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Quality of life, anxiety, depression, and distress in patients with advanced and metastatic lung cancer

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Abstract

Objective. Lung cancer (LC) patients have shown a predisposition for developing emotional and physical symptoms, with detrimental effects on the quality of life (QoL). This study evaluates the bidirectional relationship between main psychological disorders and clinical/sociodemographic factors with the QoL.

Methods. In this observational cross-sectional study, patients with a confirmed LC diagnosis from February 2015 to March 2018 were eligible for this study. Each participant completed screening instruments of anxiety, depression, distress, and QoL assessment. Other relevant clinical data were extracted from electronic health records. Then comparisons, correlations, and logistic regression analyses were performed.

Results. Two hundred and four cases were eligible; of them, the median age was 61 (24–84) years, most had clinical stage IV (95%), and most were under first-line therapy (53%). Concerning psychological status, 46% had symptoms of emotional distress, 35% anxiety, and 31% depression. Patients with psychological disorders experienced a worse global QoL than those without psychological impairment ($p < 0.001$). Increased financial issues and physical symptoms, combined with lower functioning, were also significantly associated with anxiety, depression, and distress. In the multivariate analysis, female sex and emotional distress were positively associated with an increased risk of depression; likewise, female sex, low social functioning, insomnia, and emotional distress were associated with anxiety.

Conclusions. Emotional symptoms and QoL had a significant bidirectional effect on this study; this underscores the necessity to identify and treat anxiety, depression, and distress to improve psychological well-being and the QoL in LC patients.

Introduction

Worldwide, lung cancer (LC) is the deadliest neoplasm, with 1.7 million estimated deaths in 2018 (Siegel et al., 2020), and the sixth most frequent, accounting for 8.7% of all cancer-related deaths (Ferlay et al., 2019). Unfortunately, most are diagnosed in advanced clinical stages, negatively impacting prognosis and the quality of life (QoL) (Siegel et al., 2020). Since the introduction of novel therapies (e.g., targeted therapies, immunotherapy, and antiangiogenics), treatment landscape has changed drastically as the overall prognosis and QoL in LC patients. However, those patients with advanced stages, unlikely to be cured, are still experiencing a significant impact on their psychological well-being. Indeed, a high proportion of patients invariably develop psychological disorders (15–19%) (Akechi et al., 2002; Uchitomi et al., 2003) that may modify prognosis (Weeks et al., 2012).

Distress is a multifactorial unpleasant experience of a psychological, social, spiritual, and physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment (Riba et al., 2019). In this regard, approximately 7% of the general population experience distress, whereas 25–60% of cancer patients experience distress throughout the disease (Ownby, 2019). Like other mental illnesses, distress mainly predominates in young women at the onset of cancer diagnosis and is related to unsolved needs and financial stressors (Weeks et al., 2012).

LC patients have shown higher rates of anxiety (25.7–58%), depression (17.9%), and distress (43–45%) than other types of cancer (Carlson et al., 2004). However, approximately only 33% received mental health support (Ugalde et al., 2012). In this regard, one study of

4,361 LC patients showed that this group had a lower probability of receiving treatment for mental illness despite depressive disorders (Walker et al., 2014a, 2014b). In addition, other emotional problems, such as lack of hope, suicidal ideation, and body image distortions, position LC patients in an unfavorable social environment that compromises their general well-being (Walker et al., 2014, 2014b).

Moreover, psychological disorders have been associated with detrimental effects in the QoL (Brown et al., 2014), increasing the use of antidepressants (Saunders et al., 2019), impacting negatively on treatment adherence (Colleoni et al., 2000) and compliance to medical care. Our group reported previously that anxiety and depression in advanced LC patients receiving chemotherapy might prolong hospital stay and shorten survival (Arrieta et al., 2012). Likewise, the highest levels of depression correlated significantly with females and poor performance status (Arrieta et al., 2012).

Cancer burden and intensity of cancer-related symptoms such as pain have been associated with an increased rate of psychological disorders, especially depression, and independently of personality traits (Aukst Margetić et al., 2013). Indeed, there are associations between moderate or severe pain with depression, sleep difficulties, anxiety, and fatigue in thoracic malignancies (Salminen et al., 2013). Correspondingly, depressive symptoms have been associated with a higher perceived stigma, social rejection, economic instability, social isolation, and a lower degree of social support (Gonzalez and Jacobsen, 2012; Walker et al., 2014a, 2014b). The bidirectional effect between physical and emotional symptoms with psychological alterations and *vice versa* is a vicious circle that negatively impacts the QoL (Gonzalez and Jacobsen, 2012; Walker et al., 2014a, 2014b).

