#1	The area of focus and “case report” should appear in the title	1
	#2	Two to five key words that identify topics in this case report	2
Introduction	#3a	What is unique and why is it important?	2
	#3b	The patient’s main concerns and important clinical findings.	2
	#3c	The main diagnoses, interventions, and outcomes.	2

Conclusion	#3d	What are one or more “take-away” lessons?	2
	#4	Briefly summarize why this case is unique with medical literature references.	3,4
	#5a	De-identified demographic and other patient information.	5
	#5b	Main concerns and symptoms of the patient.	6,7
	#5c	Medical, family, and psychosocial history including genetic information.	5,6
	#5d	Relevant past interventions and their outcomes.	5
	#6	Relevant physical examination (PE) and other clinical findings.	10
	#7	Relevant data from this episode of care organized as a timeline (figure or table).	115
	#8a	Diagnostic methods (PE, laboratory testing, imaging, surveys).	5
	#8b	Diagnostic challenges.	5
	#8c	Diagnostic reasoning including differential diagnosis	5
	#8d	Prognostic characteristics when applicable	5
	#9a	Types of intervention (pharmacologic, surgical, preventive).	5
	#9b	Administration of intervention (dosage, strength, duration)	5
	#9c	Changes in the interventions with explanations.	5
	#10a	Clinician and patient-assessed outcomes when appropriate	11,12
	#10b	Important follow-up diagnostic and other test results.	11,12

#10c	Intervention adherence and tolerability (how was this assessed)?	12
#10d	Adverse and unanticipated events.	11
#11a	Strengths and limitations in your approach to this case.	3
#11b	Discussion of the relevant medical literature.	13,14
#11c	The rationale for your conclusions.	13,14
#11d	The primary “take-away” lessons from this case report.	14,15
#12	The patient can share their perspective on their case	12,13
#13	The patient should give informed consent.	8

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Predicting postoperative fatigue in surgically treated lung cancer patients – a longitudinal five-month follow-up study.

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Predicting postoperative fatigue in surgically treated lung cancer patients – a longitudinal five-month follow-up study.

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ABSTRACT

Objectives: Despite the negative influence of fatigue on quality of life in patients who undergo lung cancer surgery, little is known about the possible predictors of postoperative fatigue. The aim of this study was to examine demographic and clinical characteristics that might predict postoperative fatigue five months after lung cancer surgery.

Design: A prospective longitudinal follow up study comprising pre- and postoperative questionnaires, including Lee Fatigue Scale, and sociodemographic and clinical data.

Setting: Three university hospitals in Norway (e.g., Oslo University Hospital, St. Olav University Hospital, Haukeland University Hospital).

Participants: In total, 196 surgically treated patients who answered the questionnaires both preoperatively and at five-month follow-up with valid fatigue scores.

Results: Bivariate analyses showed that preoperative fatigue was associated with comorbidities and the symptoms of shortness of breath, cough, depression, anxiety, sleep disturbance, and pain. Only cough was directly associated with preoperative fatigue in a regression model. Comorbidities and the symptoms of shortness of breath, cough, depression, and sleep disturbance were associated with postoperative fatigue in the bivariate analyses, but only shortness of breath was associated with postoperative fatigue in the regression model. We did not find any significant correlations between fatigue and any treatment variable.

Conclusion: Clinicians should pay special attention to lung symptoms and be aware that these may lead to long-term postoperative fatigue. Further research should examine whether interventions reducing lung symptoms, such as shortness of breath and coughing, may prevent development of fatigue in patients undergoing lung cancer surgery.

Key words: Fatigue, Lung Cancer, Neoplasm, Quality of Life, Surgery

Strengths and limitations of this study

- Fatigue is a symptom that has a great impact on patients quality of life and this topic is relevant both to patients and healthcare providers
- A rather large sample of surgically treated lung cancer patients were included in the study patients', fatigue was measured both preoperatively and after surgery. This gives information about fatigue after lung cancer surgery.
- There was a five-month gap between the two measurement points. During this time, other factors might have influenced patients' fatigue experience.
- There were limited information on symptom management interventions such as physiotherapy and rehabilitation

1. Introduction

Lung cancer (LC) is presently one of the most common malignancies, and it is estimated that 20% of cancer-related deaths are caused by LC.[1] Only 20% of patients diagnosed with non-small-cell lung cancer meet the criteria for surgery due to their late stage at diagnosis; for these patients, surgery may be curative.[2] In Norway during 2014, five-year LC survival was generally 19% in women and 13% in men.[1] In surgically treated patients, the five-year survival ranges from 50% to 70%, depending on the tumor stage at surgery.

Fatigue is common among cancer patients. An estimated 75–90% of patients with LC report fatigue after cancer treatment.[3,4] Fatigue has been described as a complex, multidimensional symptom and has been defined as a sense of exhaustion, lack of energy, or tiredness distinct from sleepiness, sadness, or weakness.[5] Cancer-related fatigue is related to cancer or its treatment, and interferes with usual functioning.[3] Fatigue has a negative impact on patients' health-related quality of life (HRQOL),[6] their ability to receive treatment, and their long-term prognosis. Although there are limited data on LC and fatigue in patients who have undergone surgery, it has been shown that fatigue has a negative impact on HRQOL in

LC survivors.[7] One study showed that fatigue was a significant predictor of survival at each time point assessed.[8] In another study on symptom severity after thoracotomy, fatigue was reported as the most common and severe symptom at every time point.[7]

Several studies have reported interrelations between fatigue, cough, and dyspnea.[8–11] Fatigue is also strongly related to symptoms of depression and anxiety.[12,13] Associations between fatigue and sex, pain, insomnia, and dyspnea have also been reported.[12,14] Studies on fatigue in populations with lung cancer in different stages have also shown strong correlations between fatigue and sleep disturbance.[6,15–17] Sarna et al.,[12] found that symptom severity in surgical patients was related to the extent of their comorbid condition. Other studies of patients with LC have also shown correlations between comorbidities and fatigue,[6] as well as strong correlations between pulmonary diseases such as COPD and asthma, and fatigue.[3,18] Studies of fatigue in the general population has shown a higher proportion of severe fatigue cases among women than among men.[19,20] Thus, examining differences in fatigue in relation to sex among LC patients is of interest. Fatigue has a negative impact on both patients with LC and survivors in general;[21] however, to our knowledge, there have been no studies to date specifically investigating fatigue in surgically treated patients with LC.

Thus, our aim was to examine the relationships between fatigue and disease characteristics, treatment, and other symptoms. We hypothesized that fatigue levels at five-month follow-up would be significantly related to: (1) sex, (2) clinical variables (preoperative comorbidities, forced expiratory volume in one second [FEV1], and forced vital capacity [FVC]); (3) preoperative symptoms (shortness of breath, coughing, depression, anxiety, pain, and sleep disturbance); and (4) treatment and medical variables (surgery type, cancer stage, and adjuvant therapy).

2. Material and methods

This study is part of a larger, longitudinal investigation of symptoms in patients with LC who were eligible for surgery,[22–24] for which data were collected prior to surgery and prospectively at four time points up to one year after surgery. Here, we analyzed the data collected prior to surgery and at the five-month follow-up to gain insight into patients' experiences with fatigue before surgery and after the immediate postoperative period.

2.1. Patients and settings

Patients were included if they were 18 years or older, scheduled for primary LC surgery, and could understand, read, and write Norwegian. Patients with a benign or metastatic disease, whose surgery was canceled, or who had cognitive impairment, were excluded. We recruited patients from three university hospitals in Norway: Oslo University Hospital, St. Olav University Hospital, and Haukeland University Hospital. The recruitment started in November 2010 and was completed in March 2012.

2.2 Patient and Public Involvement

The study was founded Norwegian Cancer Society (NCS). The study was discussed with representatives from the Lung Cancer subgroup before the study started and an article about the main result from the study is published in the membership journal for patients with lung cancer.

2.3. Study procedures

Hospital research staff approached patients and explained the study purpose: 91% of the participants were recruited in the hospital 1–3 days before surgery, and the remainder in outpatient clinics prior to surgery. Patients signed a written informed consent before they completed several self-report questionnaires with information on sociodemographic and clinical characteristics, and symptoms both prior to surgery and at a five-month follow-up.

Permission to use the questionnaire was obtained from the copyright detectors before study start. Data on type of tumor, cancer stage, surgery type, and lung function were collected from the patients' medical records. FEV1 and FVC were measured preoperatively using a spirometer. Five months after surgery, patients received questionnaires by regular mail, along with a postage-paid return envelope.

