Depression in relation to lung cancer mortality and survival: a systematic review and meta-analysis of observational studies

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Abstract

Background: Depression is a common complication of malignant tumor. Lung cancer is the second most common malignancy in the world. The correlation between depression and lung cancer survival and mortality has not been analyzed. To provide an up-to-date quantification of the association between depression and lung cancer survival and mortality.

Methods: We conducted a meta-analysis of observational studies published up to November 18, 2021. We estimated the correlation between depression and lung cancer mortality risk and survival using random or fixed-effect models and performed subgroup analyses.

Results: A total of 26 studies, including 14914 patients with lung cancer, were included. Depression is associated with an increased mortality risk in lung cancer patients (RR=1.218, 95% confidence interval [CI]= 1.142-1.299), associated with reduced median survival time (RR=0.362, 95%CI =0.169-0.554), and was associated with increased mortality rate (RR=1.054, 95%CI =1.003-1.107). Subgroup analysis found a greater association among Asian participants. Depression, detected before lung cancer treatment began, was more associated with higher mortality risk and shorter survival.

Conclusions: In summary, current evidence suggests suggest that depression have adverse effects on lung cancer mortality risk and survival. Therefore, when standardizing lung cancer treatment, we should pay close attention to the emotional status of lung cancer patients to ensure the maximum benefit of anti-tumor therapy, especially for Asian patients.

1. Introduction

Emotional disorders seriously affect the survival and prognosis of patients. There is increasing evidence that that patients with mood disorders have higher chronic physical conditions and associated early mortality [1,2,3]. The main causes of premature death in patients with mood disorders are cardiovascular disease, cancer and other chronic diseases [4]. An epidemiological survey found that depression and anxiety were the most common mental disorders [5]. Importantly, depression is more common among cancer patients, affecting up to 20% of cancer patients [6]. However, the effect of depression on the prognosis of cancer patients remains unclear. Related mechanisms have been proposed at the biological and behavioral levels. Emotional disorders can affect hormone secretion level and immune-related functions in the body, thus promoting the occurrence and development of tumors [7]. Mood disorders activate cancer stem cells (CSC) in non-small cell lung cancer (NSCLC) through camp-mediated pathways induced by stress neurotransmitters (including VEGF, P-ERK, P-Akt, P-CREB, SHH and ALDH-1) and promote the occurrence and development of tumors [8]. In addition, pessimism may be associated with reduced cytotoxicity of natural killer cells and cytotoxic/inhibitory T cells, leading to squamous intraepithelial lesions and tumor development [9]. Depressed patients are more likely to have drinking, smoking, poor diet, obesity and other living habits, and reduce treatment compliance [10,11].

Despite these observations and a plausible explanation for the association between cancer and mood disorders, epidemiological studies are needed to validate the association. According to the latest global tumor epidemiology data [12], the incidence and mortality of malignant tumors are increasing year by year, which not only brings great physical and mental pain to patients and their families, but also brings heavy burden to social medical resources. In particular, the incidence and mortality of lung cancer have always been in the forefront of malignant tumors and have a trend of continuous growth [13,14]. Cancer-related depression (CRD) refers to the emotional and pathological reactions of patients, whose mental state is affected by tumor diagnosis, treatment and comorbidities. Most Cancer patients suffer from depression due to concern about prognosis and medical costs [15]. Side effects of surgery, radiation and chemotherapy can also contribute to depression. It is a refractory, recurrent and multifactorial disease, which seriously affects the physical, mental health and quality of life of cancer patients. In particular, cancer patients are affected by a variety of bad emotions, which lead to reduced treatment compliance and immune function, thus hindering disease control and increasing the risk of tumor recurrence and metastasis. These changes can significantly reduce their quality of life and shorten their survival time. Several meta-analyses and systematic reviews of depression and cancer outcomes have been published, but reports have mixed results. A meta-analysis by Satin J et al. found no increased cancer risk in patients with clinically diagnosed depression (OR 1.15; 95% CI, 0.85 – 1.56) [16]. A meta-analysis published by Wang YH et al. [17], which included 8 literatures related to lung cancer, found that depression and anxiety were closely associated with increased risk of specific death in lung cancer, bladder cancer, breast cancer, colorectal cancer, hematological system cancer, kidney cancer and prostate cancer, and were also associated with increased risk of all-cause death in lung cancer. However, the survival of lung patients was not analyzed.