The QoL has become crucial in clinical trials for evaluating the therapeutic efficacy of interventions. However, scarce information on Latin-American patients calls on assessing the impact of psychiatric disorders and the interrelationship with QoL and cancer-associated symptoms in the LC population. This assessment could develop adequate and viable interventions to improve patients' well-being. Therefore, this study evaluates the bidirectional relationship of anxiety, depression, distress, and clinical factors with QoL.

Methods

Two hundred and eighty patients were evaluated in a psycho-oncology program in the Thoracic Oncology Department at the National Cancer Institute in Mexico from February 2015 to March 2018 (Figure 1). Two hundred and four patients completed their psychological assessment and were considered eligible for this observational cross-sectional study. The institute's ethics and research committees approved the access to electronic health record (EHR) data to obtain other relevant clinical data. The study was conducted under the principles of the Declaration of Helsinki, local laws on observational studies, and applicable regulatory requirements.

All eligible patients met the following criteria: (1) LC diagnosis regardless of the histology and clinical stage; (2) all patients must be receiving active cancer therapy (chemotherapy, target therapy, or immunotherapy) regardless of the line of treatment; (3) Spanish must be the mother tongue, considering that all psychological assessments need a complete comprehension and open communication between the psychologist and the patient.

Those patients with cognitive function impairment, such as delirium or altered consciousness that did not allow them to complete the psychological evaluation, were excluded. Any other causes of noncomplete evaluation and the presence of severe physical discomforts such as pain, dyspnea, or nausea that hinder instruments' completion were also excluded. All data were collected in SPSS Statistical Software v.25.

Assessments

A psychologist specialized in psycho-oncology performed a semi-structured interview to obtain demographic data and clinical history. All analyzed patients answered the Hospital Anxiety and

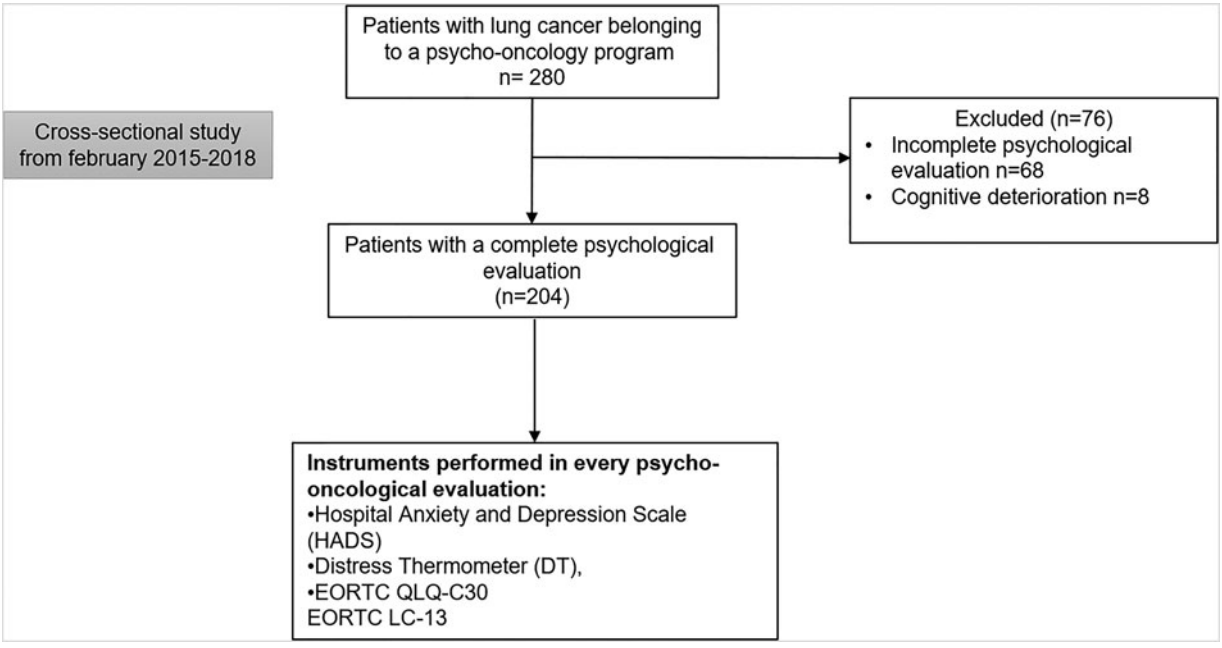

Fig. 1. STROBE flow-chart.

