

# Prevalence and correlation of anxiety and depression on the prognosis of postoperative non-small-cell lung cancer patients in North China

Xuan Huang, MB, Tian-Ze Zhang, MD, Guang-Hua Li, MM, Lei Liu, MB, Guang-Quan Xu, MD\*

## Abstract

Identify the prevalence of postoperative anxiety and depression as well as their correlations with clinical features and survival profiles in non-small-cell lung cancer (NSCLC) patients who underwent resection.

Four hundred NSCLC patients who underwent resection were recruited, and their anxiety and depression were assessed by hospital anxiety and depression scale (HADS) at discharge after surgery. Besides, 480 healthy controls (HCs) were also enrolled and assessed by HADS.

The HADS-Anxiety score of NSCLC patients ( $7.8 \pm 3.9$ ) was greatly higher than that of HCs ( $4.8 \pm 2.7$ ), and the anxiety prevalence of NSCLC patients (49.6%) were dramatically increased compared with HCs (13.8%). Furthermore, the HADS-Depression score ( $7.2 \pm 3.6$ ) of NSCLC patients was considerably increased compared with HCs ( $4.2 \pm 2.6$ ), and the depression prevalence of NSCLC patients (38.3%) was significantly raised compared with HCs (10.0%). Besides, anxiety correlated with gender, marital status, hypertension, diabetes, pathological differentiation, tumor size, lymph node metastasis, TNM stage and carcinoembryonic antigen level, meanwhile, depression correlated with marital status, employment status before surgery, diabetes, pathological differentiation, and TNM stage in NSCLC patients. Additionally, the anxiety and depression predicted shorter disease-free survival in NSCLC patients. And the anxiety predicted worse overall survival (OS), while no association of depression with OS was observed in NSCLC patients.

Post-operative anxiety and depression are highly prevalent and implicated in the ongoing care and prognosis prediction in NSCLC patients who underwent resection.

**Abbreviations:** CEA = carcinoembryonic antigen, DFS = disease-free survival, HADS = hospital anxiety and depression scale, HCs = healthy controls, IQR = interquartile range, LYN = lymph node, NSCLC = non-small-cell lung cancer, OS = overall survival, SD = standard deviation.

**Keywords:** anxiety, depression, non-small-cell lung carcinoma, prognosis, risk factors

## 1. Introduction

Lung cancer, one of the most commonly diagnosed malignancies, is the leading cause of cancer-related death worldwide with 2.1 million new cases and 1.8 million deaths estimated in 2018 based on the recent global cancer statistics.<sup>[1,2]</sup> Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung

cancers, and the majority of patients are diagnosed as locally advanced or metastatic NSCLC.<sup>[1,3]</sup> The clinical outcome of NSCLC has been improved thanks to the development and advancement in target therapies and immunotherapy during the last decade.<sup>[4]</sup> However, disease-related symptoms (such as coughing, chest pain, and hemoptysis) and aggressive treatments (such as chemotherapy and surgery) lead to physical deformities, body dysfunction, multiple side-effects, which further accelerate the occurrence and progression of psychological distress especially anxiety and depression.<sup>[5]</sup>

Anxiety and depression are serious and recurrent psychological disorders.<sup>[6]</sup> Anxiety is characterized by persistent and excessive unpleasant feelings of threat or potential harm, often accompanied by apprehension, worry, poor concentration, muscular tension, palpitations, and sweating.<sup>[7]</sup> As for depression, it is marked by low mood, loss of interest or pleasure in hobbies and activities, decreased energy, difficulties in concentrating or making decisions, appetite and sleep disturbance, psychomotor disturbances, and suicidal attempts.<sup>[8]</sup> Both anxiety and depression may decrease patients' capability to tolerate the illness burden and aggressive treatment regimens, which extends periods of hospitalization, worsens quality of life and elevates mortality rates.<sup>[9]</sup>

Existing studies display that demographic factors, social factors, health behaviors, and cancer-related variables manifest anxiety and depression in lung cancer patients.<sup>[5,10]</sup> For instance,

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Department of Thoracic Surgery, the Second Affiliated Hospital of Harbin Medical University, Harbin, China.

\* Correspondence: Guang-Quan Xu, Department of Thoracic Surgery, the Second Affiliated Hospital of Harbin Medical University, 246 Xuefu Road, Harbin 150086, China (e-mail: goudang547204227@163.com).

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cancer stage, cancer type, gender, and age correlate with depression in lung cancer patients.<sup>[5]</sup> Another study illustrates that feminine gender is associated with increased risks of anxiety and depression in NSCLC patients.<sup>[10]</sup> Nonetheless, information on factors for impacting the prevalence of anxiety and depression in NSCLC patients who underwent resection is limited. Besides, it is evident that anxiety and depression result in declined quality of life, prolonged length of hospitalization and even poor prognosis in lung cancer patients.<sup>[10,11]</sup> Based on these perceptions, we hypothesized that anxiety and depression might possess negative effect on prognosis in NSCLC patients who underwent resection as well, but no related study has been reported yet. Therefore, the aim of this study was to investigate the prevalence of postoperative anxiety/depression, and their correlations with clinical features as well as survival profile in NSCLC patients who underwent resection.

## 2. Methods

### 2.1. Participants

From July 2013 to June 2016, 480 NSCLC patients who underwent resection in our hospital were consecutively enrolled in this study. Patients were included if they met the following criteria:

1. histologically or cytologically confirmed diagnosis of primary NSCLC;
2. underwent surgery resection;
3. age above 18 years old;
4. not complicated with other malignancies;
5. no severe infection, liver, kidney, or blood coagulation dysfunction.