Therefore, comprehensive and rigorous meta-analyses are needed to understand the association between depression and long-term prognosis of cancer. While continuing to pay attention to the risk of death, the impact of survival should be explored. We add the newly published literature based on the study of Wang YH et al. [17], and focus on lung cancer patients. We used a meta-analysis to review and quantitatively integrate data on the association between depression and survival in patients with lung cancer, as defined by a symptom scale or clinical diagnosis, to identify the association between the two.

We reviewed the evidence to provide possible answers to :(1) investigate the association between depression and survival risk and mortality in patients with lung cancer, independent of potential confounding variables; (2) depression is positively or negatively correlated with lung cancer survival and death.

2. Methods

2.1 Search strategy

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; eTable 1) [18] statement and Meta-Analyses of Observational Studies in Epidemiology (MOOSE; eTable 2) [19] guidelines. Protocol in PROSPERO (CRD42020164272 at www.crd.york.ac.uk/PROSPERO) in the registration and update.

We searched the Pubmed, Embase, Scopus and Cochrane Library for cohort studies on the correlation between depression and lung cancer survival. The search timeframe included everything from the establishment of the database to November 18, 2021. In addition, manually recovered references were incorporated into the study to obtain the relevant literature. In addition, the reference lists of the identified relevant publications were reviewed to collect any additional studies that met the eligibility criteria. We had no discernible ethical issues with our study, since the data we used were extracted from published articles. The search terms were MeSH terms and text words relating to depression (depressive disorder OR depressive OR depression), cancer (cancer OR malignant OR tumor OR carcinoma OR neoplasm), lung, and endpoint (survival OR prognosis OR death). The detailed literature search strategy is shown in Appendix 1. All articles from those databases were exported to EndNote.

Furthermore, we examined a list of previously reviewed references, key papers, and other related articles identified through electronic searches. We also performed a systematic review of the content lists of major journals to identify any other study that may have been missed by the electronic search.

2.2 Inclusion and exclusion criteria

Inclusion criteria

To be eligible, studies had to meet the following criteria: (1) cohort studies with raw data, including prospective and retrospective studies, without restrictions on publication time and location; (2) lung cancer patients diagnosed by imaging or pathology, with no restrictions on age, gender, clinical stage, pathological type, or other; (3) depression as understood referring to structured clinical interview for the diagnostic and statistical manual of mental disorders [20] and considered valid by the hospital anxiety and depression scale[21], the self-rating depression scale [22,23], centre for epidemiologic studies depression scale[24], the patient health questionnaire-9 [25], and so on, or database records; (4) studies presenting clear outcome indicators, including death and end of follow-up.

Exclusion criteria

The following studies were excluded from the analysis: (1) Non-English literature; (2) research involving repeated data or the data provided is incomplete; (3) studies that do not provide the total number of people included in the study, the number of people diagnosed with depression, the number of deaths, MST, RR/HR and its 95% CI data, and the above data cannot be converted from the data provided in the article.

2.3 Study selection and data extraction

Two researchers independently screened documents, extracted data, and cross-checked them. In case of disagreement, the two discussed and resolved the issue. First, we evaluated the title and abstract. If it was confirmed from the abstract that an article might meet the inclusion criteria, the full text was examined. If, based on the abstract, we found that an article was clearly not eligible, the article was deleted immediately. If the eligibility could not be determined based on the abstract alone, the full text was examined. If any key information was missing, we contacted the author. If this was impossible or it revealed that the study did not meet the inclusion criteria, the study was rejected.

The main information extracted from the data includes: (1) the basic information about the study, including the first author, publication time, location, published magazine, and impact factor; (2) the baseline characteristics of the research object, including the sample size of each group, tumour stage, and diagnosis time and tools, follow-up time, etc.; (3) the number of people diagnosed with depression, survivors, deaths, MST, the adjusted RR/HR of death and 95% CI.

2.4 Quality assessment

Two researchers independently adopted the Newcastle-Ottawa Scale (NOS) [26] to conduct a bias risk assessment on the included studies. NOS, with a total score of 9 stars, has a total of 8 items. If there was a disagreement, the two decided after a discussion; if it could not be resolved, a third researcher would assist.