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Depression Scale (HADS), Distress Thermometer (DT), and QoL questionnaires.

Hospital Anxiety and Depression Scale

The HADS (Zigmond and Snaith, 1983) is one of the most extensively evaluated screening instruments in cancer patients (Schellekens et al., 2016). The validated version for the Mexican population keeps the anxiety and depression subscales (6 items each, range 0–3) (Galindo Vázquez et al., 2015). In each subscale, scores can be rated as normal (0–5), mild (6–8), moderate (9–11), and severe (12–18). HADS has demonstrated in previous works an adequate consistency in our population ($\alpha = 0.86$) in the total score and on each subscale (anxiety, $\alpha = 0.79$; depression, $\alpha = 0.80$) that explains 48.04% of the variance.

Distress thermometer

The DT is a self-reported tool to screen for distress symptoms using a 0–10 rating visual analog scale. Distress was defined with a cutoff point score of ≥4. This scale has been translated into many languages, including the Spanish version employed in the present study. This scale has been validated in the Mexican population with a sensitivity of 93% and a specificity of 76%. Positive and negative predictive values of 82% and 90%, respectively (de Jesús Almanza-Muñoz et al., 2008).

EORTC QLQ-30 and LC-13 module

The European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) and the EORTC-LC13 are the most frequently used measurement instruments in LC trials (Park, 2008; Damm et al., 2013). The first consists of 30 ordinal items that evaluate health status performance in three dimensions. The functional dimension is made up of five domains: physical, role, cognitive, emotional, and social functioning. Six items were analyzed to assess the severity of cancer treatment symptoms. Similarly, QLQ-LC13 was included in every patient evaluation that consists of 13 questions concerning the most common LC symptoms associated with the disease itself and the most common reactions to medical treatment.

The EORTC QLQ-C30 and its supplemental lung cancer-specific module (QLQ LC-13) translated Spanish version were validated in the Mexican population (Oñate-Ocaña et al., 2009; Arrieta et al., 2012; Cerezo et al., 2012), and both had an adequate internal consistency ($\alpha = 0.9$; $\alpha = 0.94$) ($p < 0.0001$).

Statistical methods

Sample size was estimated to obtain a statistical power of 0.95, with an alpha error of 0.05 and 95% CI adjusting for a finite population, obtaining a minimum value of 166 cases. Continuous variables were summarized as medians with interquartile ranges or means with standard deviations (SDs), depending on data distribution. Data distribution was assessed using the Shapiro–Wilk test. Differences between two groups for quantitative variables were tested using Student's *t*-test or Mann–Whitney *U* depending on data distribution. Spearman's test was used to evaluate the correlation between two variables.

A Cox multivariate analysis was performed with statistically significant and borderline variables. Therefore, we developed two models, one for depression and one for anxiety. Statistical significance was determined as $p \leq 0.05$ with a two-sided test. All data were analyzed using the SPSS software package version 23 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 280 cases were examined for eligibility, 68 were not eligible due to missing information, and 8 patients presented significant cognitive dysfunction; thus, finally, 204 confirmed cases were considered for the final analysis (Figure 1). The median age was 61 years (24–84), 79% were female (sex assigned at birth), most had a clinical-stage IV (95%), and ECOG PS (0–1) in 88% of the patients. Remarkably, 86% of our population were never smokers, 67% of the patients harbor an EGFR mutation, and 63% received a tyrosine kinase inhibitor (TKI) irrespective of the line of treatment. Table 1 summarizes the main baseline characteristics.

Anxiety, depression, and emotional distress

Of 204 patients who completed the psychological assessment, 35% had suggestive anxiety symptoms and 31% had symptoms compatible with depression. Almost half of the patients (46%) reported having distress in the DT. Anxiety and depression were more frequent in females than males: anxiety (4.94 vs. 2.07, $z = -4.644$, $p < 0.001$) and depression (5.15 vs. 2.43, $z = -3.481$, $p < 0.001$), respectively. Depression was also associated with education level; those with a lower level exhibited higher scores compared to those with higher educational levels (5.17 vs. 3.95, $z = -2.132$, $p = 0.03$).

