

PAPER

Comparison of fatigue, depression, and anxiety as factors affecting posttreatment health-related quality of life in lung cancer survivors

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Funding information

National Cancer Center, South Korea, Grant/Award Number: 0710410 and 1010470; The R&D Program for National Research Foundation of Korea (NRF), Grant/Award Number: 2010-0028631; The R&D Program for Cancer Control, Ministry of Health and Welfare, South Korea, Grant/Award Number: 1320330

Abstract

Objective: To compare the effects of fatigue, anxiety, and depression on health-related quality of life (HRQoL) in survivors of surgically resectable lung cancer.

Methods: In total, 830 lung cancer survivors participated in the study. They completed a questionnaire consisting of items pertaining to sociodemographic characteristics, clinical variables, and HRQoL. We calculated prevalence rates for fatigue, anxiety, and depression and performed multiple logistic regression and general linear modeling to determine the main factors affecting HRQoL.

Results: The prevalence rates for moderate fatigue (Brief Fatigue Inventory mean score: ≥ 4), borderline depression (Hospital Anxiety and Depression Scale-Depression score: ≥ 8), and borderline anxiety (Hospital Anxiety and Depression Scale-Anxiety score: ≥ 8) were 42.2%, 38.9%, and 20.9%, respectively. The main factor was fatigue, which demonstrated the strongest explanatory power for HRQoL including all 5 functional HRQoL components (ie, physical, role, emotional, cognitive, and social functioning) and global health status (partial R^2 range: .13 to .19). However, anxiety (partial $R^2 = .21$) and fatigue (partial $R^2 = .19$) both demonstrated strong explanatory power for emotional HRQoL. In addition, depression demonstrated weak explanatory power for HRQoL including emotional HRQoL.

Conclusions: Relative to depression and anxiety, fatigue exerted a stronger effect on lung cancer survivors' HRQoL. Health professionals should consider the reduction of fatigue a priority in improving cancer patients' HRQoL following the completion of cancer treatment.

KEYWORDS

anxiety, depression, fatigue, health-related quality of life, lung cancer, psycho-oncology, survivorship

1 | INTRODUCTION

Lung cancer is one of the most prevalent cancers and has a low survival rate. The global 5-year survival rate for lung cancer is 4 to 5 times lower relative to that observed for other prevalent types of cancer such as breast and prostate cancer. However, it has increased steadily from 12% in 1975 to 18% in 2015.¹ Health-related quality of life (HRQoL) following treatment for lung cancer is a concern for patients, as they experience physical and psychological symptoms subsequent to survival.

The most common physical and psychological symptoms experienced by lung cancer survivors include fatigue, depression, and anxiety. Fatigue (experienced by approximately 75% of survivors) is the most common physical symptom^{2,3} and a major factor in differentiating between lung cancer survival and mortality rates⁴; in addition, depression (experienced by 8.9% to 33% of survivors) and anxiety (experienced by 19.7% to 34% of survivors) are prevalent psychological symptoms.⁵⁻¹⁰ Moreover, lung cancer patients are 3 times more likely, relative to other cancer patients, to develop symptoms of psychological distress, such as depression and anxiety,

which contribute to reductions in psychological well-being and quality of life.^{7,8}

Numerous studies have examined fatigue, depression, and anxiety separately in lung cancer survivors⁹⁻¹³ or explored the relationships between fatigue and depression and between anxiety and depression^{8,14,15} to explain HRQoL. In addition, some studies have examined the associations between fatigue, depression, and between anxiety in lung cancer survivors.^{7,16-18} However, these studies did not consider depression and anxiety as independent explanatory factors for HRQoL but examined them as influential factors to demonstrate their effects on fatigue.

No previous studies have examined fatigue, depression, and anxiety simultaneously to determine which of these factors exerts the strongest effect on HRQoL in lung cancer survivors. However, concurrent examination of fatigue, depression, and anxiety in lung cancer survivors, to determine the contribution made by each factor to HRQoL, could provide survivorship care professionals with insight into effective posttreatment interventions for lung cancer survivors.