2.5 Statistical strategy

Pooled Effect Sizes (ESs) were calculated for the outcome. In each study, the number of depression and non-depressive lung cancer patients, the number of deaths and adjusted RR of survival were extracted. If the RR was not reported, we assumed that other risk measures (e.g., OR or HR) could be considered approximatively equivalent to the RR [27]. Log RRs and the corresponding SEs were calculated, and then we weighted the effect size by the inverse of the standard deviation. STATA 15.1 software was used for the meta-analysis, calculating the comprehensive effect value (RR/ HR) and 95% CI, to draw forest maps.

Before the meta-analysis, the heterogeneity test was first performed using the I^2 test. If the heterogeneity was small ($P > 0.05$ and $I^2 < 50\%$), the fixed effect (FE) model was used for analysis. The random effect (RE) model would be used, when the heterogeneity was large ($P \leq 0.05$ or $I^2 \geq 50\%$).

The method of deleting studies one by one needed to be used to complete the sensitivity analysis of the results to ensure stability. The subgroup analysis of the meta-analysis results for each outcome was required. The subgroup only includes items related to the study design, for example, stage (Ⅰ-Ⅱ and Ⅲ-Ⅳ), measure of mental status (Symptom scale and Clinical diagnosis), diagnosis time of mental status (Pre to treatment and Following treatment), study quality (≥ 8 and <8), and geographical region (Europe, North America and Asia).

3. Results

3.1 Study characteristics

We identified 652 articles from PubMed, 834 articles from EMbase, 455 articles from the Cochrane Library, and 302 articles from Scopus (see Fig. 1). After removing the duplicates and papers that failed to meet the inclusion criteria based on the title and abstract, 53 articles remained for a full-text review. Upon completion, 53 articles were excluded as follows: three studies were reviews, meta-analyses, or commentaries; 21 studies lacked depression-related survival data in lung cancer patients; one was from the same database as the other one, one case in each cohort was not reported, and one was not English. In the end, 26 articles [28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53], which comprised 14914 lung cancer patients with a mean follow-up of about 3 years, were included in our meta-analysis. The detailed study characteristics are shown in Table 1.

Table 1

Characteristics of included studies.

Author, publication year	Journal Title; Impact Factor	Study Design; Location	N	Group	Death	N (each group)	MST(in months)	RR/HR of death(95%CI)	Adjusted major confounders	Stage	T
Buccheri G, 1998	European Respiratory Journal, 16.671	Cohort Study, Italy	95	Non-depression	21	53	n.a.		-	I-IV	A
				Depression	22	42	n.a.	n.a.	-		
Faller H, 1999	Archives of General Psychiatry, n.a.	Cross-sectional Study, Germany	92	Non-depression	n.a.	51	12		-	I-IV	A I t
				Depression	n.a.	41	10	n.a.	-		
Faller H, 2002	American Journal of Psychiatry, 18.112	Cohort Study, Germany	93	Non-depression	n.a.	n.a.	n.a.	-	-	I-IV	A C I
				Depression	n.a.	n.a.	n.a.	1.91 (1.32–2.77)	-		
Stommel M, 2002	Cancer, 6.860	Cohort Study, U.S.	871	Non-depression	8	188	18.53	-	-	I-IV	A
				New Depression	22	203	18.07	1.66 (1.16–2.37)	-		
Faller H, 2004	Psycho-Oncology, 3.894	Cohort Study, Germany	57	Non-depression	n.a.	n.a.	n.a.	-	-	□-IV	A I t
				Depression	n.a.	n.a.	n.a.	1.05 (0.98–1.13)	iomedicalprognostic factors		
Nakaya N, 2006	Cancer Science, 4.966	Cohort Study, Japan	229	Non-depression	50	216	69			IA-IIIA	I
				Depression	5	13	66	2.2(0.8-6.0)	age in years at the time of cancer diagnosis (≤ 59, 60–69, ≥ 70), sex, smoking status (never smokers, past smokers, quit smokers or continued smokers), methods of diagnosis (mass screening or health checkup, subjective symptoms, follow up for other diseases or unknown), pathological stage (IA, IB, IIA, IIB or IIIA), and preoperative percentage forced expiratory volume in 1s (≥ 70 or < 70).		
Onitilo AA, 2006	General Hospital Psychiatry, 3.238	Cohort Study, U.S.	19	Non-depression	6	n.a.	n.a.			n.a.	A
				Depression		n.a.	n.a.	1.30 (0.48–3.54)	age in 1982 (years) and sex		
								1.39 (0.49–3.99)	age in 1982 (years) and sex, race/ethnicity (White vs. Black/other)		

