

## Association of Depression and Anxiety on Quality of Life, Treatment Adherence, and Prognosis in Patients with Advanced Non-small Cell Lung Cancer

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### ABSTRACT

**Background.** Symptoms of depression and anxiety are common in patients with lung cancer and may produce an impact on both health-related quality of life (HRQL) and survival. The aim of the present study was to evaluate the association of depression and anxiety on HRQL, treatment adherence, and prognosis in patients with non-small cell lung cancer (NSCLC).

**Methods.** This is a prospective study of patients with stage IIIB or IV NSCLC. Depression and anxiety were measured using the hospital anxiety and depression scale, the International Neuropsychiatric Interview, and the HRQL with the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Instruments were applied before treatment and repeated at 3 and 6 months. Lack of treatment adherence was considered as patients who stopped going to their consultation appointments.

**Results.** A total of 82 patients were included. At the initial evaluation, depression and anxiety were found in 32.9 and 34.1 % of patients, respectively. Depression was associated with feminine gender ( $p = 0.034$ ) and poor performance status ( $p = 0.048$ ). Depression and anxiety showed an association with HRQL. Patients with depression showed median overall survival of 6.8 months, whereas that for nondepressed patients was 14 months (hazard ratio [HR], 1.9; 95 % confidence interval (95 % CI), 1.03–3.7;  $p = 0.042$ ). The 58 % of patients with depression had poor treatment adherence versus 42 % of patients without depression ( $p = 0.004$ ). **Conclusions.** Depression and anxiety were present in one-third of patients with recently diagnosed NSCLC. Depression and anxiety were associated with decreased HRQL scales, and depression was independently associated with treatment adherence and with poor prognosis.

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Lung cancer (LC) is the leading cause of cancer-related mortality worldwide. In 2008, 1.6 million new cases were diagnosed, representing 13 % of all malignant neoplasms, and there were 1.3 million deaths.<sup>1</sup>

In Mexico, LC is the fourth most common cause of mortality after prostate, breast, and cervix-uteri cancers.<sup>1</sup> Non-small cell lung cancer (NSCLC) corresponds to 87 % of all cases of LC. The majority of patients are diagnosed at advanced stages, when palliative treatment is aimed at improving health-related quality of life (HRQL) and overall survival (OS), providing the clinical benefit of

chemotherapy.<sup>2-4</sup> Platinum-based cytotoxic chemotherapy is the standard first-line treatment in patients with NSCLC without epidermal growth factor receptor (EGFR) mutation and good performance status. Treatment results in symptom improvement, better HRQL, and prolonged OS compared with best supportive care.<sup>5,6</sup> Despite this, prognosis is poor, with a median OS of 12–14 months.<sup>7,8</sup> The combination of chemotherapy with targeted therapies slightly increased median OS.<sup>9,10</sup>

Symptoms of depression and anxiety are identified in patients with cancer at a frequency of 12–24 %. These symptoms are associated with poorer treatment adherence, increased length of hospital stay, ideation of death, suicide, and poor HRQL.<sup>11</sup> The highest frequencies of depression and anxiety are presented in patients with gastric, pancreatic, head and neck, and LC.<sup>12</sup> The frequency of depression and anxiety in patients with LC is variable, depending on the particular measurement scale used to define symptom severity and the timing of the evaluation. A recent study of patients with LC, using the hospital anxiety and depression scale (HADS), reported a prevalence of depression and anxiety of 25 and 28 %, respectively.<sup>13</sup> This scale has been used in several randomized and quasi-randomized patients with LC.<sup>14,15</sup> In the terminal phase, the prevalence of general symptoms increased in parallel with the increase of symptoms of depression and anxiety, whose prevalence can be as high as 71 %.<sup>16</sup>

Conventionally, the results of LC treatments are measured depending on tumor response rates, and even on progression-free survival (PFS) or OS. Currently, attention is being focused on measuring the perception of patients regarding the impact of disease and its treatments.<sup>17</sup> NSCLC is characterized by poor survival as well as by symptoms related to tumor burden and with symptoms generated by treatments indicated for disease control, all of these contributing to the deleterious effect on HRQL. General health status including fatigue and pain, comorbidities, and psychological symptoms are strongly correlated with decreased HRQL.<sup>18</sup> However, studies that prospectively evaluate psychological symptoms in patients with NSCLC are scarce.