Therefore, this study aimed to examine the prevalence of fatigue, anxiety, and depression concurrently and determine which of these factors exerted the strongest effect on HRQoL.

2 | METHODS

2.1 | Participants and procedure

Approximately 2049 lung cancer patients were treated at 2 medical institutions in South Korea (ie, the National Cancer Center and Samsung Medical Center) between 2001 and 2006.

Potential participants were contacted via telephone and invited to participate in the study. In total, 830 survivors agreed to complete the questionnaire at home or participate in interviews conducted by a qualified interviewer at one of the medical institutions. Data regarding participants' sociodemographic characteristics and clinical variables were obtained from the institutions at which they received treatment, and questionnaires were used to measure psychological distress and quality of life. Detailed information regarding the recruitment procedure and participants' demographic characteristics was reported in a previous research article.¹⁹

2.2 | Measures

2.2.1 | Fatigue

The Korean version of the Brief Fatigue Inventory (BFI), which was validated in a previous study,² was used to measure the severity of participants' fatigue. The BFI consists of 9 items that measure the severity of fatigue according to the following 4 categories: current fatigue level, usual fatigue level during the preceding 24 hours, worst fatigue level during the preceding 24 hours, and the extent to which fatigue interferes with daily life. Responses are provided using a numeric rating scale ranging from 0 to 10, with higher scores indicating fatigue of greater severity. Scores for the 9 items are averaged to provide a comprehensive fatigue score. Scores of ≥ 4 indicate clinically moderate (ie, 4-6) to severe (ie, 7-10) fatigue, scores of 1 to 3 indicate mild fatigue, and a score of 0 indicates an absence of fatigue.⁵ Cronbach's α for the scale was .95.

2.2.2 | Psychological distress

The Korean version of the Hospital Anxiety and Depression Scale (HADS), which was validated in a previous study,⁶ was used to measure the severity of participants' anxiety and depression. The HADS consists of 14 items divided equally between the following 2 subscales: anxiety and depression. Responses are provided using a 4-point Likert scale ranging from 0 to 3, and 8 of the items are reverse scored. Total scores for each subscale range from 0 to 21, and higher scores indicate anxiety or depression of greater severity (cut-off scores: 0-7 = no depression/anxiety; 8-10 = borderline depression/anxiety; ≥ 11 = severe depression/anxiety).^{20,21} Cronbach's α for the scale was .72.

2.2.3 | Quality of life

The Korean version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, which was specifically designed for use with cancer patients, was used to measure generic quality of life characteristics.²² The questionnaire consists of 30 items divided between functional scales (physical functioning: 5 items, role functioning: 2 items, emotional functioning: 4 items, cognitive functioning 2 items, and social functioning: 2 items), symptom scales, (fatigue: 3 items, nausea and vomiting: 2 items, pain: 2 items, dyspnea: 1 item, insomnia: 1 item, appetite loss: 1 item, constipation: 1 item, diarrhea: 1 item, and financial difficulties: 1 item), and global health status (2 items). Scores for each item range from 0 to 100. Higher functional scale and global health status scores and lower symptom scale scores indicate better quality of life.

2.3 | Statistical analysis

Descriptive statistics were used to analyze participants' sociodemographic and clinical characteristics. The cut-off points for fatigue, depression, and anxiety were based on those used for the respective measurement instruments in previous studies.⁷ Univariate analysis was performed to identify independent factors that exerted significant effects on participants' fatigue, depression, and anxiety levels. The significance level was set at $P < .05$. Multiple logistic regression and multiple linear regression analyses were performed to examine the effects of sociodemographic characteristics, clinical variables, fatigue, depression, and anxiety on HRQoL. The univariate analysis was performed first to identify correlated factors affecting HRQoL. Initially, fatigue, anxiety, depression, and all of the sociodemographic and clinical variables for which results were significant in the univariate analysis were included in a multiple regression model. A backward selection procedure, with a significance level of $P < .10$, was used to determine which variables would be retained in the final multiple regression model. The resultant adjusted odds ratios and partial R^2 values were used to examine each variable's explanatory power and association with HRQoL. Statistical analyses were performed using the Statistical Analysis System (version 9.4) software suite.