Patients were excluded if they:

1. received anxiolytic or antidepressants treatment within 3 months before enrollment;
2. received neoadjuvant chemotherapy or radiation therapy before enrollment;
3. have cognitive impairments or neurological diseases and unable to understand daily questions accurately;
4. complicated with uncontrolled cardio-cerebrovascular diseases (such as hypertension, cardiac arrhythmia, or unstable angina pectoris).

In addition, 480 healthy subjects were recruited as healthy controls (HCs) during the same period. The screening criteria of HCs included:

1. no history of malignancies or severe infection;
2. no obvious biochemical indexes abnormalities confirmed by physical examination;
3. age  $\geq$  18 years;
4. not complicated with uncontrolled cardio-cerebrovascular diseases (such as hypertension, cardiac arrhythmia, or unstable angina pectoris).

All participants provided written informed consents, and the Institutional Review Board of our hospital approved this study.

### 2.2. Data collection and assessment

Demographic and clinical characteristics of NSCLC patients were recorded after enrollment, which included age, gender, smoking status, history of drink, marital status, employment status before

surgery, level of education, hypertension, hyperlipidemia, diabetes, pathological differentiation, tumor size, lymph node (LYN) metastasis, TNM stage, and carcinoembryonic antigen (CEA) level. Regarding smoking status, patients were divided into current smokers (continued their smoking habit at the enrollment), former smokers (had quit smoking 1 or more years before the enrollment), quit smokers (had stopped smoking within 1 year before the enrollment) and never smoker (had never smoked before). Besides, anxiety and depression of NSCLC patients was assessed using the Hospital Anxiety and Depression Scale (HADS) at discharge after surgery, and the anxiety and depression of HCs was evaluated using HADS at enrollment. The HADS has 14 items, which were designed to measure anxiety (HADS-A) and depression (HADS-D), and the total score on each subscale ranging from 0 to 21.<sup>[12]</sup> According to the total score of HADS-A and HADS-D, the severity of anxiety and depression were classified as 4 grades:

1. no anxiety or depression (total score  $<$  8);
2. mild anxiety or depression (total score: 8–11);
3. moderate anxiety or depression (total score 11–14);
4. severe anxiety or depression (total score  $>$  14).<sup>[12]</sup>

### 2.3. Follow-up

After surgery, patients received appropriate adjuvant therapy if clinically indicated (e.g., chemotherapy and radiation therapy), according to NCCN guideline of NSCLC.<sup>[13]</sup> Regularly follow-up was performed by telephone or clinical visit, and all patients were followed up to death or 36 months. Throughout follow-up, disease relapse and death were recorded. The disease-free survival (DFS) was calculated from the date of entry into the study to the date of relapse or death, and for the patients without information of relapse or death at last follow-up, they were censored on the date of relapse or last visit. The OS was calculated from the date of entry into the study to the date of death, and for the patients not known to have died at last follow-up, they were censored on the date of last known to be alive.

### 2.4. Statistical analysis

Statistical analyses were performed using SPSS 22.0 software (IBM, Chicago, IL, USA), and figures were plotted using GraphPad Prism 7.01 software (GraphPad Software, San Diego, California, USA). Data were presented as mean  $\pm$  standard deviation (SD), median and interquartile range (IQR), or count (percentage). Comparison between 2 groups was analyzed by Student *t* test, Wilcoxon rank sum test or Chi-Squared test. Kaplan–Meier curves were plotted to display DFS and OS, and the difference of DFS and OS between 2 groups was determined by Log-rank test. All tests were two-tailed, and *P* value  $<$  .05 was considered significant.

## 3. Results

### 3.1. Study flow

Initially, 566 NSCLC patients were invited, among which 86 patients were excluded (35 patients were not suitable for resection; 24 patients presented with relapsed or secondary NSCLC; 13 patients refused to sign the informed consents; 8 patients received anxiolytic or antidepressant treatments in the past 3 months; 6 patients were complicated with uncontrolled cardio-cerebrovascular diseases) (Fig. 1). Then, 480 eligible

