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# BMJ Open Health-related quality of life in Chinese inpatients with lung cancer treated in large general hospitals: a cross-sectional study

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To cite: Gu W, Xu Y-M, Zhong B-L. Health-related quality of life in Chinese inpatients with lung cancer treated in large general hospitals: a crosssectional study. BMJ Open 2018;8:e019873. doi:10.1136/ bmjopen-2017-019873

Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi. org/10.1136/bmjopen-2017-019873).

Received 29 September 2017 Revised 22 March 2018 Accepted 6 April 2018



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## **ABSTRACT**

**Objective** In China, psychosocial problems of patients with cancer are under-recognised and undertreated in medical oncology practice. This study examined the health-related quality of life (QOL) in inpatients with lung cancer treated in large general hospitals and explored the demographic, clinical and psychosocial factors associated with QOL.

**Design** Cross-sectional study.

Participants and setting Altogether, 148 inpatients with lung cancer were consecutively recruited from two large general hospitals in Tianjin, China.

Main outcome measured QOL, pain intensity, depressive and anxiety symptoms, and social support were assessed with WHO QOL Scale Brief Version, four-point Verbal Rating Scale, Hospital Anxiety and Depression Scale and Social Support Rating Scale, respectively.

**Results** Compared with the normative data for the Chinese general population, patients had significantly lower scores in physical (t=-25.860, p<0.001) and psychological (t=-18.225, p<0.001) QOL. Being unmarried ( $\beta = -2.471$ , 95% Cl -4.908 to -0.034), poor economic status ( $\beta$ =-1.764, 95% CI -2.964 to -0.564), cancer metastasis ( $\beta = -1.328$ , 95% CI -2.632 to -0.024), poor performance status ( $\beta$ =-0.959, 95% CI -1.542 to -0.376), depression ( $\beta = -0.465$ , 95% CI -0.631 to -0.299), anxiety ( $\beta$ =-0.208, 95% CI -0.354 to -0.062) and low utilisation of social support ( $\beta=-0.344$ , 95% CI -0.577 to -0.111) were independently associated with poor physical QOL, while female gender ( $\beta$ =-1.494, 95% CI -0.649 to -2.339), less education years  $(\beta = -0.209, 95\% \text{ Cl } -0.294 \text{ to } -0.123)$ , currently receiving chemotherapy ( $\beta$ =-1.536, 95% CI -3.051 to -0.021), small-cell cancer ( $\beta = -1.157$ , 95% CI -2.223 to -0.091), more intense pain ( $\beta = -0.535$ , 95% CI -0.919 to -0.151), poor performance status ( $\beta$ =-0.930, 95% CI -1.383 to -0.477), anxiety ( $\beta = -0.178$ , 95% CI -0.248 to -0.108) and inadequate subjective social support ( $\beta=-0.137$ , 95% CI -0.153 to -0.121) were independently associated with poor psychological QOL.

Conclusions Inpatients with lung cancer treated in Chinese large general hospitals have poorer QOL than the general population. Effective prevention and management of psychosocial problems are potentially effective to improve their QOL.

# Strengths and limitations of this study

- This study assessed psychosocial factors that were potentially associated with quality of life (QOL) of patients with lung cancer in China.
- The relatively small sample size of patients and recruiting patients from inpatient departments of large general hospitals only may limit the generalisability of the findings.
- ► The direction of causality between psychosocial factors and QOL could not be ascertained due to the cross-sectional design of this study.
- This study assessed QOL of patients with lung cancer with a generic QOL scale, not a lung cancer-specific measure.
- Age-matched and sex-matched healthy controls were not included for comparison.

#### INTRODUCTION

During the recent decades, health-related quality of life (QOL) has become an important outcome measure in medical oncology research and clinical practice because it can comprehensively assess the effectiveness of an anticancer regimen and the impact of cancer on a patient's physical, functional, social and emotional well-being. In addition, the QOL outcome is also an important prognostic indicator which can be used to predict the survival time of a patient with cancer. <sup>2</sup> Cancer treatment is challenging because many physical and psychosocial problems are present at all stages of the disease but conventional treatment for cancer such as chemotherapy focuses on addressing the physical dimensions of cancer (ie, stopping or slowing the growth of cancer cells). 3 4 Given that QOL is a comprehensive assessment of clinical outcome, examining the level and predictors of QOL in patients with cancer is essential in developing measures to improve quality of care and treatment outcomes.