2.4. Instruments and assessment

2.4.1. Sociodemographic, clinical, symptom, and fatigue characteristics

Patients provided information on their sex, marital status, living situation, level of education, and employment status. Information on age, smoking status, FEV1, tumor histology, cancer stage, type of surgery, pre- and postoperative treatment, postoperative complications, and TNM classification were collected from patients' medical records; the TNM classification is a system for cancer staging based on tumor (T), node (N), and metastasis (M).

2.4.2. Comorbidities

Comorbidities were measured using the Self-administered Comorbidity Questionnaire-19 (SCQ-19),[25] on which scores can range from 0 to 57, with a higher score indicating a more severe comorbidity profile. The SCQ includes 16 comorbidities and three optional conditions. Patients indicated whether or not they had the comorbid condition (yes/no); if they had the condition they were asked if they received treatment for it; and finally if it limited their activities. The SCQ-19 has well-established validity and reliability and has been used to assess comorbidity in Norwegian oncology patients.[25] Only the number of comorbidities was used in the present study.

2.4.3. Fatigue

The Lee Fatigue Scale (LFS),[5] was used to measure fatigue at baseline and five-month follow-up. The LFS consists of 18 items designed to assess fatigue (13 items) and energy (5 items). We used only the 13 fatigue items in this study. Patients were asked to rate each item on a 0–10 scale, with a higher score indicating greater fatigue severity. A fatigue score was calculated using the mean of the 13 items at each measurement. The LFS has well-established validity and reliability.[26,27] Fatigue scores at baseline were defined as preoperative fatigue and at five-month follow-up as postoperative fatigue.

2.4.4. Shortness of breath and cough

The European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire – Lung Cancer Module (EORTC QLQ-LC13),[28] was used to measure shortness of breath and cough. Patients were asked to rate their severity on each shortness of breath and cough item using a four-point Likert scale where 1 = not at all; 2 = a little; 3 = quite a bit; and 4 = very much. The EORTC QLQ-LC13 has been validated in Norwegian LC patients.[29,30]

2.4.5. Depression

The Center for Epidemiologic Studies – Depression Scale (CES-D),[31] was used to measure depression symptoms. The scale has 20 items related to depression and patients were asked to report how they felt during the past week. Each item was rated on a four-point Likert scale and scores ranged from 0 to 60, with a higher score indicating a higher level of depression. A total depression score was calculated as the mean of all the sub scores. Acceptable reliability and validity have been reported in a previous study.[32]

2.4.6. Anxiety

The State-Trait Anxiety Inventory (STAI, Y-2),[33] was used to measure anxiety. The STAI includes 20 items related to anxiety rated on a four-point Likert scale. Scores range

from 20 to 80, with a higher score indicating a higher level of anxiety. The STAI has been validated in patients with LC.[34]

2.4.7. Sleep disturbance

The General Sleep Disturbance Scale (GSDS),[35] was used to measure sleep disturbance. The GSDS consists of 21 items related to sleep disturbance. Each item is rated on a numeric rating scale ranging from 0 (never) to 7 (every day). A sleep disturbance score was calculated from the mean of all scale items. Higher scores indicate more severe sleep disturbance. The GSDS has been validated in cancer patients.[26]

2.4.8. Pain

The Brief-Pain Inventory (BPI),[36] was used to measure pain interference. The BPI is a multidimensional questionnaire measuring pain intensity (four items), pain interference (seven items), pain relief (one item), and pain location (body map). Only pain interference was used in the present study. The seven interference items (general activity, normal work, walking ability, mood, relationships with other people, sleep, and enjoyment of life) were combined into a single interference item. The measurement scale ranges from 0 to 10, with higher scores indicating more pain interfering with daily living. The BPI has been validated in Norwegian cancer patients.[37]

2.5. Ethics

The Regional Ethics Committee for the South-East 2010/1508, and the Institutional Review Boards (Personvernombudet) at each hospital approved the study. Each participant received written information about the study and signed informed consent. The article complies with the STROBE guidelines.[38]

2.6. Statistical analyses

Descriptive statistics were used to describe the sociodemographic, clinical, and treatment characteristics of the patient sample. Differences between sexes were analyzed using a chi-squared test for categorical variables and an independent Student's *t* test for the continuous variables. One-way ANOVA was used to explore differences within groups on levels of pre- and postoperative fatigue. Patients with more than 20% of missing items on the LFS were excluded from analyses. If the scales had less than 20% missing, the score were calculated from the mean of the particular patient's valid scores. The bivariate relationships between symptoms and fatigue at baseline were assessed using Pearson correlation analyses. Variables with significant correlation coefficients on bivariate analyses were included in a hierarchical linear analyses.

Two stepwise multivariate regression analyses were performed. In the first analysis, preoperative fatigue was the dependent variable. In the second analysis, postoperative fatigue was the dependent variable. In both analyses, age and sex were entered in step one. Clinical variables including comorbidities, FEV1, and FVC were entered in step two. Finally, the symptom variables of shortness of breath, cough, depression, anxiety, sleep disturbance, and pain interference were entered in step three. For the second regression analysis, the model also included a fourth step in which preoperative fatigue was included as an independent variable.

The entry of variables in different model steps was carried out according to theoretical and logical considerations. For all analyses, $p<0.05$ was considered statistically significant. Post hoc statistical power was calculated for hierarchical multiple regression: with an effect size (f^2) for set B (five-month follow-up) at 0.15 (medium),[39] 11 predictors in set A and 12 in set B, a probability level of 0.05, and a sample size of 196, the observed power for the addition of set B was 0.95.[40] Data were analyzed using SPSS (IBM Corporation, Armonk, NY, USA) version 24.0.

Table 1
Demographic, clinical, and treatment characteristics of the patients (N=196).

	Total	Men	Women	Statistics	p-value
Sociodemographics					
Age in years (mean, SD)	196	66.7 (8.2)	64.1 (7.9)	t 2.28 (194)	**0.024**
		% (n)	% (n)	χ (df)	
Cohabitation (living with someone)	147	84.0 (89)	(69.0) 58	5.95 (1)	**0.015**
Work status					
Full or part time	58	27.6 (29)	34.9 (29)	.80 (2)	0.25
Sick leave or disability	47	22.9 (24)	27.7 (23)		
Retired	83	49.5 (52)	37.3 (31)		
Education					
≤12 years	158	81.1(86)	86.7 (72)	1.07 (1)	0.30
≥13 years	31	18.9 (20)	13.3 (11)		
Clinical variables		Mean (SD)	Mean (SD)	t (df)	
Comorbidities (SCQ)	193	3.72 (3.3)	4.67 (4.0)	–1.74 (161.4)	0.08
FEV1 (expected %)	190	76.7 (19.2)	80.4 (22.8)	–1.20 (188)	0.23
FVC (expected %)	183	91.2 (15.00)	102.4 (19.4)	t –4.30(149.8)	**<.001**

3. Results

3.1. Sample characteristics

Statisticians calculated that 300 should be included in the study to ensure sufficient strength. Totally, 375 patients with presumptive primary lung cancer were asked to participate in the study and 307 agreed to participate (Fig 1). Among these, 196 patients who answered the questionnaire both preoperatively and at five-month follow-up and had valid fatigue scores at both measurement points were included in the study. Sample characteristics are shown in Table 1. Although women were younger, more women lived alone, reported higher FVC, less shortness of breath and had a higher proportion of adenocarcinoma cancer type, and was more active in physiotherapy and rehabilitation than men, their level of fatigue did not differ. Most of the sample had adenocarcinoma stage 1A or 1B, received no preoperative treatment and had a lobectomy.

The mean preoperative fatigue scores were 2.49 (SD=2.02) for men and 2.47 (SD=1.96) for women. At the five-month follow-up, the postoperative fatigue scores were 3.0 (SD=2.1) for men and 2.9 (SD=2.1) for women. There were no significant differences in fatigue level preoperatively between those who completed or did not complete the postoperative fatigue scale.