Nakaya N, 2008	Psycho-Oncology, 3.894	Cohort Study, Japan	1178	Non-depression	506	917	n.a.			I-IV	A
				Depression	180	261	17	1.8(1.5–2.3)	age at diagnosis, sex, histologic type, educational level (high school or lower or higher), marital status (married or unmarried), cohabitation (live alone or live with someone), and smoking (never smokers, ex-smokers, current smokers of 1–19 cigarettes per day, or current smokers of 20 or more cigarettes per day)		
Pirl WF, 2008	Psychosomatics, 2.386	Cohort Study, U.S.	43	Non-depression	7	33	10.4			IIIB-IV	A
				Depression	6	10	2.5	1.89(0.88–4.06)	performance status		
Akechi T, 2009	Psycho-Oncology, 3.894	Cohort Study, Japan	122	Non-depression	n.a.	n.a.	n.a.			III-IV	A
				Depression	n.a.	n.a.	n.a.	0.79 (0.32–1.95)	PS, disease stage, histology, hemoglobin, serum LDH, and chemotherapy		
Angulo CLP, 2011	14th World Conference on Lung Cancer, n.a.	Cohort Study, Mexico	82	Non-depression	n.a.	n.a.	6.8		-	IIIB-IV	A
				Depression	n.a.	n.a.	14	n.a.	-		
Chen ML, 2011	Support Care Cancer, 2.754	Cohort Study, Taiwan, China	90	Non-depression	29	70	24.47			III-IV	I
				Depression	14	20	11.83	2.18(1.11–4.28)	depressive symptoms, disease stage, gender, and performance status		
Pirl W, 2011	Psycho-Oncology, 3.894	Cohort Study, U.S.	115	Non-depression	n.a.	n.a.	n.a.	-	-	IV	A
				Depression	n.a.	n.a.	n.a.	1.56	n.a.		
Nunez-Valencia C, 2012	Journal of clinical oncology, 44,544	Cohort Study, U.S.	82	Non-depression	n.a.	55	14			IIIB-IV	A
				Depression	n.a.	27	6.8	1.9 (1.03–3.7)	n.a.		
Pirl WF, 2012	Journal of clinical oncology, 44,544	Cohort Study, U.S.	150	Non-depression	n.a.	129	10			III-IV	A
				Depression	n.a.	21	5.4	1.82(1.10, 3.01)	PS, age, sex, race, marital status, and smoking history		
Arrieta O, 2013	Annals of Surgical Oncology, 5.344	Cohort Study, Mexico	82	Non-depression	n.a.	27	14			IIIB-IV	A
				Depression	n.a.	55	6.8	1.9 (1.03–3.7)	n.a.		
Sullivan DR, 2014	Clinical Oncology, 3.047	Cohort Study, U.S.	3869	Non-depression	3001	3320	6.47			I-IV	I
				Depression	497	549	7.23	1.14(1.03–	age, year of		