In China, lung cancer is the most prevalent type of cancer and the leading cause of mortality of cancer-related death. In 2013, population-based cancer registration data estimated that the crude incidence and mortality rates of lung cancer in China were as high as 70.1 and 36.8 per 100 000, respectively, and the two rates have been stable in recent years. 67 Meanwhile, due to the poor quality of care and limited medical treatment for lung cancer, the overall 5-year survival rate of lung cancer remains low in China (16.1%), particularly in rural regions (11.2%).<sup>78</sup> Because the survival time of patients with lung cancer is very likely to be short and treatments of lung cancer are expected to be toxic and limited in efficacy, QOL is particularly important for patients with lung cancer. Until now, QOL of patients with lung cancer have been extensively studied in international literature, and most studies were conducted in Western countries. 9–15 These studies have shown that QOL among patients with lung cancer was associated with gender, age, performance status, fatigue, metastasis, cough, pain, social support, depression and anxietv.9-15

There is convincing evidence that sociocultural factors significantly impact QOL. <sup>16 17</sup> Therefore, findings reported in Western countries might not apply to patients with lung cancer living under Chinese sociocultural settings. To date, there have been a few studies examining the QOL of Chinese patients with lung cancer. <sup>18–23</sup> These studies reported a variety of factors associated with QOL of Chinese patients with lung cancer, including age, marital status, income, cancer stage, treatment regimen and cell type. <sup>18–23</sup> However, compared with international studies, very few of them focused on the roles of psychosocial factors on QOL: only one reported the significant association between social support and the global QOL in patients with newly diagnosed lung cancer. <sup>23</sup>

Because of Chinese oncologists' limited knowledge and the lack of training in clinical psychiatry, patients' psychosocial problems are not routinely screened for by oncology providers, resulting in a serious under-recognition/undertreatment of psychosocial problems in clinical oncology practice.<sup>24</sup> More fundamentally, the specific psychosocial and psycho-oncology services for patients with cancer are still not available in nearly all of the Chinese general hospitals.<sup>25</sup> Given the important roles of psychosocial factors in cancer incidence and prognosis,<sup>26</sup> the associations between psychosocial factors and QOL need to be further examined in Chinese patients with lung cancer which can increase Chinese oncologists' understanding on the importance of psychosocial interventions.

In China, more than two-thirds of patients with cancer prefer to seek treatment from oncology departments of large general hospitals (ie, secondary and tertiary hospitals). <sup>27</sup> <sup>28</sup> Large general hospitals may provide a good setting to examine the QOL of patients with lung cancer due to their representative samples. The objective of this study was to investigate the QOL of Chinese inpatients with lung cancer in large general hospitals and explore

the demographic, clinical and psychosocial characteristics associated with QOL.

# METHODS Subjects

This study was part of a large-scale collaborative project investigating the mental health, suicidal behaviours and QOL of oncology inpatients in two large general hospitals in Tianjin, China.<sup>29</sup> The cross-sectional survey was conducted between February and December 2015, and its details have been published elsewhere.<sup>29</sup> Briefly, adult patients who were diagnosed with lung cancer and hospitalised in the two hospitals at the time of the survey were consecutively invited to participate in the study. Eligible subjects were those who were aware of the diagnosis of lung cancer (ascertained by histological examination), aged 18 years and above, and had the capacity to provide informed consent. We excluded patients who were too ill, had cognitive disorders (ie, dementia) or had difficulties in communicating with others.

# **Assessments**

Demographic and clinical data were collected with a form designed for the present study, followed by a careful review of medical records and an interview with patients and their treating oncologists (when necessary).

Demographic variables included gender, age, education, marital status and self-rated economic status (poor, fair, good).