Symptoms					
Fatigue (LFS) baseline	196	2.50 (2.0)	2.48 (2.0)	t –0.07 (194)	0.94
Fatigue (LFS) 5-month follow-up	196	3.0 (2.2)	2.9 (2.1)	t 0.32 (194)	0.75
Shortness of breath (EORTC)	194	2.24 (0.8)	2.00 (0.7)	t –2.28 (192)	**0.023**
Cough (EORTC)	193	1.96 (0.7)	1.98 (0.8)	t –0.11 (191)	0.92
Depression (CES-D)	190	10.49 (8.8)	12.92 (8.8)	t –1.89 (188)	0.06
Anxiety (STAI)	192	51.22 (3.1)	50.80 (2.9)	t 0.96 (190)	0.34
Sleep disturbance (GSDS)	191	2.26 (1.05)	2.32 (1.00)	t –0.36 (189)	0.72
		% (n)	% (n)	χ (df)	p-value
Pain (BPI) yes	171	40.0 (38)	51.3 (39)	2.18 (1)	0.14
Pathology and treatment					
Tumor type					
Adenocarcinoma	106	45.0 (50)	65.9 (56)	24.00 (4)	**<.001**
Squamous cell	66	45.0 (50)	12.9 (11)		
Small cell	5	1.8 (2)	3.5 (3)		
Carcinoid	6	1.8 (2)	4.7 (4)		
Other	18	6.3 (7)	12.9 (11)		
Stage of cancer disease					
IA	58	25.2 (27)	41.3 (31)	9.12 (4)	0.06
IB	59	35.5 (38)	28.0 (21)		
II	35	24.3 (26)	12.0 (9)		
IIIA	31	14.0 (15)	18.7 (14)		
IIIB-IV	1	0.9 (1)	–		
Preoperative treatment					
None	192	97.3 (108)	98.8 (84)	1.58 (3)	0.66
Radiation	1	0.9 (1)	–		
Chemotherapy	1	0.9 (1)	–		
Combination	2	0.9 (1)	1.2 (1)		
Type of surgery					
Lobectomy	133	67.6 (75)	68.2 (58)	1.26 (4)	0.87
Bilobectomy	15	6.3 (7)	9.4 (8)		
Pneumonectomy	18	9.0 (10)	9.4 (8)		
Wedge resection	18	9.9 (11)	8.2 (7)		
Thoracoscopic	12	7.2 (8)	4.7 (4)		
Postoperative complications					
Reoperation	9	3.6 (4)	5.9 (5)	0.57 (1)	0.45
Pneumonia	50	27 (30)	23.8 (20)	0.26 (1)	0.61
Posttreatment					
Radiation therapy	16	9.9 (11)	5.9 (5)	1.04 (1)	0.31
Chemotherapy	57	30.6 (34)	27.1 (23)	0.30 (1)	0.59
Physiotherapy	58	24.3 (26)	38.1 (32)	4.24 (1)	**0.04**
Rehabilitation	24	7.5 (8)	19.3 (16)	5.90 (1)	**0.015**

Abbreviations: SCQ, Self-administered Comorbidity Questionnaire; FEV1, forced expiratory volume in one second; FVC, Forced vital Capacity; EORTC, European Organization for Research and Treatment of Cancer; CES-D, Center for Epidemiologic Studies – Depression Scale; STAI, State-Trait Anxiety Inventory; GSDS, General Sleep Disturbance Scale; BPI, Brief Pain Inventory; LFS, Lee Fatigue Inventory.
Notes: Fatigue, range 0–10, higher score indicating greater fatigue severity; shortness of breath and cough range 1–4, higher score indicating more shortness of breath and cough; depression, range 0–60, higher score indicating more depression; pain, range 0–10, higher score indicating more pain; comorbidity, range 0–57, higher score indicating more comorbidity; anxiety, range 20–80, higher score indicating more anxiety; sleep disturbance, range 0–7, higher score indicating more severe sleep disturbance.
Bold numbers represent significant relationships.

3.2. Bivariate analyses

The bivariate analyses between the symptom variables are shown in Table 2. Medical and treatment characteristics including cancer stage, tumor type, type of surgery, and postoperative treatment such as radiation therapy, chemotherapy, physiotherapy, and rehabilitation were not significantly correlated with either preoperative or postoperative

fatigue and, thus, were not included in the final model. Sociodemographic variables including work, education, and cohabitation were excluded before the final analyses for the same reason.

Table 2
Correlation matrix for symptoms at baseline, and fatigue baseline and 5-month follow-up (N=196).

	1	2	3	4	5	6	7	8	9	10	11	12	13
1 Age	1												
2 Sex	–.16*	1											
3 FEV1	.06	.09	1										
4 FVC	.02	.31*	.65*	1									
5 Fatigue (LFS) baseline	–.23*	–.01	–.19*	–.14	1								
6 Fatigue (LFS) 5-month follow-up	–.16*	–.02	–.22*	–.17*	.52*	1							
7 Comorbidities (SCQ)	.04	.13	–.23*	–.12	.29*	.31*	1						
8 Shortness of breath (EORTC)	–.03	–.16*	–.25*	–.24*	.35*	.62*	.31*	1					
9 Cough (EORTC)	–.04	.01	–.14	–.15*	.33*	.33*	–.04	.17*	1				
10 Depression (CES-D)	–.15*	.14	–.07	–.03	.47*	.31*	.17*	.17*	.12	1			
11 Anxiety (STAI)	.06	–.07	.08	–.00	–.24*	–.12	–.08	–.01	–.1	–.28*	1		
12 Sleep disturbance (GSDS)	–.22*	.03	–.09	–.08	.50*	.41*	.18*	.26*	.14	.57*	–.22*	1	
13 Pain (BPI)	.1	–.11	.09	.1	–.25*	–.23*	–.18*	–.15	–.02	–.08	.18*	–.23*	1

* Correlation is significant at the 0.05 level (2-tailed).
Abbreviations: SCQ, Self-administered Comorbidity Questionnaire; FEV1, Forced expiratory volume in one second; FVC, Forced vital Capacity; EORTC, European Organization for Research and Treatment of Cancer; CES-D, Center for Epidemiologic Studies – Depression Scale; STAI, State-Trait Anxiety Inventory; GSDS, General Sleep Disturbance Scale; BPI, Brief Pain Inventory; LFS, Lee Fatigue Inventory.

3.3. Multivariate analyses

Hierarchical multiple regression analyses were used to assess the impact of the selected variables on levels of preoperative and postoperative fatigue (Table 3). Age, sex, and clinical variables were unrelated to preoperative fatigue.

Table 3
Results from the two hierarchical multivariate linear regression analyses with preoperative fatigue and postoperative fatigue (at 5-month follow-up) were used as dependent variables (N=196).

	Preoperative fatigue			Postoperative fatigue		
	Beta	β	p-value	Beta	β	p-value
Sociodemographics						
Age	–0.04	–0.14	0.13	–0.02	–0.07	0.26
Sex	–0.39	–0.10	0.16	0.03	0.01	0.93
Explained variance (R^2)		**5.5%**	**0.01**		2.9%	0.10
Clinical variables						
FEV1	–0.00	–0.05	0.63	–0.00	–0.03	0.71
FVC	–0.01	0.04	0.61	0.00	0.04	0.65
Comorbidity	0.10	0.18	0.008	0.05	0.08	0.19
R^2 change		**10.6%**	**<0.001**		**12.1%**	**<0.001**
Explained variance		16.1			15.0	
Fatigue at baseline						
Fatigue				**0.18**	**0.17**	**0.03**
R^2 change					**16.2%**	**<0.001**
Explained variance					31.2%	
Other symptoms at baseline						
Shortness of breath	0.33	0.13	0.06	**1.27**	**0.46**	**<0.001**
Cough	**0.64**	**0.25**	**<0.001**	**0.50**	**0.18**	**0.004**
Depression	**0.05**	**0.23**	**0.003**	0.01	0.04	0.63
Anxiety	–0.05	–0.07	0.29	0.00	0.00	0.95
Sleep disturbance	**0.02**	**0.20**	**0.01**	0.01	0.11	0.12
Pain	**0.44**	**0.20**	**0.01**	–0.29	–0.07	0.26
R^2 change		**30.5%**	**<0.001**		**23.2%**	**<0.001**
Explained variance		46.6%			54.3%	

Abbreviations: FEV1, Forced expiratory volume in one second; FVC, Forced vital capacity.
Note: Bold numbers represent significant relationships.

At baseline, patients who reported pain scored higher on fatigue (M=2.9, SD=2.05) compared with patients who reported no pain (M=2.03, SD=1.8, t=3.28, p=0.001). Patients who reported pain at baseline also reported higher mean fatigue at five-month follow-up (M=3.54, SD=2.21) compared with those who reported no pain at baseline (M=2.55,

SD=2.04, t=3.08, p=0.002). Among the reported symptoms, coughing, depression, sleep disturbance, and pain interference were related to preoperative fatigue after controlling for age, sex, clinical variables, and the other symptoms. The total model explained 46.6% of variance, while 30.5% was explained by the other symptoms.

At five-month follow-up, the only variables that predicted fatigue after controlling for age, sex, clinical variables, preoperative fatigue, and symptoms were shortness of breath and coughing. The total model explained 54.3% of variance, while 23.2% was explained by the other symptoms.

4. Discussion

To our knowledge, this is the first study examining fatigue in surgically treated patients with LC , including both preoperative data and data from five-month follow-up. Preoperative fatigue was significantly correlated with comorbidities and all the included symptoms in the bivariate analyses, while postoperative fatigue was significantly correlated with comorbidities and four out of six measured symptoms. However, shortness of breath was the only baseline variable that predicted postoperative fatigue.