Anxiety was higher in non-smokers than those who have smoked (4.66 vs. 3.34, $z = -2.175$, $p = 0.03$), and in patients going through a second-line or further lines of treatment, than those receiving a first-line treatment (4.89 vs. 3.87, $z = -2.079$, $p = 0.03$). No relevant differences in anxiety, depression, or distress scores were found based on the mutational status or type of administered treatment (chemotherapy vs. targeted therapy).

Quality of life

Most frequent symptoms reported in the EORTC QLQ-C30 and the LC-13 module were cough (70%), fatigue (65%), loss of appetite (63%), pain (62%), dyspnea (61%), nausea or vomit (51%), peripheral neuropathy (48%), and alopecia (47%). Financial difficulties were observed in 71%, reduced emotional functioning in 54%, and impaired role functioning in 45%.

The comparative analysis of the different functional subscales based on the presence or absence of psychological symptoms is described in Table 2. Of note, significant differences favored patients without psychological disorders (anxiety, depression, and emotional distress) in almost all functional subscales of QoL (physical, role, cognitive, emotional, and social functioning) compared with patients with a psychological disorder. Those patients without depression (63.41 ± 23.79 vs. 44.97 ± 24.88), distress (63.33 ± 24.42 vs. 51.15 ± 25.38; $p < 0.001$), and anxiety (63.4 ± 24.2 vs. 47.06 ± 24.72; $p < 0.001$) had a significantly better global QoL than those with any of those mentioned above, respectively. In contrast, patients with any psychological affection were strongly correlated with more financial difficulties and worse physical symptoms scales. Increased severity of symptoms such as dyspnea, pain, fatigue, and insomnia were associated with the presence of anxiety, depression, and distress.

The severity of anxiety, depression, and distress scores according to the presence or absence of main symptoms subscales is summarized in Table 3. Remarkably, higher levels of anxiety, depression, and emotional distress were strongly correlated with the presence of physical symptoms. Chest pain, fatigue, insomnia,

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Table 1. Baseline characteristics of patients ($N = 204$)

	N (%)		*N* (%)
Age (median) 61 (IQR 24–84)			
Gender		**Treatment**	
Male	42 (21)	EGFR-TKI	129 (63)
Female	162 (79)	Chemotherapy	75 (37)
Marital status		**Line of treatment**	
Partner	130 (64)	1st line	107 (53)
No partner	74 (36)	≥2nd line	97 (47)
Educational level		**ECOG**	
≤Middle school	107 (52)	0–1	180 (88)
≥High school	97 (48)	2	24 (12)
Stage			
II–III	10 (5)	**Smoking status**	
IV	194 (95)	Never smokers	175 (86)
EGFR status		Current or ever smokers (≥10 pack/year)	29 (14)
Mutant	136 (67)	Median pack/year (range) in current or ever smokers	18 (10–195)
Wild type	68 (33)		

QR, interquartile range; EGFR, epidermal growth factor receptor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

loss of appetite, nausea or vomiting, and constipation were consistently and significantly associated with higher anxiety, depression, and distress scores. Likewise, financial difficulties contribute to worsening the three psychological disorder scores. Diarrhea, commonly associated with targeted therapies and chemotherapy, did not impact anxiety, depression, and distress levels. In this regard, cough, a typical LC symptom, did not impact psychological disorders scores.

Bivariate analysis for global QoL showed that female sex, second or further lines of treatment, depression, anxiety, and emotional distress (DT and HADS total score) were variables significantly associated with worse QoL ($p < 0.05$).

The Spearman correlation test showed a positive and moderate association between anxiety, depression ($r_s = 0.664$, $p = <0.01$), and emotional distress ($r_s = 0.527$, $p = <0.01$). Moreover, higher levels of anxiety had a negative impact on emotional functioning ($r_s = -0.527$, $p = <0.01$) and global QoL ($r_s = -0.325$, $p = <0.01$), and correlates positively with higher levels of pain ($r_s = 0.308$, $p = <0.01$), fatigue ($r_s = 0.300$, $p = <0.01$), and insomnia ($r_s = 0.353$, $p = <0.01$).