Clinical factors included cancer stage (metastatic vs not metastatic), <sup>30</sup> cell type (small vs non-small cell), pain intensity, time since the diagnosis of cancer, functional status and current treatment regimen (chemotherapy, radiotherapy, surgery). A validated four-point Verbal Rating Scale was used to assess the pain intensity: patients were asked to rate their pain intensity in the last month choosing from the four category responses (1=none, 2=mild, 3=moderate and 4=severe). The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale was adopted to assess the impact of cancer on patients' daily living abilities which was rated on a scale from 0 (fully active) to 5 (dead), with higher score denoting poorer function. <sup>32</sup>

Psychosocial factors, including depression, anxiety and social support, were collected by a self-administered questionnaire. The validated Chinese version of the Hospital Anxiety and Depression Scale (HADS) was used to assess the presence and severity of depressive and anxiety symptoms in patients. <sup>33</sup> <sup>34</sup> This 14-item scale consists of two subscales: seven items for depression and the remaining seven for anxiety. Each item is rated on a 0–3 scale, yielding a total score ranging between 0 and 21 for each subscale. Higher scores denote more severe symptoms of depression or anxiety. <sup>33</sup> <sup>34</sup> Social support was assessed with the validated Chinese Social Support Rating Scale (SSRS) which was developed by Xiao *et al.* <sup>35</sup> This 10-item scale evaluates three dimensions of social support: objective

support (actual received practical support and available social networks), subjective support (emotional and perceived support) and utilisation of support (one's use of social network). A higher total score in each subscale indicates a higher level of social support.

QOL was assessed with the validated Chinese WHO QOL Scale Brief Version (WHOQOL-BREF). 36-38 To reduce the survey burden on patients, only items of the physical and psychological domains of WHOQOL-BREF were used in the present study. The two subscales use seven and six items to assess the physical and psychological QOL in the past month, respectively. Each item is rated on a 5-point Likert scale ranging between 1 ('very dissatisfied/very poor') and 5 ('very satisfied/very good'). The two QOL domains are scaled in a positive direction with higher scores indicating a better OOL.

Data were collected in places of the hospitals that were deemed convenient and could provide reasonable privacy for respondents (oncologists' office, sickroom, etc). All patients independently and anonymously completed the questionnaires on demographic characteristics, HADS, SSRS and WHOQOL-BREF. Trained investigators interviewed patients and their treating oncologists and reviewed medical records to collect data on clinical factors.

# Patient and public involvement

The role of patients in this study was participants. They were not involved in the development of the research question and outcome measures, the recruitment of subjects and the undertaking of the study. After the completion of the study, we had sent each participant a letter describing the resulting of the present study in detail.

# Statistical analysis

Data analyses were conducted with SPSS V.16.0. By using the recommended formulas, <sup>38</sup> the raw scores of physical and psychological QOL domains were transformed to a 0–100 scale before the analysis. We used the independent-samples t-test to compare QOL between patients and the normative data which was derived from a representative sample (n=1052) of Chinese general adult population. <sup>39</sup>

Multivariable linear regression analysis that entered all demographic, clinical and psychosocial factors as independent variables and physical or psychological QOL as the outcome variable was conducted to examine the independent relationships of QOL with all variables. The assumptions of linearity, normality, homoscedasticity and absence of multicollinearity for multiple linear regression analysis were tested prior to the formal analysis. Because there were no curvilinear relationships in scatter plots of outcome variables versus continuous independent variables, and no clear distribution patterns in scatter plots of residuals (errors between observed and predicted outcome values) versus predicted outcome values, our data met the assumptions of linearity and homoscedasticity. We found a normal distribution of residuals for

physical (K-S statistic=0.064, p=0.20) and psychological QOL (K-S statistic=0.068, p=0.10) in the Kolmogorov-Smirnov test. We also found a very low degree of multicollinearity among independent variables because Variance Inflation Factor values of all independent variables ranged from 1.13 to 5.77, markedly below the critical threshold of 10. The statistical significance level was set at p<0.05 (two-sided).

#### **RESULTS**

Altogether, 735 eligible inpatients with cancer were invited and 517 completed the survey. For lung cancer, the numbers of patients who were invited and completed the survey were 179 and 148, respectively. The average age of the 148 inpatients with lung cancer was 64.8 years (SD 11.5, range 20–99), and 94 (63.5%) were men. Table 1 displays the demographic, clinical and psychosocial characteristics of the participants.

Scores of physical (t=-25.860, p<0.001) and psychological (t=-18.225, p<0.001) domains of QOL were significantly lower in patients with lung cancer than the normative data of the Chinese general population (table 2).