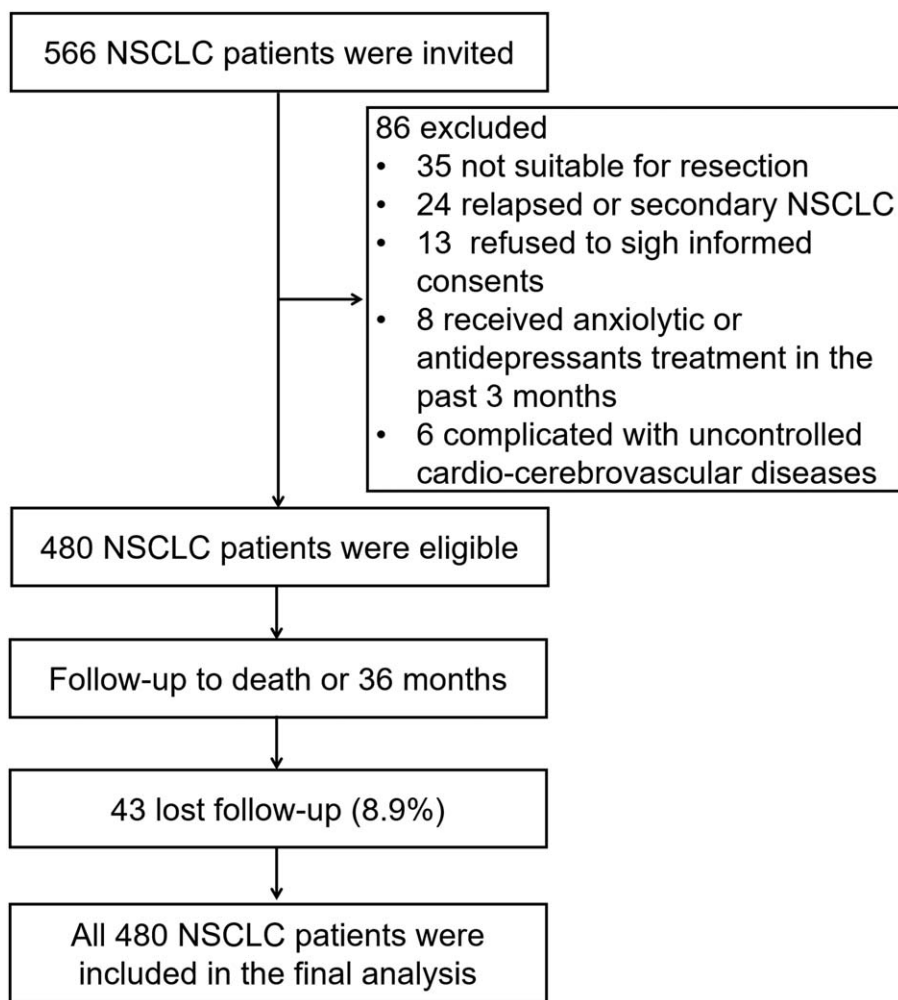


Figure 1. Study flow. NSCLC, non-small-cell lung cancer.

NSCLC patients were followed up to death or 36 months. During the follow-up, 43 patients were lost follow-up. All 480 NSCLC patients were included in the final analysis.

### 3.2. NSCLC patients' characteristics

The mean age of NSCLC patients was  $61.0 \pm 9.9$  years, and there were 118 (24.6%) females as well as 362 (75.4%) males. As for smoking status, there were 23 (4.8%), 82 (17.1%), 156 (32.5%) and 219 (45.6%) current smokers, former smokers, quit smokers and never smokers, respectively. History of drink was found in 261 (54.4%) and 184 (38.3%) NSCLC patients. Furthermore, 182 (37.9%), 144 (30.0%) and 85 (17.7%) NSCLC patients had hypertension, hyperlipidemia, and diabetes, respectively. Additionally, there were 149 (31.0%) NSCLC patients with TNM stage I, 168 (35.0%) with TNM stage II and 163 (34.0%) with TNM stage III. Other detailed characteristics of NSCLC patients were listed in Table 1.

### 3.3. Prevalence and severity of anxiety in NSCLC patients and HCs

The HADS-A score of NSCLC patients ( $7.8 \pm 3.9$ ) was higher than that of HCs ( $4.8 \pm 2.7$ ) ( $P < .001$ ) (Fig. 2A). And the

prevalence of anxiety was elevated in NSCLC patients (49.6%) compared with HCs (13.8%) ( $P < .001$ ) (Fig. 2B). As for anxiety severity, 115 (48.3%), 99 (41.6%) and 24 (10.1%) NSCLC patients were with mild, moderate and severe anxieties, respectively, whereas 55 (83.3%), 11 (16.7%) and 0 (0%) HCs presented mild, moderate, and severe anxieties respectively ( $P < .001$ ) (Fig. 2C). These data implied anxiety was much more prevalent and severe in NSCLC patients compared to HCs.

### 3.4. Prevalence and severity of depression in NSCLC patients and HCs

The HADS-D score was  $7.2 \pm 3.6$  in NSCLC patients, which was raised compared with that in HCs ( $4.2 \pm 2.6$ ) ( $P < .001$ ) (Fig. 3A). Regarding depression prevalence, it was higher in NSCLC patients (38.3%) than that in HCs (10.0%) ( $P < .001$ ) (Fig. 3B). Furthermore, 94 (51.1%), 74 (40.2%), and 16 (8.7%) NSCLC patients presented with mild, moderate, and severe depression respectively, whereas 44 (91.7%), 4 (8.3%) and 0 (0%) HCs were with mild, moderate, and severe depressions respectively ( $P < .001$ ) (Fig. 3C). These findings suggested that depression was much more prevalent and severe in NSCLC patients compared with HCs.

**Table 1**  
**Sociodemographic and clinical characteristics of NSCLC patients.**

Items	NSCLC patients (N = 480)
Sociodemographic characteristics	
Age (years), mean±SD	61.0±9.9
Gender, No. (%)	
Female	118 (24.6)
Male	362 (75.4)
Smoking status, No. (%)	
Current smoker	23 (4.8)
Former smoker	82 (17.1)
Quit smoker	156 (32.5)
Never smoker	219 (45.6)
History of drink, No. (%)	184 (38.3)
Marital status, No. (%)	
Married	334 (69.6)
Divorced/widowed	90 (18.7)
Single	56 (11.7)
Employment status before surgery, No. (%)	
Unemployed	304 (63.3)
Employed	176 (36.7)
Level of education, No. (%)	
Primary school or less	45 (9.4)
High school	220 (45.8)
Undergraduate	164 (34.2)
Graduate or above	51 (10.6)
Clinical characteristics	
Hypertension, No. (%)	182 (37.9)
Hyperlipidemia, No. (%)	144 (30.0)
Diabetes, No. (%)	85 (17.7)
Pathological differentiation, No. (%)	
Well	93 (19.4)
Moderate	268 (55.8)
Poor	119 (24.8)
Tumor size (cm), mean±SD	5.4±2.1
LYN metastasis, No. (%)	161 (33.5)
TNM stage, No. (%)	
I	149 (31.0)
II	168 (35.0)
III	163 (34.0)
CEA (ng/mL), median (IQR)	6.6 (2.9–27.6)

CEA = carcinoembryonic antigen, IQR = interquartile range, LYN = lymph node, NSCLC = non-small cell lung cancer, SD = standard deviation.