4.1. Relationship between postoperative fatigue level and preoperative symptoms

Shortness of breath, coughing, depression, anxiety, sleep disturbance, and pain interference were significantly correlated with level of preoperative fatigue. Except for anxiety and pain interference, the same symptoms were associated with postoperative fatigue in the bivariate analyses at five-month follow-up. Before surgery, cough was significantly associated with fatigue, while shortness of breath was the symptom predictive of postoperative fatigue. Shortness of breath is a prevalent and disturbing symptom in these patients, which is physiologically based on disease location, damage caused by lung tumors, and history of smoking. Shortness of breath requires intensive effort to breath, thus making

patients tired. The constant use of rib and respiratory muscles caused by shortness of breath can exacerbate fatigue.[41] These patients may benefit from prescribed bronchodilators and non-pharmacological treatment such as physical activity. For some, it may be useful to learn how to manage shortness of breath by controlled breathing techniques and practicing calming techniques during shortness of breath episodes.

Consistent with previous research, we found that fatigue in patients with LC undergoing surgery is correlated with their symptoms and might cluster with other symptoms.[2,42] Cheville et al.,[2] found a cluster of fatigue, cough, and dyspnea in LC survivors lasting for eight years; however, in a later study, the same group found that the cluster did not predict patient outcomes but that fatigue and dyspnea, alone and together, were sufficient to predict important outcomes.[8]

4.2. Relationship between fatigue and patients' disease characteristics and treatment

Although comorbidities did not predict postoperative fatigue in our analyses, there was a bivariate relationship with fatigue both pre- and postoperatively. Others have also reported correlations between comorbidity and fatigue.[6,12] Respiratory comorbidities and cardiac disease are especially related to fatigue in patients with LC.[3,43] We also found a correlation between fatigue and spirometry results, with lower FEV1 and FVC related to higher levels of fatigue at both measurement times. These variables were related to comorbidity and are an important factor in identifying and screening patients at risk for developing fatigue. Poorer respiratory test outcomes could indicate shortness of breath or respiratory comorbidities, such as COPD, and may lead to distress and exhaustion and contribute to fatigue in these patients.

Surgery type has been established as a predictor of fatigue in LC survivors and surgery has been associated with a greater symptom burden generally.[21] In the present study, treatment and disease variables did not correlate with postoperative fatigue at five-month follow-up. These findings are inconsistent with other reports in which correlations have been

found between fatigue and chemotherapy,[9] and radiotherapy.[11] However, our findings are consistent with those from a general cancer population on the symptom cluster of pain, fatigue, sleep disturbance, and depression. That group found that symptom experiences were independent of demographic, disease, or treatment effects; their findings suggest that different subgroups of patients may harbor different determinants (e.g., genetic) for experiencing symptoms and suggested etiology that are independent of demographic, disease, or treatment characteristics.[44]

4.3. Limitations

Some study limitations need to be acknowledged. There was a five-month gap between the two measurement points. During this time, other factors might have influenced patients' fatigue experience. Surgery type might also be a predictor of patient fatigue.[21] In this study, only 6% of patients had video-assisted thoracoscopy; thus, it is not possible to determine whether this influenced postoperative fatigue. Detailed information on symptom management interventions such as physiotherapy and rehabilitation was not collected. However, even if these variables had been included, no detailed information about the type and length of these therapies was available.

5. Conclusions

Based on the findings in the present study, patients should be screened for symptoms before surgery and offered treatment for their symptoms to reduce pre- and postoperative fatigue. Special attention should be given to treating patients' shortness of breath, since this is a modifiable predictor for which treatments are available. Further research should pay specific attention to the pair of symptoms of shortness of breath and fatigue, and to the effects on fatigue and QOL when shortness of breath is treated.

Fig. 1. Flowchart of the enrollment and exclusion of patients in the study.

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Footnotes

Contributors: TR and TO conceptualised the study. TO wrote the protocol manuscript and TR contributed to protocol development. TO had responsibility for data collection. TH and AL conducted the data analyses and drafted the initial report. TO and TR critically reviewed and edited the manuscript. All authors read and approved the final manuscript. Each author contributed to interpreting the analyses and to critically revising the article, and approved the final draft.

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Patient consent: Each participant signed informed consent.

Ethics approval The Regional Ethics Committee for the South-East 2010/1508, and the Institutional Review Boards (Personvernombudet) at each hospital approved the study. Each participant received written information about the study and signed informed consent.

Data availability statement: All data relevant to the study are included in the article.

Competing interests: None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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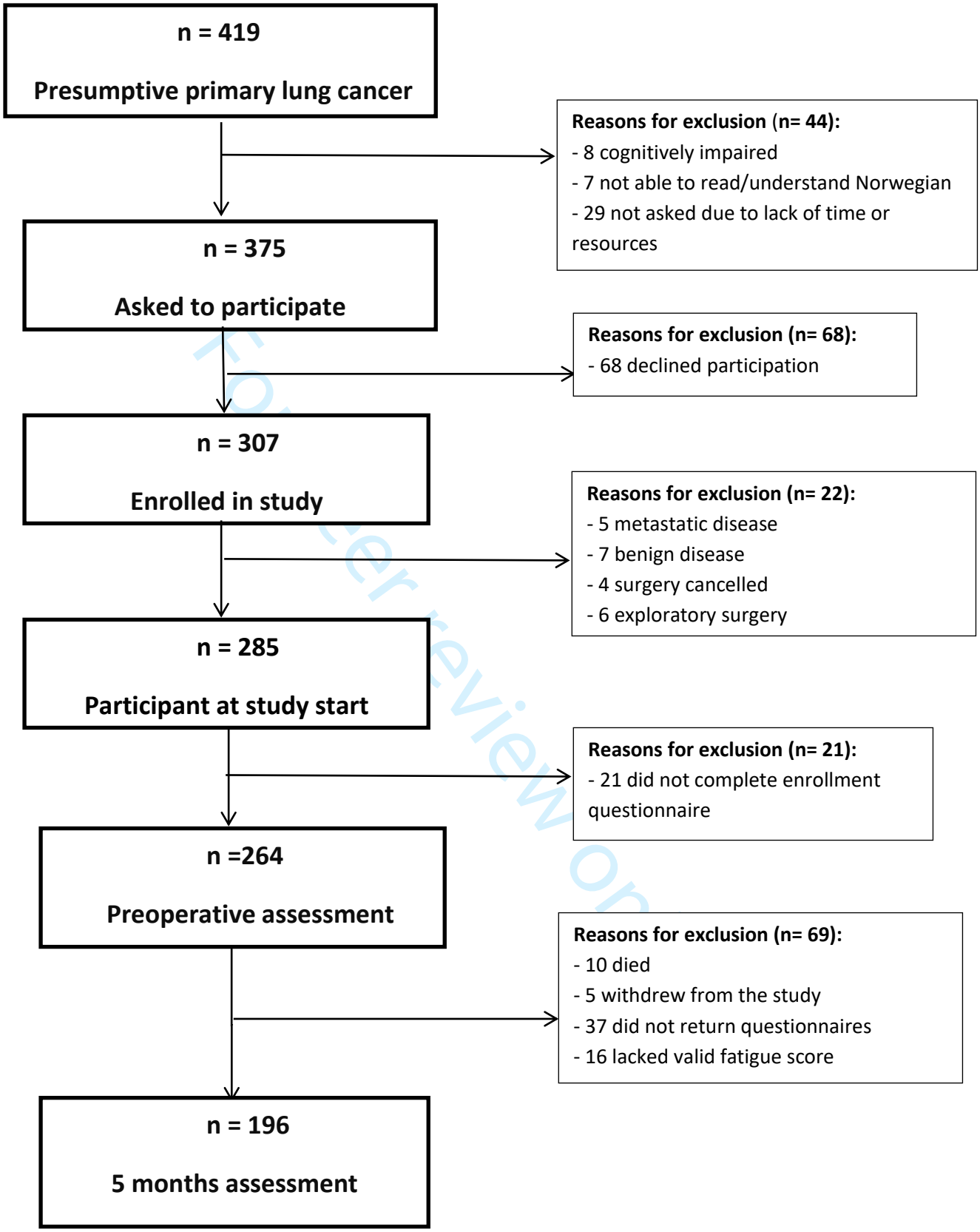

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page: 1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page: 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page: 3 and 4
Objectives	3	State specific objectives, including any prespecified hypotheses Page: 4
Methods		
Study design	4	Present key elements of study design early in the paper Page: 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page: 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page: 5 and 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Page: Not actual
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page: 5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page: 5-8
Bias	9	Describe any efforts to address potential sources of bias Page: Not actual
Study size	10	Explain how the study size was arrived at Page: 10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page:
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page: 9
		(*b*) Describe any methods used to examine subgroups and interactions Page: 9
		(*c*) Explain how missing data were addressed Page: 9
		(*d*) If applicable, explain how loss to follow-up was addressed Page: 9
		(*e*) Describe any sensitivity analyses Page: 9

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page: Fig 1, page 10
		(b) Give reasons for non-participation at each stage Page: Fig 1, page 10
		(c) Consider use of a flow diagram Page: Fig 1, page 10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page: 11
		(b) Indicate number of participants with missing data for each variable of interest Page: 11
		(c) Summarise follow-up time (eg, average and total amount) Page: 11
Outcome data	15*	Report numbers of outcome events or summary measures over time Page: 10 -12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page: 12
		(*b*) Report category boundaries when continuous variables were categorized Page: 12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Page: Not actual
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page: Not actual
Discussion		
Key results	18	Summarise key results with reference to study objectives Page: 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page: 2 + 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page: 15 and 16
Generalisability	21	Discuss the generalisability (external validity) of the study results Page: 16
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page: 18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Predicting postoperative fatigue in surgically treated lung cancer patients in Norway– a longitudinal five-month follow-up study.