Multiple linear regression analyses (table 3) revealed that marital status of 'unmarried' (unstandardised coefficient ( $\beta$ )=-2.471, 95% CI -4.908 to -0.034), poor economic status ( $\beta$ =-1.764, 95% CI -2.964 to -0.564), metastatic cancer ( $\beta$ =-1.328, 95% CI -2.632 to -0.024), a high ECOG performance status score ( $\beta$ =-0.959, 95% CI -1.542 to -0.376), more depressive symptoms ( $\beta$ =-0.465, 95% CI -0.631 to -0.299), more anxiety symptoms  $(\beta=-0.208, 95\% \text{ CI} -0.354 \text{ to } -0.062)$  and a low score of utilisation of social support ( $\beta$ =-0.344, 95% CI -0.577 to -0.111) were independently associated with poor physical QOL, while female gender ( $\beta$ =-1.494, 95% CI -0.649 to -2.339), less education years ( $\beta$ =-0.209, 95% CI -0.294to -0.123), currently receiving chemotherapy ( $\beta$ =-1.536, 95% CI -3.051 to -0.021), small-cell type of lung cancer  $(\beta=-1.157, 95\% \text{ CI} -2.223 \text{ to } -0.091)$ , more intense pain  $(\beta=-0.535, 95\% \text{ CI} -0.919 \text{ to } -0.151), \text{ a high ECOG}$ performance status score ( $\beta$ =-0.930, 95% CI -1.383 to -0.477), more anxiety symptoms ( $\beta$ =-0.178, 95% CI -0.248 to -0.108) and a low score of subjective social support ( $\beta$ =-0.137, 95% CI -0.153 to -0.121) were independently associated with poor psychological QOL.

## DISCUSSION

Although significant advances in cancer treatment have been achieved in recent decades, the survival of patients with lung cancer remains limited. Therefore, improving the QOL of patients with limited life expectancy should be a primary priority in lung cancer treatment practice. In the present study, patients with lung cancer had significantly poorer QOL in both physical and psychological domains than the Chinese general population which is in line with the findings of prior studies conducted

**Table 1** Demographic, clinical and psychosocial characteristics of inpatients with lung cancer\*

	Total sample (n=148)		
Characteristics	n	%	
Gender			
Male	94	63.5	
Female	54	36.5	
Marital status			
Married	140	94.6	
Never married	1	0.7	
Separated/divorced	5	3.4	
Widowed	2	1.4	
Self-rated economic status			
Poor	54	36.5	
Fair	81	54.7	
Good	13	8.8	
Cancer staging			
Metastatic	38	25.7	
Not metastatic	110	74.3	
Current treatment regimen			
Chemotherapy	135	91.2	
Radiotherapy	8	5.4	
Surgery	5	3.4	
Pathological type			
Small cell	32	21.6	
Non-small cell	116	78.4	
	Mean	SD	
Age (years)	64.8	11.5	
Education (years)	8.1	3.0	
Score of pain intensity	1.9	1.1	
Time since cancer diagnosis (months)	24.9	18.4	
ECOG Scale score of performance status	2.0	1.0	
Depressive symptoms: HADS-D score	8.2	3.2	
Anxiety symptoms: HADS-A score	7.8	3.2	
SSRS: objective social support score	7.7	1.8	
SSRS: subjective social support score	24.7	4.0	
SSRS: utilisation of social support score	7.7	1.9	

\*Demographic factors included gender, age, education, marital status and self-rated economic status. Clinical factors included cancer stage, pathological type, pain intensity, time since the diagnosis of cancer, ECOG scale and current treatment regimen. Psychosocial factors included HADS-D, HADS-A and SSRS. In this study, the ECOG scale score ranged between 0 and 4: 1=restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work; 2=ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3=capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4=completely disabled, cannot carry on any self-care, totally confined to bed or chair.

ECOG, Eastern Cooperative Oncology Group; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; SSRS, Social Support Rating Scale.

in Western and Chinese contexts. 40–43 Many symptoms of lung cancer such as cough, chest pain, loss of appetite and shortness of breath could negatively impact the physical health of patients. Psychological distress after cancer diagnosis, fear of death, depression, hopelessness and even suicidality further worsen the mental health of patients who are experiencing the physical pain of cancer. In addition, side effects caused by cancer treatment can exacerbate the health of patients. Therefore, we found a markedly impaired physical and psychological QOL in patients with cancer compared with the general population.

This study found a number of demographic and clinical correlates of QOL in patients with lung cancer. Female patients with lung cancer had worse psychological QOL which may be related to gender difference in the prevalence of risk factors associated with poor QOL, for example, female patients with cancer may have more psychological and social issues than male patients. The study by Montazeri, *et al* reported significant association between a low socioeconomic status and poor QOL in patients with lung cancer in Iran. This similarly, we found the significant association of poor QOL with less education years and poor economic status in Chinese patients with lung cancer. Consistent with previous findings, the found that unmarried patients had poorer physical QOL than married patients.