**3.5. Correlation of anxiety with sociodemographic characteristics in NSCLC patients**

Anxiety correlated with gender (female) ( $P=.026$ ) and marital status (single, divorced/widowed vs married) ( $P<.001$ ) in

NSCLC patients (Table 2). While no correlation of anxiety with age ( $P=.360$ ), smoking status ( $P=.529$ ), history of drink ( $P=.675$ ), employment status before surgery ( $P=.890$ ), or level of education ( $P=.836$ ) was observed in NSCLC patients.

**3.6. Correlation of anxiety with clinical characteristics in NSCLC patients**

Anxiety correlated with hypertension ( $P=.016$ ), diabetes ( $P<.001$ ), poorer pathological differentiation ( $P<.001$ ), larger tumor size ( $>5$  cm) ( $P=.005$ ), LYN metastasis ( $P=.011$ ), advanced TNM stage ( $P<.001$ ), and higher concentration of CEA ( $>5$  ng/ml) ( $P=.038$ ) in NSCLC patients (Table 2). While no correlation of anxiety with hyperlipidemia ( $P=.905$ ) was revealed in NSCLC patients.

**3.7. Correlation of depression with sociodemographic characteristics in NSCLC patients**

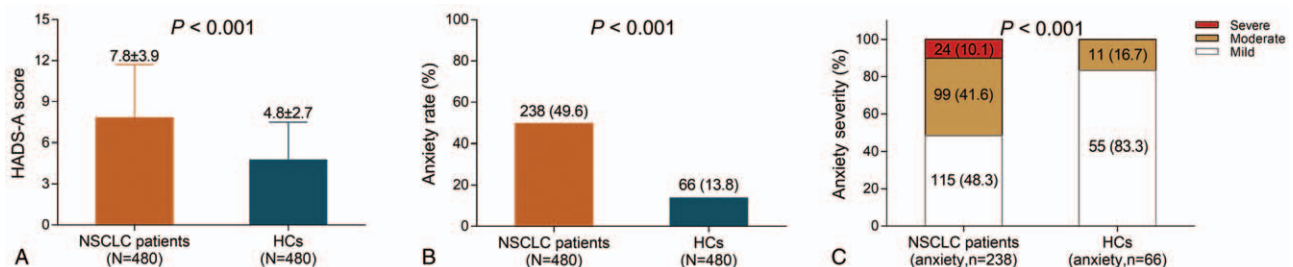
Depression correlated with marital status (single, divorced/widowed vs married) ( $P<.001$ ) and employment status before surgery (employed) ( $P=.040$ ) in NSCLC patients (Table 3). While there was no correlation of depression with age ( $P=.675$ ), gender ( $P=0.299$ ), smoking status ( $P=.246$ ), history of drink ( $P=.099$ ), and level of education ( $P=.186$ ) in NSCLC patients.

**3.8. Correlation of depression with sociodemographic and clinical characteristics in NSCLC patients**

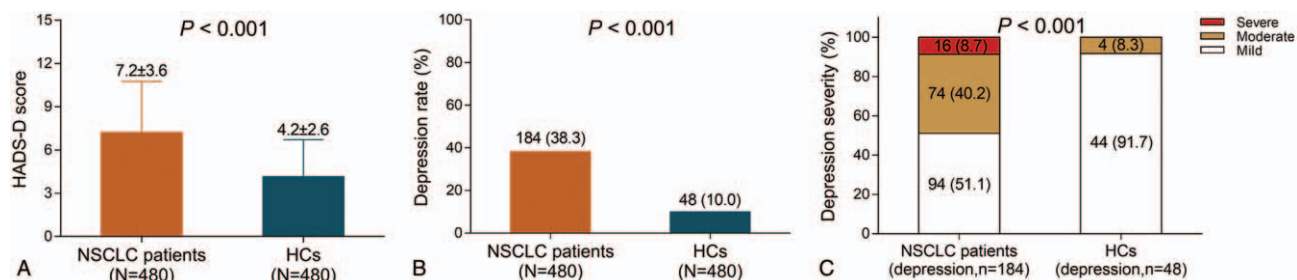
Depression correlated with diabetes ( $P<.001$ ), poorer pathological differentiation ( $P<.001$ ) and advanced TNM stage ( $P=.012$ ) in NSCLC patients (Table 3). While there was no correlation of depression with hypertension ( $P=.074$ ), hyperlipidemia ( $P=.235$ ), tumor size ( $P=.074$ ), LYN metastasis ( $P=.293$ ) or CEA ( $P=.261$ ) in NSCLC patients.

**3.9. Correlation of anxiety with sociodemographic and clinical characteristics by multivariate logistic regression model**

Multivariate logistic regression analysis exhibited that marital status (divorced/widowed vs married) ( $P=.047$ , OR=1.713), marital status (single vs married) ( $P<.001$ , OR=5.522), hypertension ( $P=.035$ , OR=1.646), diabetes ( $P<.001$ , OR=4.593), poorer pathological differentiation ( $P<.001$ , OR=1.793), and advanced TNM stage ( $P<.001$ , OR=2.086)



**Figure 2.** HADS-A score, anxiety rate and severity in NSCLC patients and HCs. Comparisons of HADS-A score (A), anxiety rate (B) and anxiety severity (C) between NSCLC patients and HCs. Comparison of HADS-A score between NSCLC patients and HCs was assessed by Student *t* test, and comparison of anxiety rate between NSCLC patients and HCs was performed by Chi-Squared test. Furthermore, comparison of anxiety severity was evaluated by Wilcoxon rank sum test. *P* value  $<.05$  was considered significant. HADS-A, hospital anxiety and depression scale-anxiety; NSCLC, non-small-cell lung cancer; HC, healthy controls.