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ABSTRACT

Objectives: Despite the negative influence of fatigue on quality of life in patients who undergo lung cancer surgery, little is known about the possible predictors of postoperative fatigue. The aim of this study was to examine demographic and clinical characteristics that might predict postoperative fatigue five months after lung cancer surgery.

Design: A prospective longitudinal follow up study comprising pre- and postoperative questionnaires, including Lee Fatigue Scale, and sociodemographic and clinical data.

Setting: Three university hospitals in Norway (e.g., Oslo University Hospital, St. Olav University Hospital, Haukeland University Hospital).

Participants: In total, 196 surgically treated patients who answered the questionnaires both preoperatively and at five-month follow-up with valid fatigue scores.

Results: Bivariate analyses showed that preoperative fatigue was associated with comorbidities and the symptoms of shortness of breath, cough, depression, anxiety, sleep disturbance, and pain. Only cough was directly associated with preoperative fatigue in a regression model. Comorbidities and the symptoms of shortness of breath, cough, depression, and sleep disturbance were associated with postoperative fatigue in the bivariate analyses, but only shortness of breath was associated with postoperative fatigue in the regression model. We did not find any significant correlations between fatigue and any treatment variable.

Conclusion: Clinicians should pay special attention to lung symptoms and be aware that these may lead to long-term postoperative fatigue. Further research should examine whether interventions reducing lung symptoms, such as shortness of breath and coughing, may prevent development of fatigue in patients undergoing lung cancer surgery.

Key words: Fatigue, Lung Cancer, Neoplasm, Quality of Life, Surgery

Strengths and limitations of this study

- Fatigue is a symptom that has a great impact on patients quality of life and this topic is relevant both to patients and healthcare providers
- A rather large sample of surgically treated lung cancer patients were included in the study patients', fatigue was measured both preoperatively and after surgery. This gives information about fatigue after lung cancer surgery.
- There was a five-month gap between the two measurement points. During this time, other factors might have influenced patients' fatigue experience.
- There were limited information on symptom management interventions such as physiotherapy and rehabilitation

1. Introduction

Lung cancer (LC) is presently one of the most common malignancies, and it is estimated that 20% of cancer-related deaths are caused by LC.[1] Only 20% of patients diagnosed with non-small-cell lung cancer meet the criteria for surgery due to their late stage at diagnosis; for these patients, surgery may be curative.[2] In Norway during 2014, five-year LC survival was generally 19% in women and 13% in men.[1] In surgically treated patients, the five-year survival ranges from 50% to 70%, depending on the tumor stage at surgery.

Fatigue is common among cancer patients. An estimated 75–90% of patients with LC report fatigue after cancer treatment.[3,4] Fatigue has been described as a complex, multidimensional symptom and has been defined as a sense of exhaustion, lack of energy, or tiredness distinct from sleepiness, sadness, or weakness.[5] Cancer-related fatigue is related to cancer or its treatment, and interferes with usual functioning.[3] Fatigue has a negative impact on patients' health-related quality of life (HRQOL),[6] their ability to receive treatment, and their long-term prognosis. Although there are limited data on LC and fatigue in patients who have undergone surgery, it has been shown that fatigue has a negative impact on HRQOL in

LC survivors.[7] One study showed that fatigue was a significant predictor of survival at each time point assessed.[8] In another study on symptom severity after thoracotomy, fatigue was reported as the most common and severe symptom at every time point.[7]

Several studies have reported interrelations between fatigue, cough, and dyspnea.[8–11] Fatigue is also strongly related to symptoms of depression and anxiety.[12,13] Associations between fatigue and sex, pain, insomnia, and dyspnea have also been reported.[12,14] Studies on fatigue in populations with lung cancer in different stages have also shown strong correlations between fatigue and sleep disturbance.[6,15–17] Sarna et al.,[12] found that symptom severity in surgical patients was related to the extent of their comorbid condition. Other studies of patients with LC have also shown correlations between comorbidities and fatigue,[6] as well as strong correlations between pulmonary diseases such as COPD and asthma, and fatigue.[3,18] Studies of fatigue in the general population has shown a higher proportion of severe fatigue cases among women than among men.[19,20] Thus, examining differences in fatigue in relation to sex among LC patients is of interest. Fatigue has a negative impact on both patients with LC and survivors in general;[21] however, to our knowledge, there have been no studies to date specifically investigating fatigue in surgically treated patients with LC.

Thus, our aim was to examine the relationships between fatigue and disease characteristics, treatment, and other symptoms. We hypothesized that fatigue levels at five-month follow-up would be significantly related to: (1) sex, (2) clinical variables (preoperative comorbidities, forced expiratory volume in one second [FEV1], and forced vital capacity [FVC]); (3) preoperative symptoms (shortness of breath, coughing, depression, anxiety, pain, and sleep disturbance); and (4) treatment and medical variables (surgery type, cancer stage, and adjuvant therapy).

2. Material and methods

This study is part of a larger, longitudinal investigation of symptoms in patients with LC who were eligible for surgery,[22–24] for which data were collected prior to surgery and prospectively at four time points up to one year after surgery. Here, we analyzed the data collected prior to surgery and at the five-month follow-up to gain insight into patients' experiences with fatigue before surgery and after the immediate postoperative period.

2.1. Patients and settings

Patients were included if they were 18 years or older, scheduled for primary LC surgery, and could understand, read, and write Norwegian. Patients with a benign or metastatic disease, whose surgery was canceled, or who had cognitive impairment, were excluded. We recruited patients from three university hospitals in Norway: Oslo University Hospital, St. Olav University Hospital, and Haukeland University Hospital. The recruitment started in November 2010 and was completed in March 2012.

2.2 Patient and Public Involvement

The study was founded Norwegian Cancer Society (NCS). The study was discussed with representatives from the Lung Cancer subgroup before the study started and an article about the main result from the study is published in the membership journal for patients with lung cancer.

2.3. Study procedures

Hospital research staff approached patients and explained the study purpose: 91% of the participants were recruited in the hospital 1–3 days before surgery, and the remainder in outpatient clinics prior to surgery. Patients signed a written informed consent before they completed several self-report questionnaires with information on sociodemographic and clinical characteristics, and symptoms both prior to surgery and at a five-month follow-up.

Permission to use the questionnaire was obtained from the copyright detectors before study start. Data on type of tumor, cancer stage, surgery type, and lung function were collected from the patients' medical records. FEV1 and FVC were measured preoperatively using a spirometer. Five months after surgery, patients received questionnaires by regular mail, along with a postage-paid return envelope.

2.4. Instruments and assessment

2.4.1. Sociodemographic, clinical, symptom, and fatigue characteristics

Patients provided information on their sex, marital status, living situation, level of education, and employment status. Information on age, smoking status, FEV1, tumor histology, cancer stage, type of surgery, pre- and postoperative treatment, postoperative complications, and TNM classification were collected from patients' medical records; the TNM classification is a system for cancer staging based on tumor (T), node (N), and metastasis (M).

2.4.2. Comorbidities

Comorbidities were measured using the Self-administered Comorbidity Questionnaire-19 (SCQ-19),[25] on which scores can range from 0 to 57, with a higher score indicating a more severe comorbidity profile. The SCQ includes 16 comorbidities and three optional conditions. Patients indicated whether or not they had the comorbid condition (yes/no); if they had the condition they were asked if they received treatment for it; and finally if it limited their activities. The SCQ-19 has well-established validity and reliability and has been used to assess comorbidity in Norwegian oncology patients.[25] Only the number of comorbidities was used in the present study.