As expected, metastasis was negatively associated with physical QOL. Due to a worse global health status, impaired physical functioning and more physical symptoms associated with metastatic cancer, patients with metastatic lung cancer reported poorer QOL. Because of the rapid progression of small-cell cancer, most patients with small-cell lung cancer have been at terminal stage when their cancer is diagnosed 18 48 which could explain the significant relationship between small-cell type and poor psychological QOL in our study. Cheng and colleagues found that QOL of patients with lung cancer varied across different treatment regimens, with chemotherapy having the worst QOL and surgery having the best QOL. 18 Our finding on the poor psychological QOL among patients receiving chemotherapy relative to other treatments is in accordance with it which may be explained by the many unbearable side effects of chemotherapy and deteriorating physical health of patients receiving chemotherapy. In this study, patients who experience more intense pain had poorer psychological QOL; this might be due to the deleterious effects of pain on patients' mental health, employment status, sleep and personal relationships.<sup>49</sup> Studies have shown that the ability to perform daily activities and self-care are two important determinants of QOL in patients with cancer. <sup>50</sup> <sup>51</sup> Owing to functional limitations in hospitalised patients with lung cancer, the significant association between poor performance status and low physical and psychological QOL is expected.

In addition to the significant contributions of demographic and clinical factors to QOL of patients with lung cancer, the significant association of QOL with

Table 2 Comparison of quality of life (QOL) between inpatients with lung cancer and the general population

	Patients (n=148)		Normative data of the Chinese general population (n=1052) <sup>39</sup>			
QOL	Mean	SD	Mean	SD	t	P values
Physical	39.02	10.62	66.00	12.56	-25.860	<0.001
Psychological	38.85	10.28	60.55	13.96	-18.225	<0.001

psychosocial factors is also demonstrated in this study, suggesting that psychosocial factors exert an important influence on the QOL of Chinese patients with lung cancer. This finding is in keeping with our expectations. According to the theory of QOL satisfaction model,<sup>52</sup> unmet social needs reduce QOL of patients even if they are receiving treatment in hospitals. Empirical evidence shows that social support can act as a buffer against the negative consequences of stress, protects against physical and mental morbidities and promotes mental adjustment to chronic medical conditions, including cancer. 53 54 For patients with lung cancer, being diagnosed with cancer and treated for cancer such as surgery are all very stressful, therefore social support is particularly important for the clinical management of hospitalised cancer patients. As a result of this, it is plausible to observe the poor physical QOL in patients with low use of social support and the poor psychological QOL in patients who perceived a low level of social support. At the same time, depression and anxiety were associated with poor QOL in Chinese patients with lung cancer. These associations can be ascribed to the negative effects of depression and anxiety on the physical and mental health. <sup>12</sup> Importantly, because depressive disorders in Chinese inpatients with cancer are often under-recognised and undertreated, <sup>24</sup> untreated depression (and other mental health problems) may have a more profound effect on the health of patients.

There are some limitations in our study. First, this is a cross-sectional survey, so the causality of relationships between QOL and its correlates could not be ascertained. Second, some social factors related to QOL, such as stigma, were not assessed. Third, the WHOQOL-BREF is a generic QOL scale and not a lung cancer-specific instrument on QOL. Although the WHOQOL-BREF could be used for assessing QOL of any populations including the patients with cancer, it is not sensitive enough to capture

Table 3 Multivariable linear regression analyses on correlates of physical and psychological QOL