**Figure 3.** HADS-D score, depression rate and severity in NSCLC patients and HCs. Comparisons of HADS-D score (A), depression rate (B) and depression severity (C) between NSCLC patients and HCs. Comparison of HADS-D score between NSCLC patients and HCs was assessed by Student *t* test. As for depression rate, its comparison between NSCLC patients and HCs was conducted by Chi-Squared test. Besides, comparison of depression severity was analyzed by Wilcoxon rank sum test. *P* value < .05 was considered significant. HADS-D, hospital anxiety and depression scale-depression; NSCLC, non-small-cell lung cancer; HC, healthy controls.

**Table 2**  
**Correlation of anxiety with sociodemographic and clinical characteristics.**

Items	No.	Non-anxiety (n=242)	Anxiety (n=238)	<i>P</i> value
Sociodemographic characteristics				
Age, No. (%)				.360
≤60 years	238	125 (51.7)	113 (47.5)	
>60 years	242	117 (48.3)	125 (52.5)	
Gender, No. (%)				.026
Female	118	49 (20.2)	69 (29.0)	
Male	362	193 (79.8)	169 (71.0)	
Smoking status, No. (%)				.529
Current smoker	23	15 (6.2)	8 (3.4)	
Former smoker	82	40 (16.5)	42 (17.6)	
Quite smoker	156	79 (32.6)	77 (32.4)	
Never smoker	219	108 (44.6)	111 (46.6)	
History of drink, No. (%)				.675
No	296	147 (60.7)	149 (62.6)	
Yes	184	95 (39.3)	89 (37.4)	
Marital status, No. (%)				<.001
Married	334	192 (79.3)	142 (59.7)	
Divorced/widowed	90	38 (15.7)	52 (21.8)	
Single	56	12 (5.0)	44 (18.5)	
Employment status before surgery, No. (%)				.890
Un-employed	304	154 (63.6)	150 (63.0)	
Employed	176	88 (36.4)	88 (37.0)	
Level of education, No. (%)				.836
Primary school or less	45	14 (5.8)	31 (13.0)	
High school	220	122 (50.4)	98 (41.2)	
Undergraduate	164	84 (34.7)	80 (33.6)	
Graduate or above	51	22 (9.1)	29 (12.2)	
Clinical characteristics				
Hypertension, No. (%)				.016
No	298	163 (67.4)	135 (56.7)	
Yes	182	79 (32.6)	103 (43.3)	
Hyperlipidemia, No. (%)				.905
No	336	170 (70.2)	166 (69.7)	
Yes	144	72 (29.8)	72 (30.3)	
Diabetes, No. (%)				<.001
No	395	225 (93.0)	170 (71.4)	
Yes	85	17 (7.0)	68 (28.6)	
Pathological differentiation, No. (%)				<.001
Well	93	60 (24.8)	33 (13.9)	
Moderate	268	142 (58.7)	126 (52.9)	
Poor	119	40 (16.5)	79 (33.2)	
Tumor size, No. (%)				.005
≤5 cm	275	154 (63.6)	121 (50.8)	
>5 cm	205	88 (36.4)	117 (49.2)	
LYN metastasis, No. (%)				.011
No	319	174 (71.9)	145 (60.9)	
Yes	161	68 (28.1)	93 (39.1)	
TNM stage, No. (%)				<.001
I	149	99 (40.9)	50 (21.0)	
II	168	77 (31.8)	91 (38.2)	
III	163	66 (27.3)	97 (40.8)	
CEA, No. (%)				.038
≤5 ng/mL	198	111 (45.9)	87 (36.6)	
>5 ng/mL	282	131 (54.1)	151 (63.4)	

Boldface was considered significant (*P* value < .05). Comparison was determined by Chi-Squared test or Wilcoxon rank sum test. CEA = carcinoembryonic antigen, LYN = lymph node, NSCLC = non-small cell lung cancer.

independently correlated with higher anxiety risk, whereas level of education (high school vs primary school or less) (*P* = .044, OR = 0.436) independently correlated with lower anxiety risk in NSCLC patients (Table 4).

**3.10. Correlation of depression with sociodemographic and clinical characteristics by multivariate logistic regression model**

Multivariate logistic regression analysis displayed that marital status (divorced/widowed vs married) (*P* < .001, OR = 3.036), marital status (single vs married) (*P* = .002, OR = 2.739), employed before surgery (*P* = .001, OR = 2.139), diabetes (*P* < .001, OR = 4.978), poorer pathological differentiation (*P* = .003, OR = 1.651), and advanced TNM stage (*P* = .042, OR = 1.479) independently correlated with higher depression risk, whereas level of education (undergraduate vs primary school or less) (*P* = .002, OR = .269) independently correlated with lower depression risk in NSCLC patients (Table 5).

**3.11. Correlations of anxiety and depression with DFS in NSCLC patients**

NSCLC patients with anxiety exhibited shorter DFS compared to NSCLC patients without anxiety (*P* = .011) (Fig. 4A). Meanwhile, NSCLC patients with depression showed shorter DFS compared with NSCLC patients without depression as well (*P* = .035) (Fig. 4B).

**3.12. Correlations of anxiety and depression with OS in NSCLC patients**

NSCLC patients with anxiety presented shorter OS compared to NSCLC patients without anxiety (*P* = .038) (Fig. 5A). While, no correlation of depression with OS was observed in NSCLC patients (*P* = .148) (Fig. 5B).