2.4.3. Fatigue

The Lee Fatigue Scale (LFS),[5] was used to measure fatigue at baseline and five-month follow-up. The LFS consists of 18 items designed to assess fatigue (13 items) and energy (5 items). We used only the 13 fatigue items in this study. Patients were asked to rate each item on a 0–10 scale, with a higher score indicating greater fatigue severity. A fatigue score was calculated using the mean of the 13 items at each measurement. The LFS has well-established validity and reliability.[26,27] Fatigue scores at baseline were defined as preoperative fatigue and at five-month follow-up as postoperative fatigue.

2.4.4. Shortness of breath and cough

The European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire – Lung Cancer Module (EORTC QLQ-LC13),[28] was used to measure shortness of breath and cough. Patients were asked to rate their severity on each shortness of breath and cough item using a four-point Likert scale where 1 = not at all; 2 = a little; 3 = quite a bit; and 4 = very much. The EORTC QLQ-LC13 has been validated in Norwegian LC patients.[29,30]

2.4.5. Depression

The Center for Epidemiologic Studies – Depression Scale (CES-D),[31] was used to measure depression symptoms. The scale has 20 items related to depression and patients were asked to report how they felt during the past week. Each item was rated on a four-point Likert scale and scores ranged from 0 to 60, with a higher score indicating a higher level of depression. A total depression score was calculated as the mean of all the sub scores. Acceptable reliability and validity have been reported in a previous study.[32]

2.4.6. Anxiety

The State-Trait Anxiety Inventory (STAI, Y-2),[33] was used to measure anxiety. The STAI includes 20 items related to anxiety rated on a four-point Likert scale. Scores range

from 20 to 80, with a higher score indicating a higher level of anxiety. The STAI has been validated in patients with LC.[34]

2.4.7. Sleep disturbance

The General Sleep Disturbance Scale (GSDS),[35] was used to measure sleep disturbance. The GSDS consists of 21 items related to sleep disturbance. Each item is rated on a numeric rating scale ranging from 0 (never) to 7 (every day). A sleep disturbance score was calculated from the mean of all scale items. Higher scores indicate more severe sleep disturbance. The GSDS has been validated in cancer patients.[26]

2.4.8. Pain

The Brief-Pain Inventory (BPI),[36] was used to measure pain interference. The BPI is a multidimensional questionnaire measuring pain intensity (four items), pain interference (seven items), pain relief (one item), and pain location (body map). Only pain interference was used in the present study. The seven interference items (general activity, normal work, walking ability, mood, relationships with other people, sleep, and enjoyment of life) were combined into a single interference item. The measurement scale ranges from 0 to 10, with higher scores indicating more pain interfering with daily living. The BPI has been validated in Norwegian cancer patients.[37]

2.5. Ethics

The Regional Ethics Committee for the South-East 2010/1508, and the Institutional Review Boards (Personvernombudet) at each hospital approved the study. Each participant received written information about the study and signed informed consent. The article complies with the STROBE guidelines.[38]

2.6. Statistical analyses

Descriptive statistics were used to describe the sociodemographic, clinical, and treatment characteristics of the patient sample. Differences between sexes were analyzed using a chi-squared test for categorical variables and an independent Student's *t* test for the continuous variables. One-way ANOVA was used to explore differences within groups on levels of pre- and postoperative fatigue. Patients with more than 20% of missing items on the LFS were excluded from analyses. If the scales had less than 20% missing, the score were calculated from the mean of the particular patient's valid scores. The bivariate relationships between symptoms and fatigue at baseline were assessed using Pearson correlation analyses. Variables with significant correlation coefficients on bivariate analyses were included in a hierarchical linear analyses.

Two stepwise multivariate regression analyses were performed. In the first analysis, preoperative fatigue was the dependent variable. In the second analysis, postoperative fatigue was the dependent variable. In both analyses, age and sex were entered in step one. Clinical variables including comorbidities, FEV1, and FVC were entered in step two. Finally, the symptom variables of shortness of breath, cough, depression, anxiety, sleep disturbance, and pain interference were entered in step three. For the second regression analysis, the model also included a fourth step in which preoperative fatigue was included as an independent variable.

The entry of variables in different model steps was carried out according to theoretical and logical considerations. For all analyses, $p<0.05$ was considered statistically significant. Post hoc statistical power was calculated for hierarchical multiple regression: with an effect size (f^2) for set B (five-month follow-up) at 0.15 (medium),[39] 11 predictors in set A and 12 in set B, a probability level of 0.05, and a sample size of 196, the observed power for the addition of set B was 0.95.[40] Data were analyzed using SPSS (IBM Corporation, Armonk, NY, USA) version 24.0.

Table 1
Demographic, clinical, and treatment characteristics of the patients (N=196).

	Total	Men	Women	Statistics	p-value
Sociodemographics					
Age in years (mean, SD)	196	66.7 (8.2)	64.1 (7.9)	t 2.28 (194)	**0.024**
		% (n)	% (n)	χ (df)	
Cohabitation (living with someone)	147	84.0 (89)	(69.0) 58	5.95 (1)	**0.015**
Work status					
Full or part time	58	27.6 (29)	34.9 (29)	.80 (2)	0.25
Sick leave or disability	47	22.9 (24)	27.7 (23)		
Retired	83	49.5 (52)	37.3 (31)		
Education					
≤12 years	158	81.1(86)	86.7 (72)	1.07 (1)	0.30
≥13 years	31	18.9 (20)	13.3 (11)		
Clinical variables		Mean (SD)	Mean (SD)	t (df)	
Comorbidities (SCQ)	193	3.72 (3.3)	4.67 (4.0)	–1.74 (161.4)	0.08
FEV1 (expected %)	190	76.7 (19.2)	80.4 (22.8)	–1.20 (188)	0.23
FVC (expected %)	183	91.2 (15.00)	102.4 (19.4)	t –4.30(149.8)	**<.001**
Symptoms					
Fatigue (LFS) baseline	196	2.50 (2.0)	2.48 (2.0)	t –0.07 (194)	0.94
Fatigue (LFS) 5-month follow-up					

3. Results

3.1. Sample characteristics

Totally, 375 patients with presumptive primary lung cancer were asked to participate in the study and 307 agreed to participate (Fig 1). Among these, 196 patients who answered the questionnaire both preoperatively and at five-month follow-up and had valid fatigue scores at both measurement points were included in the study. Sample characteristics are shown in Table 1. Although women were younger, more women lived alone, reported higher FVC, less shortness of breath and had a higher proportion of adenocarcinoma cancer type, and was more active in physiotherapy and rehabilitation than men, their level of fatigue did not differ. Most of the sample had adenocarcinoma stage 1A or 1B, received no preoperative treatment and had a lobectomy.

The mean preoperative fatigue scores were 2.49 (SD=2.02) for men and 2.47 (SD=1.96) for women. At the five-month follow-up, the postoperative fatigue scores were 3.0 (SD=2.1) for men and 2.9 (SD=2.1) for women. There were no significant differences in fatigue level preoperatively between those who completed or did not complete the postoperative fatigue scale.

	196	3.0 (2.2)	2.9 (2.1)	t 0.32 (194)	0.75
Shortness of breath (EORTC)	194	2.24 (0.8)	2.00 (0.7)	t –2.28 (192)	**0.023**
Cough (EORTC)	193	1.96 (0.7)	1.98 (0.8)	t –0.11 (191)	0.92
Depression (CES-D)	190	10.49 (8.8)	12.92 (8.8)	t –1.89 (188)	0.06
Anxiety (STAI)	192	51.22 (3.1)	50.80 (2.9)	t 0.96 (190)	0.34
Sleep disturbance (GSDS)	191	2.26 (1.05)	2.32 (1.00)	t –0.36 (189)	0.72
		% (n)	% (n)	χ (df)	p-value
Pain (BPI) yes	171	40.0 (38)	51.3 (39)	2.18 (1)	0.14
Pathology and treatment					
Tumor type					
Adenocarcinoma	106	45.0 (50)	65.9 (56)	24.00 (4)	**<.001**
Squamous cell	66	45.0 (50)	12.9 (11)		
Small cell	5	1.8 (2)	3.5 (3)		
Carcinoid	6	1.8 (2)	4.7 (4)		
Other	18	6.3 (7)	12.9 (11)		
Stage of cancer disease					
IA	58	25.2 (27)	41.3 (31)	9.12 (4)	0.06
IB	59	35.5 (38)	28.0 (21)		
II	35	24.3 (26)	12.0 (9)		
IIIA	31	14.0 (15)	18.7 (14)		
IIIB-IV	1	0.9 (1)	–		
Preoperative treatment					
None	192	97.3 (108)	98.8 (84)	1.58 (3)	0.66
Radiation	1	0.9 (1)	–		
Chemotherapy	1	0.9 (1)	–		
Combination	2	0.9 (1)	1.2 (1)		
Type of surgery					
Lobectomy	133	67.6 (75)	68.2 (58)	1.26 (4)	0.87
Bilobectomy	15	6.3 (7)	9.4 (8)		
Pneumonectomy	18	9.0 (10)	9.4 (8)		
Wedge resection	18	9.9 (11)	8.2 (7)		
Thoracoscopic	12	7.2 (8)	4.7 (4)		
Postoperative complications					
Reoperation	9	3.6 (4)	5.9 (5)	0.57 (1)	0.45
Pneumonia	50	27 (30)	23.8 (20)	0.26 (1)	0.61
Posttreatment					
Radiation therapy	16	9.9 (11)	5.9 (5)	1.04 (1)	0.31
Chemotherapy	57	30.6 (34)	27.1 (23)	0.30 (1)	0.59
Physiotherapy	58	24.3 (26)	38.1 (32)	4.24 (1)	**0.04**
Rehabilitation	24	7.5 (8)	19.3 (16)	5.90 (1)	**0.015**