The relationship between depression and survival is debatable. Two prospective studies evaluated the association of depression on OS in patients with NSCLC. One study found that patients with depression have a fourfold decrease in OS compared with patients without depression.<sup>19</sup> The second study only found an association of severity of disease-related symptoms with OS, but not with depression, in multivariate analysis.<sup>20</sup> Consequently, the aim of the present study was to evaluate the association of depression and anxiety on HRQL, treatment adherence, and prognosis in patients with NSCLC.

## MATERIALS AND METHODS

### *Patients*

Consecutive patients with NSCLC with confirmed histopathological diagnosis who attended the outpatient Thoracic Oncology Clinic at the Instituto Nacional de Cancerología (INCan) in Mexico City from March 2008 to June 2010 were invited to participate in this study. Inclusion criteria were patients with Karnofsky performance status (KPS) of 70 % or better, clinical stage IIIB/IV who were candidates to receive chemotherapy. Patients with uncontrolled comorbidities (diabetes, hypertension, etc.) or with acute/chronic complications (acute or chronic cardiac failure, acute or chronic renal failure), presence of brain metastasis, and previous treatment for depression were excluded from the study, as well as patients with delirium or inability to understand or complete the questionnaires. This protocol was accepted by the local institutional review board (IRB) and Ethics committee (registration numbers 008/028/OMI and CB458). All patients signed the informed consent form.

### *Depression, Anxiety, and Treatment Adherence*

Depression and anxiety were evaluated using the HADS and the International Neuropsychiatric Interview (MINI) instruments. HADS is used in patients with cancer because its content is focused on psychological symptoms and not on depression and anxiety-associated physical complaints. HADS contains two 7-item scales to measure depression and anxiety during the previous week. Although HADS is not a diagnostic instrument, a range of cutoff scores on the subscales has been established to identify probable cases of anxiety and depressive disorders. A cutoff value of 8 or more on each subscale is used to define anxiety and depression.<sup>21</sup> The HADS scale has been validated in Mexican patients.<sup>22</sup> The MINI is a brief structured diagnostic interview for making a categorical diagnosis of the major Axis I psychiatric disorders according to the DSM-IV, and good clinical acceptability and reliability have been reported. The MINI allows for the diagnosis of minor depressive disorder.<sup>23</sup> In the protocol, 3 measurements of depression and anxiety were planned: at the beginning of the study, and at 3 and at 6 months. Patients with depression or/and anxiety were offered both psychological and pharmacological treatment depending on symptom severity and patient preference.

Lack of treatment adherence was defined as patients who stopped attending consultation appointments.

### *HRQL*

Health-related quality of life was assessed using the Mexican-Spanish version of the EORTC QLQ-C30 and

QLQ-LC13 questionnaires.<sup>24</sup> The EORTC QLQ-C30 (v.3.0) assesses 5 functioning scales (physical, role, emotional, cognitive, and social performance), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health/quality of life (QoL) scale. The EORTC QLQ-LC13 module consists of 13 items covering LC symptoms (dyspnea, pain, hemoptysis, and cough) and the side effects of chemotherapy and radiotherapy (alopecia, neuropathy, mouth pain, and dysphagia). This instrument has been validated through its application at 2 international multicenter studies, showing adequate levels of reliability and validity.<sup>25</sup> Both questionnaires have been validated in their original versions in English and translated into several languages including Spanish.<sup>25–27</sup>

### *Clinical Data and Outcomes Measures*

Clinical data were obtained during patient visits prior to initiation of treatment with chemotherapy and included: past medical history, sociodemographic data, and definitive histopathological diagnosis and KPS (determined by a medical oncologist). The sixth edition of the Tumor Node Metastasis (TNM) Staging System of the American Joint Committee on Cancer (AJCC) was used to define clinical stages.<sup>28</sup> Cytotoxic chemotherapy was the standard, platinum-based chemotherapy including paclitaxel-carboplatin, paclitaxel-cisplatin, or vinorelbine-cisplatin. OS was defined as the time from histopathological diagnosis until death or the last follow-up visit to the clinic.