**4. Discussion**

In the present study, we discovered that:

1. NSCLC patients who underwent resection had higher prevalence and severity of anxiety as well as depression than HCs.
2. Anxiety was associated with gender (female), marital status (single, divorced, and widowed vs married), hypertension, diabetes, poorer pathological differentiation, larger tumor size, LYN metastasis, advanced TNM stage, and higher

**Table 3**  
**Correlation of depression with sociodemographic and clinical characteristics.**

Items	No.	Non-depression (n = 296)	Depression (n = 184)	P value
<b>Sociodemographic characteristics</b>				.675
Age, No. (%)				
≤60 years	238	149 (50.3)	89 (48.4)	
>60 years	242	147 (49.7)	95 (51.6)	
Gender, No. (%)				.299
Female	118	68 (23.0)	50 (27.2)	
Male	362	228 (77.0)	134 (72.8)	
Smoking status, No. (%)				.246
Current smoker	23	17 (5.7)	6 (3.3)	
Former smoker	82	55 (18.6)	27 (14.7)	
Quit smoker	156	98 (33.1)	58 (31.5)	
Never smoker	219	126 (42.6)	93 (50.5)	
History of drink, No. (%)				.099
No	296	174 (58.8)	122 (66.3)	
Yes	184	122 (41.2)	62 (33.7)	
Marital status, No. (%)				<.001
Married	334	228 (77.0)	106 (57.6)	
Divorced/widowed	90	42 (14.2)	48 (26.1)	
Single	56	26 (8.8)	30 (16.3)	
Employment status before surgery, No. (%)				.040
Un-employed	304	198 (66.9)	106 (57.6)	
Employed	176	98 (33.1)	78 (42.4)	
Level of education, No. (%)				.186
Primary school or less	45	23 (7.8)	22 (12.0)	
High school	220	134 (45.2)	86 (46.7)	
Undergraduate	164	108 (36.5)	56 (30.4)	
Graduate or above	51	31 (10.5)	20 (10.9)	
<b>Clinical characteristics</b>				
Hypertension, No. (%)				.074
No	298	193 (65.2)	105 (57.1)	
Yes	182	103 (34.8)	79 (42.9)	
Hyperlipidemia, No. (%)				.235
No	336	213 (72.0)	123 (66.8)	
Yes	144	83 (28.0)	61 (33.2)	
Diabetes, No. (%)				<.001
No	395	271 (91.6)	124 (67.4)	
Yes	85	25 (8.4)	60 (32.6)	
Pathological differentiation, No. (%)				<.001
Well	93	69 (23.3)	24 (13.1)	
Moderate	268	168 (56.8)	100 (54.3)	
Poor	119	59 (19.9)	60 (32.6)	
Tumor size, No. (%)				.074
≤5 cm	275	179 (60.5)	96 (52.2)	
>5 cm	205	117 (39.5)	88 (47.8)	
LYN metastasis, No. (%)				.293
No	319	202 (68.2)	117 (63.6)	
Yes	161	94 (31.8)	67 (36.4)	
TNM stage, No. (%)				.012
I	149	105 (35.5)	44 (23.9)	
II	168	99 (33.4)	69 (37.5)	
III	163	92 (31.1)	71 (38.6)	
CEA, No. (%)				.261
≤5 ng/mL	198	128 (43.2)	70 (38.0)	
>5 ng/mL	282	168 (56.8)	114 (62.0)	

Boldface was considered significant ( $P$  value < .05).

Comparison was determined by Chi-Squared test or Wilcoxon rank sum test. CEA = carcinoembryonic antigen, LYN = lymph node, NSCLC = non-small cell lung cancer.

concentration of CEA in NSCLC patients; Depression was associated with marital status (single, divorced, and widowed vs married), employment status before surgery (employed), diabetes, poorer pathological differentiation, and advanced TNM stage in NSCLC patients.

3. Anxiety and depression were associated with unfavorable prognosis in NSCLC patients who underwent resection.

Previous studies elucidate that anxiety and depression are highly prevalent in lung cancer patients.<sup>[5,10,14,15]</sup> In consistence with prior evidences, the present study observed that the anxiety

**Table 4**  
Multivariate logistic regression analysis of factors affecting anxiety.

Items	Multivariate logistic regression model			
	P value	OR	95%CI	
			Lower	Higher
Age (>60 years)	.935	1.019	0.656	1.582
Male	.066	0.622	0.376	1.031
Smoke status				
Never smoker	Reference	—	—	—
Current smoker	.248	0.526	0.177	1.564
Former smoker	.525	1.212	0.670	2.192
Quit smoker	.942	1.019	0.620	1.673
History of drink	.386	0.828	0.540	1.270
Marital status				
Married	Reference	—	—	—
Divorced/widowed	<b>.047</b>	1.713	1.008	2.913
Single	<b>&lt;.001</b>	5.522	2.610	11.681
Employed before surgery	.573	1.139	0.725	1.788
Level of education				
Primary school or less	Reference	—	—	—
High school	<b>.044</b>	0.436	0.195	0.977
Undergraduate	.119	0.515	0.224	1.186
Graduate or above	.351	0.629	0.237	1.666
Hypertension, No. (%)	<b>.035</b>	1.646	1.037	2.614
Hyperlipidemia, No. (%)	.560	0.863	0.525	1.418
Diabetes, No. (%)	<b>&lt;.001</b>	4.593	2.469	8.544
Poorer pathological differentiation	<b>&lt;.001</b>	1.793	1.298	2.476
Tumor size (>5 cm)	.642	0.881	0.516	1.504
LYN metastasis	.317	0.755	0.435	1.309
Advanced TNM stage	<b>&lt;.001</b>	2.086	1.437	3.027
CEA (>5 ng/mL)	.341	1.234	0.801	1.901

Boldface was considered significant ( $P$  value<.05).  
CEA = carcinoembryonic antigen, CI = confidence interval, LYN = lymph node, OR = odds rate.