Abbreviations: SCQ, Self-administered Comorbidity Questionnaire; FEV1, forced expiratory volume in one second; FVC, Forced vital Capacity; EORTC, European Organization for Research and Treatment of Cancer; CES-D, Center for Epidemiologic Studies – Depression Scale; STAI, State-Trait Anxiety Inventory; GSDS, General Sleep Disturbance Scale; BPI, Brief Pain Inventory; LFS, Lee Fatigue Inventory.
Notes: Fatigue, range 0–10, higher score indicating greater fatigue severity; shortness of breath and cough range 1–4, higher score indicating more shortness of breath and cough; depression, range 0–60, higher score indicating more depression; pain, range 0–10, higher score indicating more pain; comorbidity, range 0–57, higher score indicating more comorbidity; anxiety, range 20–80, higher score indicating more anxiety; sleep disturbance, range 0–7, higher score indicating more severe sleep disturbance.
Bold numbers represent significant relationships.

3.2. Bivariate analyses

The bivariate analyses between the symptom variables are shown in Table 2. Medical and treatment characteristics including cancer stage, tumor type, type of surgery, and postoperative treatment such as radiation therapy, chemotherapy, physiotherapy, and rehabilitation were not significantly correlated with either preoperative or postoperative fatigue and, thus, were not included in the final model. Sociodemographic variables including

work, education, and cohabitation were excluded before the final analyses for the same reason.

Table 2
Correlation matrix for symptoms at baseline, and fatigue baseline and 5-month follow-up (N=196).

	1	2	3	4	5	6	7	8	9	10	11	12	13
1 Age	1												
2 Sex	–.16*	1											
3 FEV1	.06	.09	1										
4 FVC	.02	.31*	.65*	1									
5 Fatigue (LFS) baseline	–.23*	–.01	–.19*	–.14	1								
6 Fatigue (LFS) 5-month follow-up	–.16*	–.02	–.22*	–.17*	.52*	1							
7 Comorbidities (SCQ)	.04	.13	–.23*	–.12	.29*	.31*	1						
8 Shortness of breath (EORTC)	–.03	–.16*	–.25*	–.24*	.35*	.62*	.31*	1					
9 Cough (EORTC)	–.04	.01	–.14	–.15*	.33*	.33*	–.04	.17*	1				
10 Depression (CES-D)	–.15*	.14	–.07	–.03	.47*	.31*	.17*	.17*	.12	1			
11 Anxiety (STAI)	.06	–.07	.08	–.00	–.24*	–.12	–.08	–.01	–.1	–.28*	1		
12 Sleep disturbance (GSDS)	–.22*	.03	–.09	–.08	.50*	.41*	.18*	.26*	.14	.57*	–.22*	1	
13 Pain (BPI)	.1	–.11	.09	.1	–.25*	–.23*	–.18*	–.15	–.02	–.08	.18*	–.23*	1

* Correlation is significant at the 0.05 level (2-tailed).
Abbreviations: SCQ, Self-administered Comorbidity Questionnaire; FEV1, Forced expiratory volume in one second; FVC, Forced vital Capacity; EORTC, European Organization for Research and Treatment of Cancer; CES-D, Center for Epidemiologic Studies – Depression Scale; STAI, State-Trait Anxiety Inventory; GSDS, General Sleep Disturbance Scale; BPI, Brief Pain Inventory; LFS, Lee Fatigue Inventory.

3.3. Multivariate analyses

Hierarchical multiple regression analyses were used to assess the impact of the selected variables on levels of preoperative and postoperative fatigue (Table 3). Age, sex, and clinical variables were unrelated to preoperative fatigue.

Table 3
Results from the two hierarchical multivariate linear regression analyses with preoperative fatigue and postoperative fatigue (at 5-month follow-up) were used as dependent variables (N=196).

	Preoperative fatigue			Postoperative fatigue		
	Beta	β	p-value	Beta	β	p-value
Sociodemographics						
Age	–0.04	–0.14	0.13	–0.02	–0.07	0.26
Sex	–0.39	–0.10	0.16	0.03	0.01	0.93
Explained variance (R^2)		**5.5%**	**0.01**		2.9%	0.10
Clinical variables						
FEV1	–0.00	–0.05	0.63	–0.00	–0.03	0.71
FVC	–0.01	0.04	0.61	0.00	0.04	0.65
Comorbidity	0.10	0.18	0.008	0.05	0.08	0.19
R^2 change		**10.6%**	**<0.001**		**12.1%**	**<0.001**
Explained variance		16.1			15.0	
Fatigue at baseline						
Fatigue				**0.18**	**0.17**	**0.03**
R^2 change					**16.2%**	**<0.001**
Explained variance					31.2%	
Other symptoms at baseline						
Shortness of breath	0.33	0.13	0.06	**1.27**	**0.46**	**<0.001**
Cough	**0.64**	**0.25**	**<0.001**	**0.50**	**0.18**	**0.004**
Depression	**0.05**	**0.23**	**0.003**	0.01	0.04	0.63
Anxiety	–0.05	–0.07	0.29	0.00	0.00	0.95
Sleep disturbance	**0.02**	**0.20**	**0.01**	0.01	0.11	0.12
Pain	**0.44**	**0.20**	**0.01**	–0.29	–0.07	0.26
R^2 change		**30.5%**	**<0.001**		**23.2%**	**<0.001**
Explained variance		46.6%			54.3%	

Abbreviations: FEV1, Forced expiratory volume in one second; FVC, Forced vital capacity.
Note: Bold numbers represent significant relationships.

At baseline, patients who reported pain scored higher on fatigue (M=2.9, SD=2.05) compared with patients who reported no pain (M=2.03, SD=1.8, t=3.28, p=0.001). Patients who reported pain at baseline also reported higher mean fatigue at five-month follow-up (M=3.54, SD=2.21) compared with those who reported no pain at baseline (M=2.55,

SD=2.04, t=3.08, p=0.002). Among the reported symptoms, coughing, depression, sleep disturbance, and pain interference were related to preoperative fatigue after controlling for age, sex, clinical variables, and the other symptoms. The total model explained 46.6% of variance, while 30.5% was explained by the other symptoms.

At five-month follow-up, the only variables that predicted fatigue after controlling for age, sex, clinical variables, preoperative fatigue, and symptoms were shortness of breath and coughing. The total model explained 54.3% of variance, while 23.2% was explained by the other symptoms.

4. Discussion

To our knowledge, this is the first study examining fatigue in surgically treated patients with LC , including both preoperative data and data from five-month follow-up. Preoperative fatigue was significantly correlated with comorbidities and all the included symptoms in the bivariate analyses, while postoperative fatigue was significantly correlated with comorbidities and four out of six measured symptoms. However, shortness of breath was the only baseline variable that predicted postoperative fatigue.

4.1. Relationship between postoperative fatigue level and preoperative symptoms

Shortness of breath, coughing, depression, anxiety, sleep disturbance, and pain interference were significantly correlated with level of preoperative fatigue. Except for anxiety and pain interference, the same symptoms were associated with postoperative fatigue in the bivariate analyses at five-month follow-up. Before surgery, cough was significantly associated with fatigue, while shortness of breath was the symptom predictive of postoperative fatigue. Shortness of breath is a prevalent and disturbing symptom in these patients, which is physiologically based on disease location, damage caused by lung tumors, and history of smoking. Shortness of breath requires intensive effort to breath, thus making

patients tired. The constant use of rib and respiratory muscles caused by shortness of breath can exacerbate fatigue.[41] These patients may benefit from prescribed bronchodilators and non-pharmacological treatment such as physical activity. For some, it may be useful to learn how to manage shortness of breath by controlled breathing techniques and practicing calming techniques during shortness of breath episodes.