### *Statistical Analysis*

Depression and anxiety measured values were dichotomized using a HADS value of 8 as the cutoff. Therefore, patients were divided into two groups (with or without depression, and with or without anxiety). After descriptive analysis, comparisons between groups were performed using the *t* test or the Mann–Whitney *U* test for continuous variables according to normal distribution and  $\chi^2$  for categorical variables. Correlation was performed obtaining the Spearman correlation coefficient (CC). Sample-size calculation considered an 80 % power and a 2-tailed *p* value of 0.05, with a probability of survival of 40 % for the group with depression and of 79 % for the group without depression at 6 months (a 39 % difference).<sup>19</sup> A total of 36 patients per study arm were proposed. A score of 100 represents best global-health/QoL and functional scales or the poorest symptoms. Data analysis was performed independently for the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. OS was analyzed by Kaplan–Meier test, and comparisons among groups were performed using the log-rank test. Multivariate analysis of factors associated with HRQL or OS was defined using the lineal multiple

regression model or the proportional hazards (Cox) model, respectively. Hazard ratios (HR) were obtained as a measurement of association along with their 95 % confidence intervals (95 % CI). All factors associated with HRQL or OS were included in multivariate analysis if their independent probability value was 0.1 or less; a *p* value of 0.05 or less was considered significant. In all cases, 2-tailed statistics were taken into account. SPSS for Windows v. 17 program software was used to perform all computations (SPSS, Inc., Chicago, IL).

## **RESULTS**

A total of 82 patients were included in the study and were evaluated at study initiation, 54 patients were evaluated at 3 months (3 patients died and 25 were lost during follow-up, with reasons including stopping receiving treatment at the institution or discontinuing treatment), and 45 patients were evaluated at 6 months (6 died and 3 were lost during follow-up). Mean age of the cohort was 58.9 years (standard deviation [SD], 12.4 years), 58.5 % (48) were female, and 41.5 % (34) were males. Elementary education was reported in 68.3 % (56) of cases and higher education in 31.7 % (26). The majority of patients were married (64.6 %), and 50 % were smokers. Basal KPS was 100 or 90 % in 43 patients (52.4 %), and was 70–80 % in 39 (47.6 %). Adenocarcinoma was the predominant histopathology in 63 cases (76.8 %), and 66 patients were classified as stage IV (80.5 %).

A total of 34 patients (41.5 %) received pharmacological treatment for depression and anxiety.

### *Depression, Anxiety, and Treatment Adherence*

Hospital anxiety and depression scale and MINI scales presented high correlations on their depression and anxiety scales in the three sequential evaluations. CC for depression was 0.360, 0.576, and 0.759 at baseline and at 3 and 6 months, respectively; CC for anxiety was 0.601, 0.764, and 0.639 at baseline and at 3 and 6 months, respectively. We found a baseline prevalence of depression and anxiety of 32.9 and 34.1 %, according to HADS, respectively, and of 52.9 and 44.7 %, according to the MINI, respectively. Frequency of depression and anxiety decreased over time with both scales (Table 1). Poor functional status using KPS, as well as feminine gender, was associated with depression according to both univariate and multivariate analyses. Only feminine gender was associated with anxiety. Depression or anxiety was not associated with age, level of education, marital status, socioeconomic status, smoking history, comorbidities, histology, and clinical stage (Table 2). Poor treatment adherence was found for

58 % of patients with depression and 42 % of patients without depression, respectively ( $p = 0.004$ ). Poor treatment adherence was found for 42 % of patients with anxiety and 58 % of patients without anxiety, respectively ( $p = 0.4$ ).

### Association with HRQL

Depression showed association with HRQL, particularly global health status/QoL and the following functional scales: physical, role, emotional, cognitive, and social. Anxiety also showed an association with HRQL, particularly global health status/QoL and the following functional scales: physical, role, emotional, and social (all  $p \leq 0.05$ ) (Fig. 1). Neither depression nor anxiety was associated with symptomatic scales in both QLQ-C30 and QLQ-LC13 questionnaires.

### OS

Median follow-up was  $9.6 \pm 6$  months. OS was 11.7 months (95 % CI 9.8–13.6 months). Factors associated with poor OS were masculine gender, smoking history, and depression; however, in the multivariate analysis only depression was significant (HR 1.9 [95 % 1.03–3.7];  $p = 0.042$ ) (Table 3; Fig. 2).