	Physical QOL			Psychological QOL			
Variables	Unstandardised coefficient	P values	95% CI for unstandardised coefficient	Unstandardised coefficient	P values	95% CI for unstandardised coefficient	
Gender: female	-0.700	0.235	-1.010 to 2.500	-1.494	0.001	-0.649 to -2.339	
Age (years)	-0.018	0.489	-1.238 to 1.202	-0.024	0.283	-0.106 to 0.058	
Education (years)	-0.135	0.173	-0.357 to 0.087	-0.209	0.013	-0.294 to -0.123	
Marital status: unmarried*	-2.471	0.032	-4.908 to -0.034	-0.456	0.652	-2.644 to 1.732	
Self-rated economic status: poor	-1.764	0.004	-2.964 to -0.564	-0.355	0.474	-10.920 to 10.210	
Cancer staging: metastatic	-1.328	0.032	-2.632 to -0.024	-0.835	0.106	-2.047 to 0.377	
Current treatment regimen: chemotherapy	-1.068	0.281	-4.577 to 2.441	-1.536	0.043	-3.051 to -0.021	
Pathological type: small cell	-0.725	0.273	-2.979 to 1.529	-1.157	0.026	-2.223 to -0.091	
Score of pain intensity	0.170	0.556	-2.097 to 2.437	-0.535	0.015	-0.919 to -0.151	
Time since cancer diagnosis (months)	0.028	0.083	-0.030 to 0.086	0.009	0.503	-2.238 to 2.256	
ECOG Scale score of performance status	-0.959	0.003	-1.542 to-0.376	-0.930	<0.001	-1.383 to -0.477	
Depressive symptoms: HADS-D score	-0.465	<0.001	-0.631 to -0.299	-0.016	0.881	-0.087 to 0.055	
Anxiety symptoms: HADS-A score	-0.208	0.048	-0.354 to -0.062	-0.178	0.019	-0.248 to -0.108	
SSRS: objective social support	0.018	0.918	-0.055 to 0.091	0.191	0.195	-0.146 to 0.528	
SSRS: subjective social support	0.120	0.153	-0.012 to 0.252	0.137	<0.001	0.121 to 0.153	
SSRS: utilisation of social support	0.344	0.042	0.111 to 0.577	0.145	0.267	-0.214 to 0.504	

<sup>\*</sup>Unmarried' included never married, separated/divorced and widowed.

ECOG, Eastern Cooperative Oncology Group; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression; Scale-Depression; QOL, quality of life; SSRS, Social Support Rating Scale.

cancer-specific domains of OOL. Fourth, due to logistical reasons, no age-matched and gender-matched healthy controls were recruited for the study. Comparisons were conducted with the reported normative Chinese data derived by the WHOQOL-BREF. Fifth, the sample size of our study (n=148) was relatively small because we studied a total of 16 candidate predictors of QOL and the required minimum number of subjects should be 160, according to the '10 subjects per predictor' rule of thumb for minimum sample size for multiple linear regression.<sup>55</sup> The lack of statistical power might limit the ability of multiple linear regression model to identify more significant predictors of QOL. Further, due to the small number of unmarried patients (n=8) and not receiving chemotherapy (n=13), our findings on the relationships between QOL and marital status and treatment regimen might not be reliable. Large-scale studies are warranted to confirm these relationships. Finally, we recruited patients with lung cancer from inpatient departments of large general hospitals only, outpatients of general hospitals and primary care patients were not included, potentially influencing the representativeness of the sample of patients with lung cancer. We need to be cautious in generalising findings of the present study to all patients with lung cancer.

In summary, inpatients with lung cancer managed in large general hospitals have a poorer QOL than the general population in China. A variety of factors, particularly psychosocial factors, are significantly associated with QOL in Chinese patients with lung cancer. Given that psychosocial factors are preventable or modifiable, the significant associations of poor QOL with clinical and psychosocial factors suggest that in addition to conventional anticancer management, oncologists (and other medical professionals) of Chinese large general hospitals should also pay special attention to psychosocial problems of patients with lung cancer, and when necessary, refer patients for psycho-oncology services and psychiatric consultation.

**Acknowledgements** The authors thank all the patients involved in this study for their cooperation and support.

Contributors WG and B-LZ were responsible for the design of the study, interpretation of data, the manuscript draft and statistical analysis, Y-MX for the critical revision of the manuscript. All authors reviewed the data and analysis, revised the manuscript, had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis, and had authority over approval of final manuscript version and the decision to submit for publication.

**Funding** This work was supported by Wuhan Health and Family Planning Commission (grant number: WG16A02 (Bao-Liang Zhong, PI) and WX17Q30 (Yan-Min Xu, PI)).

Competing interests None declared.

Patient consent Obtained.

Ethics approval The Ethics Committee of Wuhan Mental Health Center approved the study protocol. The protocol including the methods was performed in accordance with the Declaration of Helsinki and the relevant ethical guidelines and regulations in China.

Provenance and peer review Not commissioned; externally peer reviewed.

**Data sharing statement** The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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