3 | RESULTS

3.1 | Sociodemographic and clinical characteristics

The participants' ($N = 830$) sociodemographic and clinical characteristics are presented in Table 1.

TABLE 1 Distribution of sociodemographic and clinical characteristics in the study population (n = 830)

Characteristics	Number of patients	%
Age (y)		
<70	211	74.6
≥70	619	25.4
Gender		
Female	193	23.3
Male	637	76.7
Educational level (n = 828)		
<high school graduation	387	46.6
≥high school graduation	441	53.4
Marital status		
Unmarried, divorced, or widowed	66	8.0
Currently married	764	92.0
Employment status (n = 829)		
Unemployed (never employed, retired, housewives)	507	61.1
Employed	322	38.8
Monthly income, KRW		
<3 000 000	603	72.7
≥3 000 000	227	27.3
Family number		
Living alone	50	6
≥2 members	780	93.9
Smoking status		
Current smokers	60	7.2
Former or never smokers	770	92.8
Body mass index (n = 795)		
BMI <18.5	29	3.5
BMI ≥18.5	766	92.3
Stage		
0–I	517	62.3
II–III	313	37.7
Comorbidities ^a (n = 827)		
Yes	452	54.5
No	375	45.2

BMI, body mass index.

^aMultiple responses were possible.

3.2 | Prevalence of fatigue, depression, and anxiety

The prevalence rates for moderate fatigue (BFI score: ≥4), borderline depression (HADS_D score: ≥8), and borderline anxiety (HADS_A score: ≥8) were 42.2%, 38.9%, and 20.9%, respectively (Table 2). The prevalence rates for severe fatigue (BFI score: ≥7), severe depression (HADS_D score: ≥11), and severe anxiety (HADS_D: ≥11) were 4.9%, 13.7% and 7.3%, respectively.

3.3 | Univariate analysis of factors related to fatigue, depression, and anxiety

The results of the univariate analysis showed that age, educational level, employment status, monthly household income, current

TABLE 2 Prevalence of fatigue, depression, and anxiety experienced by lung cancer survivors

Characteristic	n	%	Mean	SD	Range
BFI (average) (n = 717)					
None (BFI = 0)	59	7.1	0.00	0.00	0
Mild (BFI = 1–3)	308	37.1	2.00	0.69	2 (1–3)
Moderate/severe (BFI ≥ 4)	350	42.2	5.93	1.36	6 (4–10)
Depression (n = 824)					
None (HADS depression = 0–7)	501	60.4	3.73	2.34	7 (0–7)
Borderline (HADS depression = 8–10)	209	25.2	8.96	0.82	2 (8–10)
Severe (HADS depression = 11–21)	114	13.7	12.86	2.00	10 (11–21)
Anxiety (n = 825)					
None (HADS anxiety = 0–7)	651	78.4	2.79	2.38	7 (0–7)
Borderline (HADS anxiety = 8–10)	113	13.6	8.63	0.77	2 (8–10)
Severe (HADS anxiety = 11–21)	61	7.3	12.64	1.65	6 (11–17)

BFI, Brief Fatigue Inventory; HADS, Hospital Anxiety and Depression Scale; SD, Standard Deviation.

comorbidity, and recurrence were associated with moderate-to-severe fatigue. In addition, age, educational level, employment status, and monthly household income were associated with borderline-to-severe depression. Moreover, educational level, employment status, and monthly household income were associated with borderline-to-severe anxiety (Appendix S1).