Table 2. QoL subscales (EORTC QLQ-C30) depending on the presence or absence of anxiety, depression, or distress

	Anxiety (mean ± SD)			Depression (mean ± SD)			Distress (mean ± SD)		
EORTC QLQ-C30 scales	Absence ($n = 133$)	Presence ($n = 71$)	*P*	Absence ($n = 141$)	Presence ($n = 63$)	*P*	Absence ($n = 110$)	Presence ($n = 94$)	*P*
Global health status	63.40 ± 24.2	47.06 ± 24.72	**<0.001**	63.41 ± 23.79	44.97 ± 24.88	**<0.001**	63.33 ± 24.42	51.15 ± 25.38	**<0.001**
Physical functioning	63.05 ± 31.47	58.68 ± 27.52	0.180	67.56 ± 28.85	48.04 ± 28.84	**<0.001**	65.15 ± 29.29	57.30 ± 30.76	**0.002**
Role functioning	61.02 ± 37.71	49.53 ± 33.32	**0.019**	65.01 ± 34.92	39.15 ± 34.01	**<0.001**	62.42 ± 37.33	50.70 ± 34.81	**0.001**
Cognitive functioning	79.07 ± 24.84	66.43 ± 27.38	**<0.001**	78.72 ± 25.12	65.60 ± 27.08	**<0.001**	78.93 ± 24.69	69.68 ± 27.53	**<0.001**
Emotional functioning	76.31 ± 21.75	56.22 ± 23.85	**<0.001**	75.11 ± 21.50	56.34 ± 25.69	**<0.001**	76.81 ± 21.24	60.54 ± 25.04	**<0.001**
Social functioning	68.29 ± 32.55	49.29 ± 30.91	**<0.001**	68.20 ± 31.67	47.08 ± 32.03	**<0.001**	68.33 ± 31.36	53.90 ± 33.72	**<0.001**
Financial difficulties	62.90 ± 33.24	79.34 ± 26.04	**<0.001**	64.06 ± 32.38	78.83 ± 28.27	**0.002**	66.05 ± 32.55	71.63 ± 30.90	**0.001**
Dyspnea	24.81 ± 31.69	37.08 ± 34.06	**0.007**	25.05 ± 30.64	38.09 ± 36.34	**0.015**	24.84 ± 31.74	34.04 ± 33.85	**0.001**
Pain	29.07 ± 28.98	45.53 ± 31.49	**<0.001**	27.77 ± 26.10	50.52 ± 34.77	**<0.001**	28.93 ± 27.98	41.66 ± 32.67	**<0.001**
Fatigue	37.84 ± 27.45	51.01 ± 29.07	**0.002**	36.80 ± 27.25	55.02 ± 27.89	**<0.001**	35.45 ± 27.85	50.59 ± 27.53	**<0.001**
Insomnia	22.80 ± 30.25	41.78 ± 30.71	**<0.001**	24.82 ± 29.65	39.68 ± 33.79	**0.002**	26.36 ± 31.95	32.97 ± 31.10	**<0.001**

Note: *P*-values in bold represent those comparisons in which a statistically significant difference was reached.
EORTC QLQ-C30, European Organization of Research and Treatment on Cancer Quality of Life questionnaire – Core questionnaire.

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Table 3. Anxiety, depression, and emotional distress scores by the presence or absence of physical symptoms