								1.27)	diagnosis, Charlson Comorbidity Index, race/ethnicity, tobacco use at diagnosis, lung cancer stage and histology		
				Non-depression	n.a.	964	n.a.	-		I-II	
				Depression	n.a.	158	n.a.	1.37 (1.12–1.68)	age, year of diagnosis, Charlson Comorbidity Index, race/ethnicity and tobacco use at diagnosis		
				Non-depression	n.a.	1701	n.a.	-		III-IV	
				Depression	n.a.	265	n.a.	1.02 (0.89–1.16)	age, year of diagnosis, Charlson Comorbidity Index, race/ethnicity and tobacco use at diagnosis		
Chen J, 2015	Journal of Cancer, 4.207	Cross-sectional Study, China	126	Non-depression	n.a.	78	9.3		-	IIIB-IV	
				Depression	n.a.	48	6.3	n.a.	-		
Kovacevic T, 2016	European Respiratory Journal, 16.671	Cross-sectional Study, n.a.	79	Non-depression	n.a.	64	6.83			IIIB-IV	
				Depression	n.a.	15	7.38	n.a.	-		
Sullivan DR, 2016	Journal of Clinical Oncology, 28.245	Cohort Study, U.S.	1790	Non-depression	712	1109	26.57			I-IV	
				Depression	488	681	20.13	1.17(1.03–1.32) I-II: 1.61(1.26–2.04) III-IV: 1.05(0.91–1.22)	age, sex, race/ethnicity, lung cancer stage and histology, income, education, marital status, smoking and alcohol use, and Adult Comorbidity Evaluation-27 index		
Vodermaier A, 2017	Journal of Pain and Symptom Management, 3.612	Cohort Study, Canada	684	Non-depression	n.a.	457	n.a.			IIIA-IIIB	
				Depression	234	148	10.78	1.02 (0.99–1.05)	n.a.		
Mulick A, 2019	Journal of Psychosomatic Research, 3.006	Two-arm Parallel Group Randomised Controlled Study, England	142	Non-depression	-	-	-			I-IV	
				Depression	49	149	n.a.	0.96 (0.54, 1.71)	explicitly adjusting for cancer and depression severity at baseline and implicitly adjusting for primary cancer, age, and sex.		
Andersen BL, 2021	Psychosomatic Medicine, 4.312	Cohort Study, U.S.	157	Non-depression	n.a.	n.a.	n.a.			IV	
				Depression	n.a.	n.a.	n.a.	1.09 (1.03–1.15)	age, sex, smoking history, cancer type, treatment, education, and		

									marital status		
McFarland DC, 2021	Biological Research For Nursing, 2.522	Cohort Study, U.S.	68	Non-depression	n.a.	n.a.	18.53			IV	A
				Depression	n.a.	n.a.	16.70	1.132 (1.009–1.269)	age and BMI		
McFarland DC, 2021	Future Oncology, 3.404	Cohort Study, U.S.	123	Non-depression	n.a.	95	18.60			IV	A
				Depression	n.a.	28	10.79	1.08 (1.022-1,142)	age, sex and BMI		
Walker J, 2021	Psychosomatic Medicine, 4.312	Cohort Study, England	4476	Non-depression	n.a.	3613	n.a.			n.a.	A
				Depression	n.a.	412	n.a.	1.39 (1.24–1.56)	n.a.		

Abbreviations: BMI = Body Mass Index; CES-D = Center for Epidemiologic Studies Depression Scale; CI = Confidence Interval; D-S = Depression Scale; HADS = H
Hazard Ratio; MINI = the International Neuropsychiatric Interview; MST = median survival time; n.a.=not available; N = sample size; PHQ-9 = the Patient Health
PSSCAN = Psychosocial Screen for Cancer; RR = Relative Risk; SCID = Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental; SCL-2
Depression Scale; SDS = Self-rating depression scale; U.S.=United States

25 prospective studies and one retrospective study were included in this study. Overall, the studies were published between 1998 and 2021, involving participants from Europe (n = 6), the US (n = 14), Asia (n = 5), and the location could not be obtained (n = 1). The study sample size ranged from 19 to 4476 lung cancer participants, with a median sample size of 573. The follow-up duration ranged from 6 to 89 months. Most studies identified cancer outcomes through hospital records, death certificates, or cancer registries, while others combined self-report with record confirmation. Adjustment for confounders was performed in 14 studies, though with different types and numbers of variables across studies. The NOS score of all studies were ≥ 6 and the mean NOS score of the 26 studies was 7.7 (see Table 2).

Table 2
Newcastle-ottawa quality scale for study assessment.