3.4 | Multivariate analysis of factors correlated with functional HRQoL and global health status

The results of the logistic regression analysis indicated that all fatigue, anxiety, and depression factors were correlated with functional HRQoL and global health status. However, fatigue and anxiety were the only factors that exerted significant effects on emotional functioning and global health status (Table 3).

3.5 | GLM of the main factors correlated with functional HRQoL and global health status

The results of the GLM performed to determine the main factors associated with functional HRQoL are presented in Table 4. The analysis showed that fatigue demonstrated the strongest explanatory power for HRQoL and affected physical, role, cognitive, emotional, and social functioning and global health status (partial $R^2 = .13, .15, .14, .19, .19$, and $.19$, respectively). However, anxiety demonstrated the strongest explanatory power for emotional HRQoL (partial $R^2 = .21$). Sociodemographic characteristics, clinical variables, and depression demonstrated weak explanatory power for HRQoL.

4 | DISCUSSION

This large-scale study examined fatigue, anxiety, and depression concurrently to determine which of these factors exerted the strongest

TABLE 3 Multivariate logistic regression analysis of factors correlated with functional HRQoL and global health status with backward selection*

		Physical Function QoL			Role Function QoL			Cognitive Function QoL		
		aOR	95% CI	P-value	aOR	95% CI	P-value	aOR	95% CI	P-value
Fatigue	<4	3.41	2.39-4.86	0.00	2.46	1.71-3.54	0.00	2.97	2.03-4.36	0.00
	≥4	1(ref)			1(ref)			1(ref)		
Anxiety	<8	1.69	1.08-2.65	0.02	2.72	1.77-4.18	0.00	2.34	1.52-3.61	0.00
	≥8	1(ref)			1(ref)			1(ref)		
Depression	<8	1.52	1.05-2.21	0.03	1.46	0.99-2.12	0.05	1.63	1.10-2.41	0.01
	≥8	1(ref)			1(ref)			1(ref)		
		Emotional Function QoL			Social Function QoL			Global Health Status QoL		
		aOR	95% CI	P-value	aOR	95% CI	P-value	aOR	95% CI	P-value
Fatigue	<4	3.51	2.41-5.12	0.00	3.33	2.33-4.75	0.00	3.70	2.59-5.27	0.00
	≥4	1(ref)			1(ref)			1(ref)		
Anxiety	<8	5.35	3.53-8.12	0.00	2.51	1.60-3.92	0.00	1.84	1.16-2.94	0.01
	≥8	1(ref)			1(ref)			1(ref)		
Depression	<8				2.32	1.60-3.35	0.00	1.43	0.98-2.08	0.07
	≥8				1(ref)			1(ref)		

*Adjusted for demographic and clinical (age, sex, education, marriage, income, BMI, cancer stage, employment, smoking, comorbidities, family number) variables which were selected from univariate analysis.

aOR, adjusted Odds Ratios; 95% CI, 95% Confidence Intervals

TABLE 4 Generalized linear model analysis of the main factors correlated with functional HRQoL and global health status

	Physical Function QoL				Role Function QoL				Cognitive Function QoL			
	Estimate (B)	P	P. r ²	M. ²	Estimate (B)	P	P. r ²	M. ²	Estimate (B)	P	P. r ²	M. ²
Fatigue	-2.18	<.0001	0.13		-2.92	<.0001	0.15		-2.10	<.0001	0.14	
Anxiety	-0.44	0.03	0.02		-0.70	0.01	0.02		-0.80	<.0001	0.04	
Depression	-0.70	0.00	0.01	0.26	-0.75	0.00	0.01	0.24	-0.81	<.0001	0.02	0.26
	Emotional Function QoL				Social Function QoL				Global Health Status QoL			
	Estimate (B)	P	P. r ²	M. ²	Estimate (B)	P	P. r ²	M. ²	Estimate (B)	P	P. r ²	M. ²
Fatigue	-1.44	<.0001	0.19		-2.72	<.0001	0.19		-2.60	<.0001	0.19	
Anxiety	-2.54	<.0001	0.21		-1.29	<.0001	0.06		-0.75	0.00	0.04	
Depression	-0.42	0.01	0.00	0.43	-0.96	<.0001	0.02	0.30	-0.84	<.0001	0.02	0.32