Consistent with previous research, we found that fatigue in patients with LC undergoing surgery is correlated with their symptoms and might cluster with other symptoms.[2,42] Cheville et al.,[2] found a cluster of fatigue, cough, and dyspnea in LC survivors lasting for eight years; however, in a later study, the same group found that the cluster did not predict patient outcomes but that fatigue and dyspnea, alone and together, were sufficient to predict important outcomes.[8]

4.2. Relationship between fatigue and patients' disease characteristics and treatment

Although comorbidities did not predict postoperative fatigue in our analyses, there was a bivariate relationship with fatigue both pre- and postoperatively. Others have also reported correlations between comorbidity and fatigue.[6,12] Respiratory comorbidities and cardiac disease are especially related to fatigue in patients with LC.[3,43] We also found a correlation between fatigue and spirometry results, with lower FEV1 and FVC related to higher levels of fatigue at both measurement times. These variables were related to comorbidity and are an important factor in identifying and screening patients at risk for developing fatigue. Poorer respiratory test outcomes could indicate shortness of breath or respiratory comorbidities, such as COPD, and may lead to distress and exhaustion and contribute to fatigue in these patients.

Surgery type has been established as a predictor of fatigue in LC survivors and surgery has been associated with a greater symptom burden generally.[21] In the present study, treatment and disease variables did not correlate with postoperative fatigue at five-month follow-up. These findings are inconsistent with other reports in which correlations have been

found between fatigue and chemotherapy,[9] and radiotherapy.[11] However, our findings are consistent with those from a general cancer population on the symptom cluster of pain, fatigue, sleep disturbance, and depression. That group found that symptom experiences were independent of demographic, disease, or treatment effects; their findings suggest that different subgroups of patients may harbor different determinants (e.g., genetic) for experiencing symptoms and suggested etiology that are independent of demographic, disease, or treatment characteristics.[44]

4.3. Limitations

Some study limitations need to be acknowledged. There was a five-month gap between the two measurement points. During this time, other factors might have influenced patients' fatigue experience. Surgery type might also be a predictor of patient fatigue.[21] In this study, only 6% of patients had video-assisted thoracoscopy; thus, it is not possible to determine whether this influenced postoperative fatigue. Detailed information on symptom management interventions such as physiotherapy and rehabilitation was not collected. However, even if these variables had been included, no detailed information about the type and length of these therapies was available.

5. Conclusions

Based on the findings in the present study, patients should be screened for symptoms before surgery and offered treatment for their symptoms to reduce pre- and postoperative fatigue. Special attention should be given to treating patients' shortness of breath, since this is a modifiable predictor for which treatments are available. Further research should pay specific attention to the pair of symptoms of shortness of breath and fatigue, and to the effects on fatigue and QOL when shortness of breath is treated.

Fig. 1. Flowchart of the enrollment and exclusion of patients in the study.

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Footnotes

Contributors: TR and TO conceptualised the study. TO wrote the protocol manuscript and TR contributed to protocol development. TO had responsibility for data collection. TH and AL conducted the data analyses and drafted the initial report. TO and TR critically reviewed and edited the manuscript. All authors read and approved the final manuscript. Each author contributed to interpreting the analyses and to critically revising the article, and approved the final draft.

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Patient consent: Each participant signed informed consent.

Ethics approval The Regional Ethics Committee for the South-East 2010/1508, and the Institutional Review Boards (Personvernombudet) at each hospital approved the study. Each participant received written information about the study and signed informed consent.

Data availability statement: All data relevant to the study are included in the article.

Competing interests: None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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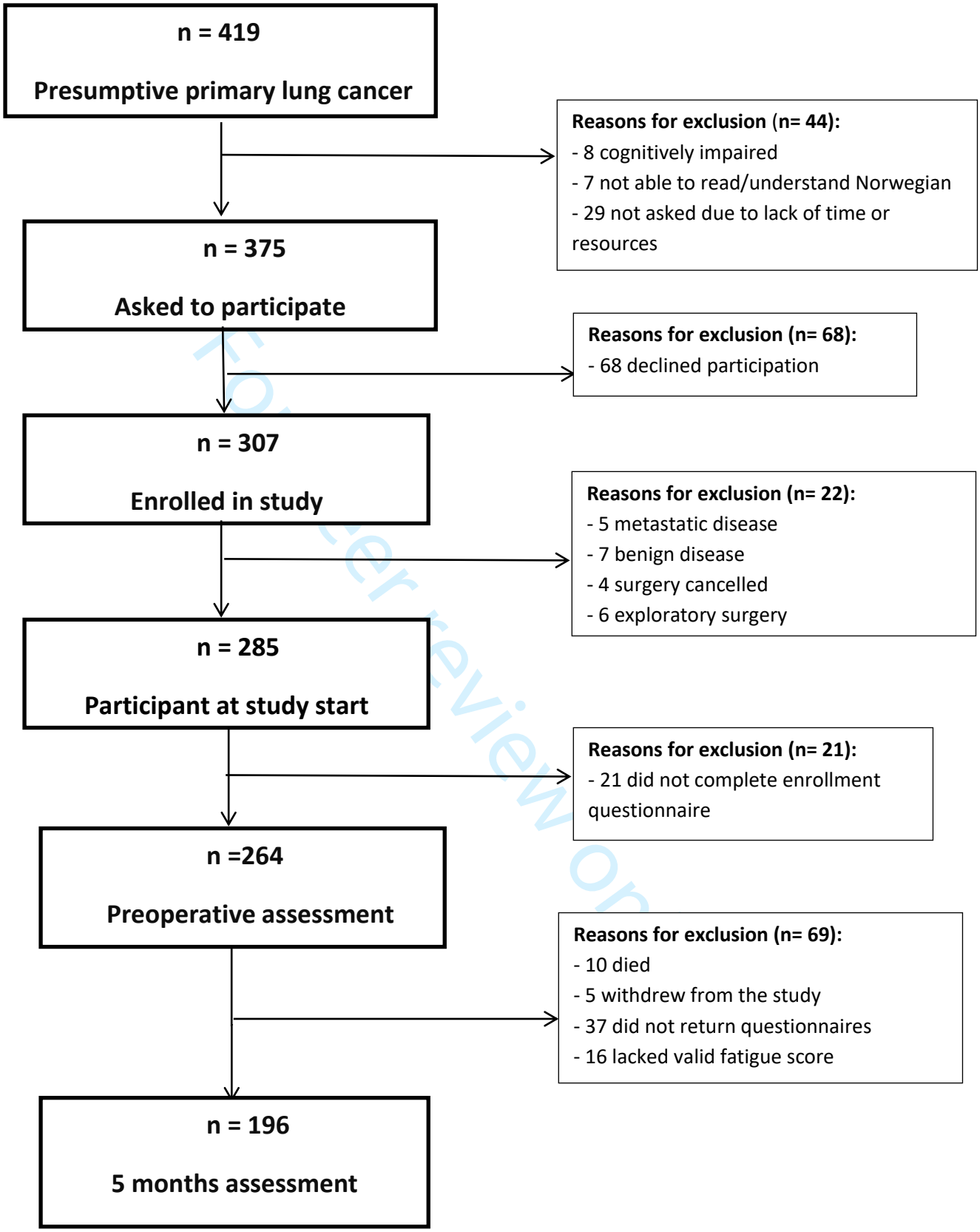

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page: 1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page: 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page: 3 and 4
Objectives	3	State specific objectives, including any prespecified hypotheses Page: 4
Methods		
Study design	4	Present key elements of study design early in the paper Page: 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page: 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page: 5 and 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed Page: Not actual
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page: 5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page: 5-8
Bias	9	Describe any efforts to address potential sources of bias Page: Not actual
Study size	10	Explain how the study size was arrived at Page: 10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page:
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page: 9
		(*b*) Describe any methods used to examine subgroups and interactions Page: 9
		(*c*) Explain how missing data were addressed Page: 9
		(*d*) If applicable, explain how loss to follow-up was addressed Page: 9
		(*e*) Describe any sensitivity analyses Page: 9

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page: Fig 1, page 10
		(b) Give reasons for non-participation at each stage Page: Fig 1, page 10
		(c) Consider use of a flow diagram Page: Fig 1, page 10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page: 11
		(b) Indicate number of participants with missing data for each variable of interest Page: 11
		(c) Summarise follow-up time (eg, average and total amount) Page: 11
Outcome data	15*	Report numbers of outcome events or summary measures over time Page: 10 -12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page: 12
		(*b*) Report category boundaries when continuous variables were categorized Page: 12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Page: Not actual
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page: Not actual
Discussion		
Key results	18	Summarise key results with reference to study objectives Page: 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page: 2 + 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page: 15 and 16
Generalisability	21	Discuss the generalisability (external validity) of the study results Page: 16
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page: 18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.