**Table 5**  
Multivariate logistic regression analysis of factors affecting depression.

Items	Multivariate logistic regression model			
	P value	OR	95%CI	
			Lower	Higher
Age (>60 years)	.480	0.850	0.542	1.334
Male	.950	0.984	0.595	1.627
Smoke status				
Never smoker	Reference	—	—	—
Current smoker	.090	0.377	0.122	1.166
Former smoker	.084	0.580	0.313	1.077
Quit smoker	.143	0.686	0.413	1.137
History of drink	.053	0.645	0.414	1.006
Marital status				
Married	Reference	—	—	—
Divorced/widowed	<b>&lt;.001</b>	3.036	1.750	5.266
Single	<b>.002</b>	2.739	1.429	5.253
Employed before surgery	<b>.001</b>	2.139	1.342	3.411
Level of education				
Primary school or less	Reference	—	—	—
High school	.055	0.461	0.209	1.017
Undergraduate	<b>.002</b>	0.269	0.118	0.613
Graduate or above	.133	0.483	0.187	1.248
Hypertension, No. (%)	.171	1.397	0.866	2.253
Hyperlipidemia, No. (%)	.624	1.136	0.682	1.891
Diabetes, No. (%)	<b>&lt;.001</b>	4.978	2.819	8.789
Poorer pathological differentiation	<b>.003</b>	1.651	1.181	2.307
Tumor size (>5 cm)	.768	1.086	0.629	1.874
LYN metastasis	.323	0.758	0.438	1.312
Advanced TNM stage	<b>.042</b>	1.479	1.014	2.157
CEA (>5 ng/mL)	.758	0.933	0.598	1.455

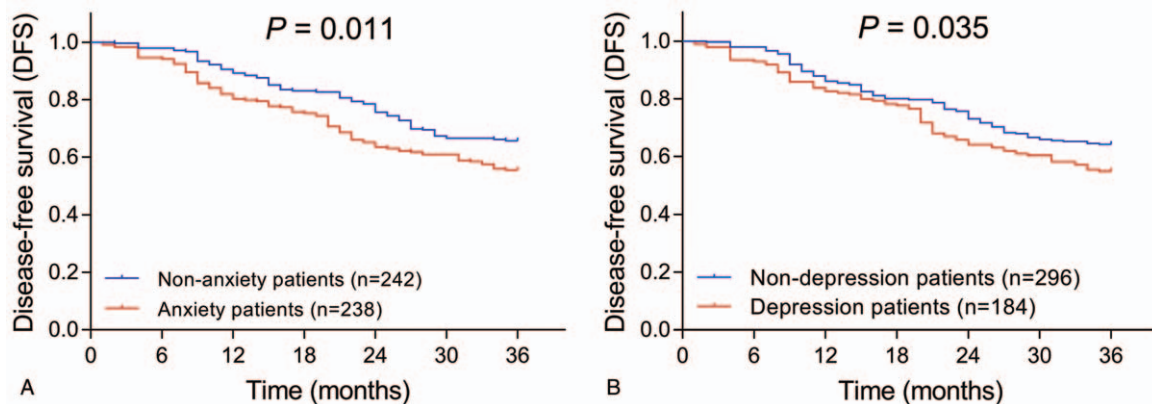
Boldface was considered significant ( $P$  value<.05).  
CEA = carcinoembryonic antigen, CI = confidence interval, LYN = lymph node, OR = odds rate.

and depression of NSCLC patients who underwent resection were much more prevalent and severe than HCs. The possible explanations might be that:

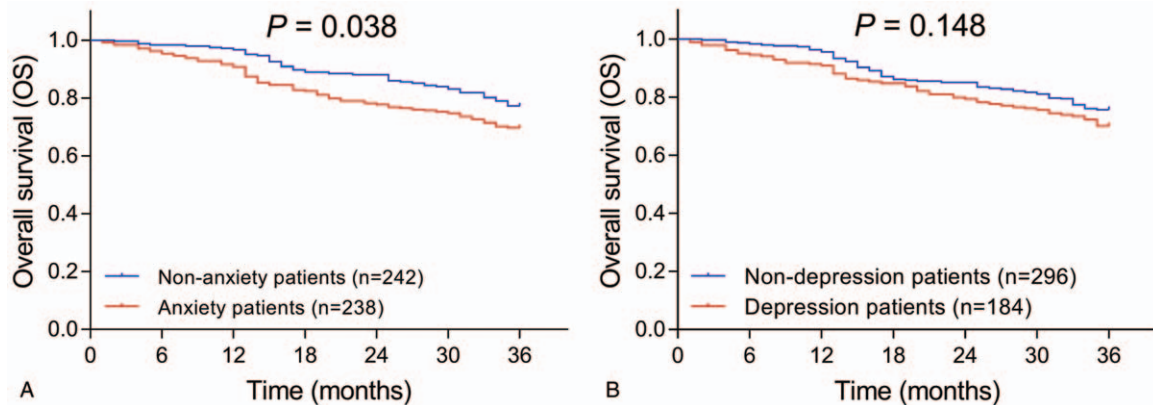
1. The terminal characteristic of NSCLC and aggressive treatment-related symptoms (such as insomnia and fatigue) might elicit shock, fear, social isolation, and hopelessness, thereby, resulting in the occurrences of anxiety and depression

as well as the acceleration of anxiety and depression in NSCLC patients who underwent resection.

2. The impaired daily activities, declined ability for maintaining their social and family roles as well as financial difficulties related with surgery might contribute to the elevated risks and severity of anxiety and depression in NSCLC patients who underwent resection.



**Figure 4.** Differences of DFS between anxiety vs non-anxiety, depression vs nondepression NSCLC patients. Comparison of DFS between NSCLC patients with and without anxiety (A). Comparison of DFS between NSCLC patients with and without depression (B). DFS was displayed with Kaplan–Meier curve, and comparisons of DFS between anxiety vs nonanxiety, depression vs nondepression NSCLC patients were determined by log-rank test.  $P$  value<.05 was considered significant. DFS, disease-free survival; NSCLC, non-small-cell lung cancer.