These models included demographic and clinical (age, sex, education, marriage, income, BMI, cancer stage, employment, smoking, comorbidities, family number) variables which were selected from univariate analysis as covariates.

P,r² means partial R square.

M. r² means model R square.

effect on HRQoL in lung cancer survivors (N = 830). Fatigue demonstrated the strongest explanatory power for all of the functional HRQoL items and global health status and strong explanatory power for emotional HRQoL; however, anxiety exhibited stronger explanatory power for this item, relative to those observed for fatigue and depression. Moreover, depression explained very small proportions of the variance in both functional and general HRQoL components.

The prevalence rates for fatigue (42.2%) and anxiety (20.9%) were similar to those observed in previous studies involving lung cancer survivors (16.8% to 57% and 19.75 to 34%, respectively).^{7-9,23,24} The prevalence rate for depression (38.9%) was somewhat higher relative to those reported in previously published research (8.9% to 33%).⁷⁻¹⁰ In addition, previous studies have reported various prevalence rates for fatigue, anxiety, and depression in lung cancer patients. This discrepancy could be explained by differences in cell types between small cell and non-small cell lung cancer. Patients with small cell lung

cancer generally exhibit poorer quality of life, relative to that observed in patients with non-small cell lung cancer, because they experience a greater symptom burden, which results in higher levels of fatigue, anxiety, and depression. Another possible reason for this discrepancy is that the cut-off points used in scoring the questionnaires varied between studies. For example, the characteristics of the patients in the current study were similar to those of participants in a study conducted by Park et al,⁸ but the prevalence rates for depression (9%) and anxiety (19%) in Park et al's study were lower relative to those observed in the current study. However, the cut-off value used for the HADS in the current study (ie, ≥8) was lower relative to that used by Park et al (ie, ≥11). A score of ≥11 indicates that the patient has severe depression or anxiety, and health care professionals recommend that patients in this category should visit a mental health clinic as soon as possible.⁸ However, scores between 8 and 10 indicate that the patient has significant clinical symptoms of anxiety or depression,

which should be managed to ensure that they do not increase in severity.^{20,25} We chose a cut-off point ≥ 8 , because our goal was to identify clinical problems and increase HRQoL for a wider range of lung cancer survivors. Higher levels of depression could occur as a consequence of Korean individuals' tendency to hide their emotions and avoid expressing negative emotions by suppressing anger when they experience adversity.²⁶ This emotional suppression often manifests as a culture-bound syndrome known as *Hwabyung*,^{27,28} which is a somatization disorder caused by the suppression of anger in situations in which individuals feel that they have been treated unfairly.

Fatigue was the main explanatory variable for functional HRQoL in lung cancer survivors. This finding was similar to those of a previous study, which showed that fatigue was a significant negative predictor of HRQoL in cancer survivors.⁴ In addition, the results of another study showed that associations between fatigue and social function, physical function, and global quality of life in lung cancer survivors were stronger relative to those observed in survivors of other types of cancer, and this was likely to have occurred because the symptom burden experienced in lung cancer is greater relative to that observed in other types of cancer.²⁹

The results also showed that fatigue and anxiety both explained large proportions of the variance in emotional HRQoL; however, anxiety demonstrated stronger explanatory power relative to that observed for fatigue. In addition, depression explained a small proportion of the variance in functional HRQoL including emotional HRQoL. This finding was inconsistent with those of previous studies, which indicated that depression management was important in the maintenance of emotional well-being in cancer survivors.^{8,10} However, some studies have shown that anxiety exerted long-term effects on cancer patients' quality of life and could persist for more than 10 years, while the risk of depression persisted for 2 years,³⁰ which suggests that the effect of anxiety could be stronger, relative to that exerted by depression, in long-term cancer survivors. Moreover, the participants in the current study were lung cancer patients who had survived for at least 12 months subsequent to diagnosis, with more than half having survived for 24 to 59 months, and 17% having survived for longer than 60 months. These long survival times were likely to have contributed to anxiety's explanatory power for emotional HRQoL.