		Anxiety		Depression		Distress	
		Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	*P*
Pain (general)	Absence	3.36 ± 3.35	**<0.001**	3.37 ± 3.63	**0.001**	2.67 ± 2.3	**0.001**
	Presence	5.08 ± 3.69		5.47 ± 4.7		4.03 ± 2.71	
Chest pain	Absence	3.69 ± 3.21	**0.008**	3.71 ± 3.65	**0.006**	3.04 ± 2.33	**0.035**
	Presence	5.21 ± 4		5.72 ± 5		4.01 ± 2.89	
Arm pain	Absence	3.98 ± 3.57	**0.049**	4.06 ± 4.07	**0.039**	3.14 ± 2.48	0.065
	Presence	4.9 ± 3.69		5.36 ± 4.76		3.92 ± 2.78	
Fatigue	Absence	3.21 ± 3.3	**<0.001**	2.75 ± 3.26	**<0.001**	2.51 ± 2.47	**<0.001**
	Presence	4.98 ± 3.68		5.59 ± 4.62		3.98 ± 2.58	
Dyspnea	Absence	3.73 ± 3.63	**0.007**	4.15 ± 4.51	0.062	3.18 ± 2.69	0.116
	Presence	4.88 ± 3.58		4.96 ± 4.28		3.7 ± 2.56	
Insomnia	Absence	2.88 ± 2.8	**<0.001**	3.28 ± 3.82	**<0.001**	2.82 ± 2.52	**0.002**
	Presence	5.5 ± 3.82		5.6 ± 4.56		3.96 ± 2.61	
Loss of appetite	Absence	3.19 ± 3.3	**<0.001**	2.67 ± 3.25	**<0.001**	2.45 ± 2.49	**<0.001**
	Presence	5.03 ± 3.67		5.71 ± 4.6		4.05 ± 2.53	
Nausea or vomit	Absence	3.57 ± 3.24	**0.004**	3.46 ± 3.61	**0.001**	2.93 ± 2.42	**0.007**
	Presence	5.12 ± 3.87		5.7 ± 4.82		3.98 ± 2.73	
Constipation	Absence	3.65 ± 3.41	**0.001**	3.83 ± 4.05	**0.004**	3.11 ± 2.58	**0.035**
	Presence	5.24 ± 3.75		5.54 ± 4.64		3.9 ± 2.63	
Diarrhea	Absence	4.04 ± 3.47	0.105	4.32 ± 4.18	0.287	3.33 ± 2.56	0.324
	Presence	4.96 ± 3.92		5.12 ± 4.77		3.72 ± 2.75	
Financial difficulties	Absence	3.08 ± 2.72	**0.003**	3.02 ± 3.36	**0.001**	2.8 ± 2.27	**0.038**
	Presence	4.87 ± 3.85		5.23 ± 4.61		3.73 ± 2.72	
Cough	Absence	3.87 ± 3.84	0.078	4.08 ± 4.28	0.212	3.29 ± 2.61	0.503
	Presence	4.56 ± 3.55		4.8 ± 4.44		3.53 ± 2.64	
Dysphagia	Absence	4.08 ± 3.72	**0.025**	4.18 ± 4.27	**0.025**	3.39 ± 2.69	0.471
	Presence	5.05 ± 3.37		5.65 ± 4.57		3.63 ± 2.46	
Peripheral neuropathy	Absence	3.89 ± 3.47	**0.05**	4.04 ± 4.12	**0.05**	3.15 ± 2.65	0.053
	Presence	4.87 ± 3.78		5.2 ± 4.63		3.8 ± 2.57	
Alopecia	Absence	3.65 ± 3.3	**0.003**	3.61 ± 3.66	**0.002**	3.3 ± 2.68	0.312
	Presence	5.16 ± 3.87		5.71 ± 4.89		3.64 ± 2.57	

Note: *P*-values in bold represent those comparisons in which a statistically significant difference was reached.

As well, higher levels of depression were associated with lower scores on global QoL ($r_s = -0.431$, $p = <0.01$), physical ($r_s = -0.413$, $p = <0.01$), role ($r_s = -0.404$, $p = <0.01$), emotional ($r_s = -0.433$, $p = <0.01$), and social functioning ($r_s = -0.338$, $p = <0.01$), and higher levels of pain ($r_s = 0.327$, $p = <0.01$), fatigue ($r_s = 0.367$, $p = <0.01$), and insomnia ($r_s = 0.332$, $p = <0.01$).

Regarding QoL analysis, logistic regression indicated an association with the line of treatment (first line vs. second-line or more) [OR: 2,367, 95% CI (1,281–4,376), $p < 0.006$]. Two additional models were designed for the multivariate analysis, one for depression and the other for anxiety. In the model design to assess factors associated with an increased risk of anxiety, emotional distress measured by the HADS total score [OR 5.9, 95% CI (2.6–12.9); $p < 0.001$] and insomnia [OR 3.3, 95% CI (1.3–8.0); $p = 0.007$] was significant. Meanwhile, in the depression model, emotional distress [OR 5.8, 95% CI (2.6–12.5); $p < 0.001$] was the only factor associated with an increased risk. Male gender seems to be a protective factor in both models for developing anxiety [OR 0.1, 95% CI (0.03–0.3); $p < 0.001$] or depression [OR 0.3, 95% CI (0.1–0.9); $p = 0.046$] (Table 4).