**Figure 5.** Differences of OS between anxiety vs non-anxiety, depression vs nondepression NSCLC patients. Comparison of OS between NSCLC patients with and without anxiety (A). Comparison of OS between NSCLC patients with and without depression (B). OS was shown by Kaplan–Meier curve, and comparisons of OS between anxiety vs non-anxiety, depression vs nondepression NSCLC patients were examined by log-rank test.  $P$  value  $< .05$  was considered significant. OS, overall survival; NSCLC, non-small-cell lung cancer.

Various factors associated with the development of anxiety and depression in lung cancer patients are revealed previously, including sociodemographic characteristics, clinical characteristics, and so on.<sup>[14,16]</sup> For example, 1 study illuminates that without surgery and younger age ( $<65$  years) are correlated with higher risks of anxiety and depression in patients with lung cancers.<sup>[14]</sup> Another study reveals that dyspnoea and lower education level are associated with post-operative anxiety, and diabetes mellitus, residual postoperative pain (VAS  $\geq 5$ ) and dyspnoea are associated with postoperative depression in primary lung cancer patients who underwent thoracoscopic surgery.<sup>[16]</sup> In the present study, we found that anxiety correlated with gender (female), marital status (single, divorced, and widowed vs married), hypertension, diabetes, poorer pathological differentiation, larger tumor size, LYN metastasis, advanced TNM stage and higher concentration of CEA in NSCLC patients; Depression correlated with marital status (single, divorced, and widowed vs married), employment status before surgery (employed), diabetes, poorer pathological differentiation, and advanced TNM stage. Additionally, marital status (single, divorced/widowed vs married), hypertension, diabetes, poorer pathological differentiation, and advanced TNM stage independently correlated with higher anxiety risk, whereas level of education (high school vs primary school or less) independently correlated with lower anxiety risk in NSCLC patients; Marital status (single, divorced/widowed vs married), employed before surgery, diabetes, poorer pathological differentiation, and advanced TNM stage independently correlated with higher depression risk, whereas level of education (undergraduate vs primary school or less) independently correlated with lower depression risk in NSCLC patients. The possible reasons were as follow:

1. Females were more prone to encounter intense hormonal fluctuations linked with reproductive events such as pregnancy and menopause, which was responsible for higher rate of anxiety.<sup>[17]</sup>
2. Single, divorced, or widowed NSCLC patients might have less emotional support, lower self-esteem and insufficient ability to cope stress, thus, leading to increased susceptibility of anxiety and depression.<sup>[18]</sup>

3. Employed NSCLC patients were more likely to experience depression due to impaired physical activities and increased work absence.
4. NSCLC patients with hypertension and diabetes suffered from a greater symptom burden, treatment-related side effects and financial difficulties, thus, contributing to higher risk of anxiety and depression.
5. NSCLC patients with poor pathological differentiation, larger tumor size, LYN metastasis, advanced TNM stage and more CEA might have more severe disease condition, cancer-related pain and more aggressive treatment-related side effects, which put NSCLC patients at higher risks of anxiety and depression.
6. NSCLC patients with higher levels of education had more knowledge in terms of cancers and had less worries about the adverse consequences of cancers and related treatments, thus, led to decreased risk of anxiety and depression.

A few studies show that anxiety and depression exert negative impact on the prognosis of NSCLC patients.<sup>[10,11]</sup> For instance, 1 study elucidates that anxiety is associated with elevated lung cancer-specific and all-cause mortality in patients with stage III NSCLC.<sup>[11]</sup> Another study reports that advanced NSCLC patients with depression exhibit decreased OS compared to patients without depression.<sup>[10]</sup> Whereas, the evidence regarding the effect of anxiety and depression on the survival in NSCLC patients who underwent resection is scarce. The present study characterized that anxiety and depression were associated with shorter survival in NSCLC patients who underwent resection. These might be explained by that:

1. NSCLC patients with anxiety and depression were less likely to comply with prescribed medication or adhere to routine physician examinations, which led to elevated disease severity and unsatisfied prognosis.
2. Anxiety and depression might activate the hypothalamic-pituitary-adrenal axis, which exerted suppressive effects on immune function such as immune surveillance of tumors via decreasing cytotoxic T-cell and natural-killer-cell activities, thereby, promoting neoplastic growth, accelerating NSCLC progression and worse survival in NSCLC patients who underwent resection.<sup>[19–21]</sup>



Our study was subject to several limitations. Firstly, all the patients were recruited from a single center, which might limit the generalizability of our findings. Secondly, only a self-administered questionnaire (HADS score) was used for anxiety and depression evaluation, which might cause an assessment bias, thus, more anxiety and depression assessments needed for further validation. Thirdly, some confounders such as the distinctions in the operation skills of surgeons were not considered in our study. Fourthly, NSCLC patients were only followed up for a relatively short-period (36 months), hence, the long-term effect of anxiety and depression on prognosis in NSCLC patients who underwent resection needed further exploration. Lastly, the detailed mechanism of the anxiety and depression in impacting the survival of NSCLC patients who underwent resection was not investigated.

In conclusion, proper management of anxiety and depression might assist the post-operative care for improving prognosis in NSCLC patients.

### Author contributions

**Conceptualization:** Guang-Quan Xu.

**Data curation:** Tian-Ze Zhang, Lei Liu.

**Formal analysis:** Xuan Huang.

**Methodology:** Guang-Hua Li.

**Supervision:** Guang-Quan Xu.

**Writing – original draft:** Xuan Huang, Tian-Ze Zhang, Guang-Hua Li.

**Writing – review & editing:** Lei Liu, Guang-Quan Xu.

Guang-Quan Xu orcid: 0000-0001-7955-6885.

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