Lung cancer survivors' HRQoL is generally low; therefore, management is crucial during the posttreatment period.^{31,32} In addition, health care professionals should consider means of reducing fatigue and anxiety levels, to improve functional HRQoL and global health status. Lung cancer professionals who provide health care for survivors should conduct research to examine the relative contributions of fatigue and anxiety to the various components of HRQoL, as the results could be used to manage posttreatment quality of life effectively.

4.1 | Limitations

The study was subject to several limitations. First, the study involved a cross-sectional design; therefore, we could not infer causality in the relationships between HRQoL and fatigue, depression, and anxiety. Second, anxiety and depression were measured using the HADS, which has been validated and is often used in clinical research; however, the results of some studies indicated that the questionnaire's sensitivity in

determining clinically meaningful symptoms of anxiety and depression varied according to the study population. In addition, its sensitivity in determining depression in cancer patients was lower relative to that observed for anxiety.³⁰ Therefore, the main factors affecting lung cancer survivors' HRQoL should be examined using alternative methods such as interview-based surveys or other psychometric questionnaires. Third, our analysis did not include examination of interactions between fatigue, depression, and anxiety; however, these factors are likely to affect each other. Therefore, further research is required to explore these interaction effects, which could aid in the development of effective treatment to improve lung cancer survivors' HRQoL.

4.2 | Clinical implications

Despite these limitations, this large-scale study was the first to examine fatigue, depression, and anxiety concurrently to determine which of these factors explained the largest proportion of the variance in HRQoL in lung cancer survivors. This information helped us to achieve our goal of prioritizing the factors in terms of their effects. The results could be used to improve lung cancer survivors' HRQoL, which should be considered a health care priority, and inform the approaches adopted by health care professionals in clinical settings. In addition, the findings could aid in the development of effective interventions to improve lung cancer survivors' HRQoL.

ACKNOWLEDGEMENTS

The study was supported by grants from National Cancer Center, National Research Foundation and Ministry of Health and Welfare in South Korea. We also wish to express our appreciation to Hyun Kyung Kim for her exceptional work as a research assistant.

AUTHORS' CONTRIBUTIONS

YHY contributed to the development of the study design, provided financial support and study materials, collected and assembled the data, interpreted the analyses, contributed to the sequence alignment, and drafted the manuscript. JYJ contributed to the development of the study design, performed the data analyses, and wrote the manuscript. JML, MSK, YMS, and JIZ contributed to the development of the study design, recruited participants, and helped to draft the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no known conflicts of interest associated with this publication, and none of the financial support provided for this work could have influenced its outcome.

ETHICAL APPROVAL STATEMENT

The study protocol was approved by the institutional review boards at the National Cancer Center and Samsung Medical Center.

AUTHORS' APPROVAL OF THE MANUSCRIPT

Juyoun Jung, Jong Mok Lee, Moon Soo Kim, Young Mog Shim, Jae Ill Zo, and Young Ho Yun approved the study and included 32 references.

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SUPPORTING INFORMATION

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How to cite this article: Jung JY, Lee JM, Kim MS, Shim YM, Zo JI, Yun YH. Comparison of fatigue, depression, and anxiety as factors affecting posttreatment health-related quality of life in lung cancer survivors. *Psycho-Oncology*. 2017;1-6. <https://doi.org/10.1002/pon.4513>