## DISCUSSION

We found in our study that the symptoms of both depression and anxiety are common in patients with advanced NSCLC; their frequency was higher when using the MINI. The MINI instrument is used as a diagnostic measure; the HADS scale excludes somatic symptoms of depression (fatigue, insomnia, and anorexia). HADS is used frequently in patients with cancer, focusing on the psychological symptoms of both anxiety and depression. This explains the differences in frequency between the scales. Notwithstanding this, we found a good correlation between them. We used HADS to determine the association with HRQL and OS, because MINI may overestimate the frequency of depression in patients with cancer. The

frequency of anxiety and depression was found to be similar to that reported in other studies of patients with NSCLC (in 23.3–49 % in patients with depression and from 28 to 32.6 % with anxiety using the same scale).<sup>13,19,29</sup> It is noteworthy that both symptoms occur less frequently over time and as patients receive treatment (Table 1). This may be due to the adaptation of the patient to the disease, improvement in tumor-associated symptoms, and to the improvement of HRQL associated with chemotherapy treatment.<sup>4</sup> One study reported a decrease in depressive symptoms in patients with different treatment modalities.<sup>30</sup> We found that feminine gender was associated with both major depression and anxiety, and functional status is also associated with depression. Univariate analysis of 1,439 patients with different types of advanced cancer found that female patients with poor functional status and primary lung tumors were more likely to report symptoms of anxiety and depression. According to the multivariate analysis, it was found that younger patients and females are more prone to anxiety symptoms; these findings support our results.<sup>31</sup>

Anxiety and depression were associated with worse HRQL, mainly according to the functional scales. In a study conducted with 217 females with NSCLC, it was found that the global, social, psychological, physical, and spiritual HRQL subscales are associated with depression.<sup>32</sup> Another study also reported that patients with depression with NSCLC have lower levels on the physical, functional, and emotional HRQL scales.<sup>33</sup> Moreover, we previously reported that the functional role scale has an association with survival in patients with advanced NSCLC.<sup>24</sup>

In our study, we found that depressive symptoms in patients with NSCLC are an independent factor for survival. Several studies have shown the association between depression and prognosis in patients with advanced LC with contradictory results. In a study performed in 122 patients with inoperable NSCLC in which depression was assessed by both DSM-IV and HADS diagnostic criteria, we found that there is little evidence that psychosocial factors exert an effect on survival.<sup>34</sup> Other studies support the hypothesis that depression is not associated with survival. Patients in early disease stages were included; thus, this cannot be compared with our study.<sup>20</sup> On the other hand, a study of 43 patients with stages IIIB and IV NSCLC assessed with the HADS scale depression found that patients with depression had higher mortality at 6 months (60 vs 21.2 %;  $p = 0.002$ ).<sup>19</sup> Another trial included 90 patients in stages III and IV; the presence of depression with HADS was also evaluated and reported that median survival in the group of patients with depression was 11.8 months compared with one of 24.4 months in patients without depression.<sup>35</sup> In a recently released study, survival was 10 months for patients without

**TABLE 1** Prevalence of depression and anxiety over time

	Depression (%)		Anxiety (%)	
	MINI	HADS	MINI	HADS
Baseline	52.9	32.9	44.7	34.1
3 months	14.1	14.1	12.9	8.2
6 months	12.9	12.9	10.6	9.4

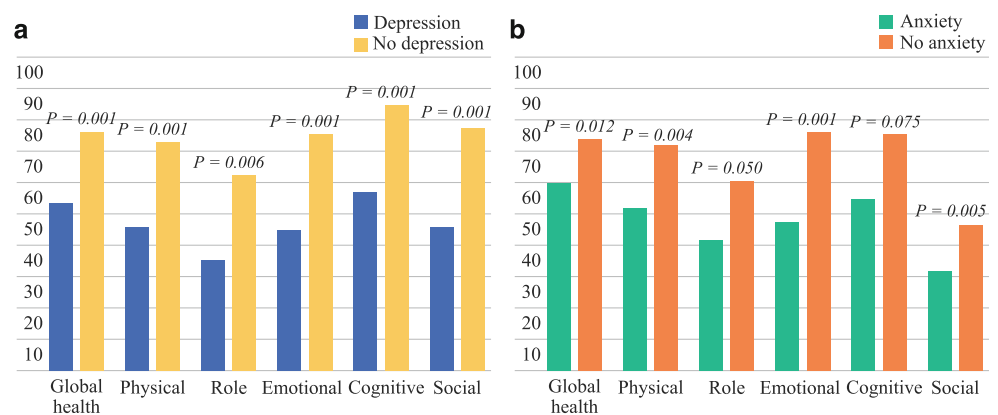
HADS hospital anxiety and depression scale, MINI International Psychiatric Interview