Discussion

Mental illness has been associated with worse health-related quality of life (HRQoL) and increased mortality in LC patients. Psychological disorders, particularly in this population, have been addressed in several studies. From all, depression is one of the most prevalent mental health disorders and correlates with

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Table 4. Multiple logistic regression analysis of main factors associated with depression and anxiety

Variables	OR (95% CI)	*P*
Model 1 (depression)	**Model**	
	Depression = emotional distress	
Sex (male)	0.328 (0.109–0.983)	**0.046**
Physical functioning (low)	0.728 (0.266–1.991)	0.536
Treatment line (second or higher)	1.064 (0.498–2.273)	0.872
Overall QoL (low)	1.037 (0.455–2.263)	0.931
Role functioning (low)	0.381 (0.137–1.061)	0.065
Financial difficulties (high)	1.736 (.665–4.529)	0.260
Social functioning (low)	0.552 (0.245–1.241)	0.150
Insomnia	1.185 (0.514–2.728)	0.691
Dyspnea	0.628 (0.277–1.424)	0.266
Fatigue	0.949 (0.318–2.827)	0.925
Pain	1.064 (0.445–2.544)	0.889
Alopecia	1.613 (0.767–3.390)	0.207
Emotional distress (HADS total score)	5.801 (2.679–12.563)	**<0.001**
Model 2 (anxiety)	**Model**	
	Anxiety = insomnia + emotional distress	
Sex (male)	0.108 (0.030–0.389)	**<0.001**
Physical functioning (low)	1.953 (0.673–5.670)	0.218
Treatment line (second or higher)	1.457 (0.665–3.188)	0.347
Overall QoL (low)	0.954(406–2.241)	0.913
Role functioning (low)	1.117 (0.371–3.363)	0.844
Financial difficulties (high)	2.442 (0.933–6.390)	0.069
Social functioning (low)	0.206 (0.083–0.508)	**<0.001**
Insomnia	3.333 (1.385–8.017)	**0.007**
Dyspnea	0.968 (0.411–2.280)	0.941
Fatigue	0.419 (0.135–1.300)	0.132
Pain	1.659 (0.677–4.066)	0.268
Alopecia	1.772 (0.825–3.806)	0.143
Emotional distress (HADS total score)	5.910 (2.693–12.970)	**<0.001**

Note: *P*-values in bold represent those comparisons in which a statistically significant difference was reached.
QoL, quality of life; HADS, Hospital, Anxiety and Depression Scale.

worse physical functioning and emotional well-being than non-depressed patients. Likewise, higher depression and functional limitations have been associated with higher overall distress levels, emphasizing the interdependence between both disorders (Meijer et al., 2013).

Our group previously evaluated rates of anxiety and depression in 84 advanced NSCLC patients, and both disorders occurred in approximately one-third of patients (Arrieta et al., 2013). Of note, anxiety and depression showed an association with HRQoL and survival. The median overall survival in patients with depression was shorter than that in non-depressed patients, 6.8 vs. 14 months (Arrieta et al., 2013).

In the present study, we found that distress (46%) was the most prevalent psychological problem found on LC patients, followed by anxiety (35%) and depression (31%). Depression and anxiety were associated with female sex, physical symptoms, and diminished functioning. These results were in line with previous reports in which female sex (Price et al., 2012; Walker et al., 2014a, 2014b) and having a lower academic level were associated with a higher risk for developing psychological disorders (Shen et al., 2015).

This study was consistent with other findings, demonstrating an association between distress, anxiety, and depression with worse global status and functioning deterioration on its five subscales (role, physical, emotional, cognitive, and social). Furthermore, those patients with distress, anxiety, and depression had an increased rate and severity of physical symptoms. Moreover, we emphasize the bidirectional effect of physical symptoms and psychological disorders. Those patients with symptoms like pain, fatigue, and insomnia, assessed in QoL scales, had increased anxiety, depression, and distress scores. In this regard, previous studies have associated pain, anxiety, depression, and fatigue with the QoL and sense of well-being (Aukst Margetić et al., 2013; Salminen et al., 2013).

According to the presence or absence of emotional symptoms, the observed differences in QoL confirm the impact of psychological disorders on the overall perception of health and functionality (Brown et al., 2014). Interestingly, we also identified that patients with financial difficulties had higher depression, anxiety, and distress scores.