**TABLE 2** Factors associated with depression and anxiety

Patient characteristics ( <i>N</i> = 82)	Depression			Anxiety		
	No depression (%)	Depression (%)	<i>p</i> value	No anxiety (%)	Anxiety (%)	<i>p</i> value
Age (years)						
≤60	72.1 (31/43)	27.9 (12/43)	0.594	62.8 (27/43)	37.2 (16/43)	0.539
>60	66.7 (26/39)	33.3 (13/39)		69.2 (27/39)	30.8 (12/39)	
Gender						
Female	<b>60.4 (29/48)</b>	<b>39.6 (19/48)</b>	<b>0.034</b>	<b>56.3 (27/48)</b>	<b>43.8 (21/48)</b>	<b>0.029</b>
Male	<b>82.4 (28/34)</b>	<b>17.6 (6/34)</b>		<b>79.4 (27/34)</b>	<b>20.6 (7/34)</b>	
Level of education						
Basic	66.1 (37/56)	33.9 (19/56)	0.321	66.1 (37/56)	33.9 (19/56)	0.951
Upper	76.9 (20/26)	23.1 (6/26)		65.4 (17/26)	34.6 (9/26)	
Marital status						
Others	69 (20/29)	31 (9/29)	0.937	58.6 (17/29)	41.4 (12/29)	0.307
Married	69.8 (37/53)	30.2 (16/53)		69.8 (37/53)	30.2 (16/53)	
Socioeconomic status						
≤3	69.6 (48/69)	30.4 (21/69)	0.981	66.7 (46/69)	33.3 (23/69)	0.721
>3	69.2 (9/13)	30.8 (4/13)		61.5 (8/13)	38.5 (5/13)	
Smoking history						
Negative	68.3 (28/41)	31.7 (13/41)	0.810	58.5 (24/41)	41.5 (17/41)	0.162
Positive	70.7 (29/41)	29.3 (12/41)		73.2 (30/41)	26.8 (11/41)	
Hypertension						
Negative	72.1 (44/61)	27.9 (17/61)	0.380	68.9 (42/61)	31.1 (19/61)	0.329
Positive	61.9 (13/21)	38.1 (8/21)		57.1 (12/21)	42.9 (9/21)	
Diabetes mellitus						
Negative	71.2 (47/66)	28.8 (19/66)	0.551	68.2 (45/66)	31.8 (21/66)	0.367
Positive	62.5 (10/16)	37.5 (6/16)		56.3 (9/16)	43.8 (7/16)	
Histology						
Others	68.4 (13/19)	31.6 (6/19)	0.906	63.2 (12/19)	36.8 (7/19)	0.777
Adenocarcinoma	69.8 (44/63)	30.2 (19/63)		66.7 (42/63)	33.3 (21/63)	
Clinical stage						
IIIB	81.3 (13/16)	18.8 (3/16)	0.256	81.3 (13/16)	18.8 (3/16)	0.148
IV	66.7 (44/66)	33.3 (22/66)		62.1 (41/66)	37.9 (25/66)	
Karnofsky performance status						
70–80	<b>59 (23/39)</b>	<b>41 (16/39)</b>	<b>0.048</b>	59 (23/39)	41 (16/39)	0.211
90–100	<b>79.1 (34/43)</b>	<b>20.9 (9/43)</b>		72.1 (31/43)	27.9 (12/43)	

Bold variables with significance less than 0.05

**FIG. 1** Association of depression (a) and anxiety (b) with health-related quality of life mean scores of functional scales of the EORTC QLQ-C30 questionnaire. *p* values correspond to differences between groups using the Mann–Whitney *U* test



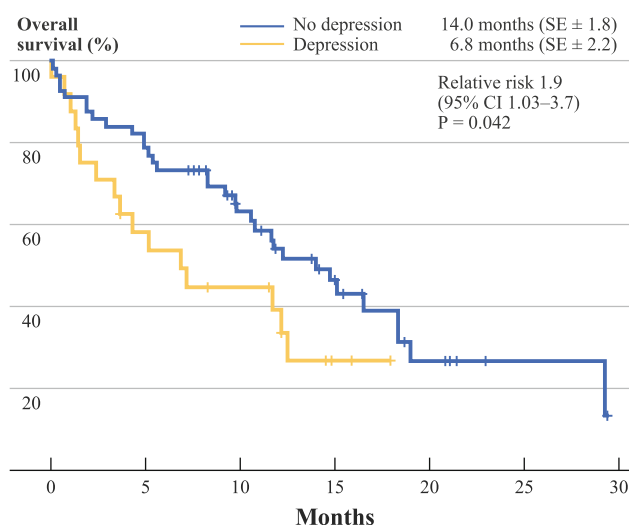


**TABLE 3** Factors associated with overall survival

Patient characteristics (N = 82)	Median ± SE (months)	95 % CI	p value		RR, 95 % CI
			Univariate analysis	Multivariate analysis	
Age (years)					
<60	12.2 ± 1.7	8.8–16.6	0.342		
≥60	10.5 ± 1.8	2.4–1.1			
Gender					
Female	<b>16.5 ± 3.1</b>	<b>10.4–22.6</b>	<b>0.018</b>	0.094	0.5 (0.2–1.2)
Male	<b>9.7 ± 2.6</b>	<b>4.6–14.1</b>			
Smoking history					
Negative	<b>16.5 ± 3.4</b>	<b>9.7–23.3</b>	<b>0.022</b>	0.405	1.3 (0.6–2.7)
Positive	<b>9.7 ± 1.5</b>	<b>6.6–12.7</b>			
Karnofsky performance status					
70–80	10.5 ± 1.8	7.1–14.1	0.342		
90–100	14 ± 3.2	7.6–20.3			
Clinical stage					
IIIB	16.5 ± 3.4	9.7–23.3	0.140		
IV	10.7 ± 1.5	7.7–13.8			
Histology					
Adenocarcinoma	14 ± 4	6.1–21.8	0.570		
Others	11.7 ± 0.9	9.7–13.6			
Depression					
Negative	<b>14 ± 1.8</b>	<b>10.3–17.6</b>	<b>0.044</b>	<b>0.042</b>	<b>1.9 (1.03–3.7)</b>
Positive	<b>6.8 ± 2.2</b>	<b>2.4–11.1</b>			
Anxiety					
Negative	14 ± 2.1	9.7–18.3	0.250		
Positive	11.6 ± 2.3	6.9–16.3			

Bold variables with significance less than 0.05

SE standard error, RR risk ratio, 95 % CI 95 % confidence interval

**FIG. 2** Association of depression with overall survival

depression and 5.4 months for patients with depression ( $p = 0.001$ ).<sup>36</sup> Anxiety had no impact on prognosis. These data are consistent with those reported in previous studies.<sup>19,35</sup> Several factors may explain why depression is

associated with decreased survival in patients with NSCLC. In patients with cancer, there is chronic activation of the hypothalamic/pituitary/adrenal axis, which has been implicated as a mechanism that promotes cancer progression.<sup>37</sup> These alterations are more evident in patients with depression and cancer.<sup>38</sup>

In addition, various cytokines involved in immune mechanisms are modified by the emotions, perpetuating chronic disorder of this axis. Levels of these proinflammatory cytokines (IL1, IL2, and TNF- $\alpha$ ) are increased in patients with depression; therefore, in patients with cancer these changes may explain poor prognosis.<sup>39,40</sup> Finally, patients with depression and cancer more frequently develop the cachexia syndrome, which contributes to a state of malnutrition that increases treatment toxicity and reduces treatment tolerance and adherence, eventually leading to decreased survival.<sup>41–44</sup> Another factor that may contribute to lower survival is the lack of treatment adherence demonstrated by patients with depression.<sup>45</sup> Our findings support this hypothesis. In a recent meta-analysis involving 25 studies with patients with different types of malignancies (breast, lung, central nervous system, melanoma, and hematological cancers), of a total of 9,417

patients we found that the presence of depressive symptoms is associated with increased mortality (1.25; 95 % CI, 1.12–1.40;  $p < 0.001$ ). This effect was greater in patients diagnosed with major depression (RR, 1.39; 95 % CI, 1.10–1.89;  $p = 0.03$ ), supporting our results.<sup>46</sup> Despite attempting to treat the symptoms with antidepressants and counseling in our study, baseline depression had a deleterious effect; it is likely that without treatment the effect may be even higher. It was recently reported that baseline depression was associated with worse survival, although improvement in depressive symptoms did not influence survival.<sup>36</sup> An important question is: What is the effect of the integral treatment of depression on HRQL and survival? Randomized studies are needed to evaluate both pharmacological and nonpharmacological management for anxiety and depression and their impact on HRQL, treatment adherence, and prognosis. The limitations of our study comprise the small number of patients and lack of homogeneity in their treatment for depression.

In conclusion, depression in patients with advanced NSCLC is strongly associated with poorer HRQL, reduced treatment adherence, and poor prognosis. It is important, therefore, to assess symptoms of depression and anxiety during the initial evaluation and to implement nonpharmacological and pharmacological strategies to control these symptoms, which may improve not only HRQL and treatment adherence, but also survival.

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**CONFLICT OF INTEREST** The authors have nothing to disclose.

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