Currently, active therapy plays a crucial role in the prognosis and QoL of LC patients. Particularly in LC patients, those receiving chemotherapy showed similar anxiety and depression scores since diagnosis and after 6 months from starting treatment. Conversely, those who received TKIs reported a significant improvement after six cycles (Arrieta et al., 2013; Gonzalez-Ling et al., 2017). Notable responses to treatment may explain these findings under targeted therapy. A lower burden of disease might diminish symptoms and improve the psychological status with fewer treatment-related adverse events. Our study could not demonstrate differences in any psychological score based on mutational status and administered therapy. It is imperative to mention that our cohort owned distinctive characteristics. More than two-thirds of patients had EGFR mutant tumors and received an EGFR-TKI. The increased number of young women, non-smokers, and enrichment of Hispanic patients may justify the high rate of EGFR mutant LC (Arrieta et al., 2015b). Moreover, current evidence suggests that EGFR mutant LC occurred more often in Hispanics than Caucasians (Arrieta et al., 2011, 2015a).

In this study, emotional distress was a significant independent factor favoring anxiety and depression regardless of gender and functioning. These results suggest that, although better therapeutic agents have been introduced recently in LC treatment landscape, improving QoL and tolerability, emotional distress remains a determinant factor in their well-being and should be identified and treated accordingly.

Our study underscores the introduction of appropriate psychological screening instruments since the first visit in LC patients. Depression and anxiety affect global QoL regardless of the severity of symptoms. Moreover, the negative impact on QoL

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might compromise the survival of LC patients. For this reason, all psychological disorders should be diagnosed earliest as possible in the course of the disease and receive treatment to ameliorate their symptoms.

Our study had some limitations, limiting the generalizability of the results. We recognize that the cross-sectional design might underestimate the prevalence of psychiatric disorders in our patients; noteworthy, our results did not differ from a previous clinical trial in our population. Another issue was that most patients who received a psycho-oncology evaluation in our institution belonged to a governmental program that supported mainly non-smokers and females, which explains the enrichment of patients with these characteristics impacting the generalizability of results.

Although this study includes relevant variables that can help explain differences in emotional distress, these do not explain the entire equation influencing emotional well-being and QoL. Considering these analyses represent a picture of emotional well-being and QoL, we suggest that more prospective evidence is required to confirm these findings.

The prevalence of anxiety, depression, and distress, considering the different phases of the disease in which these disorders could appear, has detrimental effects on LC patients; thus, we warrant applying for screening programs as a routine clinical practice. Proper recognition of pre-existing mental health disorders and the inclusion of mental health treatment programs, housing, and employment support programs might improve LC-related outcomes.

Psychological interventions should be offered alongside oncological therapy in a multidisciplinary manner to avoid factors that may compromise prognosis. Many questions remain whether the treatment of mental health diseases could mitigate disparity and impact cancer-related outcomes. Hence, identifying mental health illness in LC patients is a priority as part of an integral approach in medical care. Health outcomes could improve by attending to social and mental needs, similarly, highlighting the importance of exploring interventions, ideally in prospective trials, that could improve outcomes for patients who develop psychological disorders during cancer care.

Conclusion

At least one-third of the patients diagnosed with LC in the advanced setting will suffer from anxiety, depression, or distress. Our results warrant a proper psychological assessment in every LC patient to avoid detrimental effects on symptoms relief and QoL. Therefore, the introduction of evidence-based psychological interventions that tackle psychological disorders and adjust to public health care systems should be further investigated on this population.

Data availability statement. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions. Conception: Ana Gonzalez-Ling, Oscar Galindo Vázquez, Marcos Espinoza Bello, Rebeca Robles, María Luisa Rascón-Gasca, and Oscar Arrieta. Preparation of the manuscript: Ana Gonzalez-Ling, Oscar Galindo Vázquez' Marcos Espinoza Bello, María Luisa Rascón-Gasca, Luis Lara-Mejía, David Heredia, and Oscar Arrieta. Revision for important intellectual content: Ana Gonzalez-Ling, Oscar Galindo Vázquez, Rebeca Robles, María Luisa Rascón-Gasca, Luis Lara-Mejía, David Heredia, and Oscar Arrieta. Supervision: Ana Gonzalez-Ling and Oscar Arrieta. Manuscript writing and final approval of manuscript: all authors.

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Conflict of interest. O.A. has received honoraria as an advisor, participated in speakers' bureau, and given expert opinions to Pfizer, AstraZeneca, Boehringer-Ingelheim, Roche, Lilly, and Bristol-Myers Squibb. The other authors declare no potential conflicts of interest.

Ethical standards. Authorization for access and analysis of electronic health record (EHR) data was obtained by the institute's ethics and research committees. The study was conducted in accordance with the principles of the Declaration of Helsinki, local laws on observational studies, and applicable regulatory requirements.

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