Author, year	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	NOS score (maximum s = 9)
Buccheri G, 1998	3	2	2	7
Faller H, 1999	4	2	2	8
Faller H, 2002	3	2	2	7
Stommel M, 2002	3	2	3	8
Faller H, 2004	3	2	3	8
Nakaya N, 2006	4	2	3	9
Onitilo AA, 2006	3	2	3	8
Nakaya N, 2008	4	2	2	8
Pirl WF, 2008	4	2	3	9
Akechi T, 2009	4	2	2	8
Angulo CLP, 2011	4	2	2	8
Chen ML, 2011	4	2	2	8
Pirl W, 2011	4	1	2	7
Nunez-Valencia C, 2012	3	2	3	8
Pirl WF, 2012	4	2	2	8
Arrieta O, 2013	4	1	2	7
Sullivan DR, 2014	4	2	3	9
Chen J, 2015	3	2	2	7
Kovacevic T, 2016	3	2	2	7
Sullivan DR, 2016	4	1	2	7
Vodermaier A, 2017	3	2	2	7
Mulick A, 2019	4	2	2	8
Andersen BL, 2021	4	2	2	8
McFarland DC, 2021	4	2	2	8
McFarland DC, 2021	4	2	2	8
Walker J, 2021	3	1	2	6

3.2 Mortality risk

With high heterogeneity across studies, a significant association was found between overall depression and the mortality risk (1.218, 1.142–1.299; I^2 = 79%; Fig. 2). Depression was associated with a 21.8% increased risk of all-cause death among lung cancer patients.

Subgroup analysis showed that depression was associated with the lung cancer mortality risk in patients with both stage I-II and III-IV (1.465, 1.254–1.711 and 1.069, 1.011–1.131, respectively), and the association with I-II stage was greater (*P* value between groups <0.001). In addition, Clinically diagnosed disorders and psychological distress were both associated with the mortality risk (1.128, 1.045–1.217 and 1.076, 1.054–1.098, respectively), but there was no difference between the two groups. There was no significant difference in risk between studies assessing depression before (1.075, 1.053–1.098) and after (1.137, 1.054–1.226) the cancer treatment. High quality studies (1.112, 1.079–1.145) showed stronger correlations than low quality studies (1.053, 1.025–1.082) (*P* = 0.008). The association between depression and mortality risk in Asian participants (1.773, 1.459–2.155) was significantly higher than that in European participants (1.148, 1.082–1.219) and North American participants (1.065, 1.042–1.087).

Table 1
The effect of depression on mortality risk: results of the subgroup analyses

Subgroup analysis	No. of studies	Combined effect size			*P* value for heterogeneity	*P* value between groups
		RR (95%CI)	*P* Value	I^2 Value		
Overall analysis	24*	1.218 (1.142–1.299)	<0.001	79.0%	<0.001	NA
Stage#						<0.001
I-II	2	1.465 (1.254–1.711)	<0.001	1.0%	0.315	
III-IV	9	1.069 (1.011–1.131)	0.020	55.9%	0.020	
Measure of mental status						0.243
Symptom scale	21	1.076 (1.054–1.098)	<0.001	80.4%	<0.001	
Clinical diagnosis	3	1.128 (1.045–1.217)	0.002	65.4%	0.055	
Diagnosis time of mental status						0.162
Pre to treatment	20	1.075 (1.053–1.098)	<0.001	80.6%	<0.001	
Following treatment	4	1.137 (1.054–1.226)	0.001	68.1%	0.024	
Study quality						0.008
≥ 8	18	1.112 (1.079–1.145)	<0.001	70.3%	<0.001	
<8	6	1.053 (1.025–1.082)	<0.001	88.9%	<0.001	
Geographical region						<0.001
Europe	4	1.148 (1.082–1.219)	<0.001	87.7%	<0.001	
North America	16	1.065 (1.042–1.087)	<0.001	70.4%	<0.001	
Asia	4	1.773 (1.459–2.155)	<0.001	17.4%	0.304	

*Eighteen articles reported the stratified results of staging, and two of them divided staging into subgroups, so there were 22 reports from eighteen articles. # Of the 22 reports, six reported stage I-V, nine reported stage III-IV, three reported stage IV, two reported stage I-II, and one reported stage I-III and III. To avoid overlapping of stage, only I-II and III-IV were selected for subgroup analysis. CI confidence interval, RR risk ratio

3.3 MST

A total of thirteen studies reported MST in depressed and non-depressed lung cancer patients. The meta-analysis results of thirteen studies showed that overall depression were associated with a significantly shorter MST in lung cancer patients from random-effects model (RR: 0.362, 95% CI: 0.169–0.554; Fig. 3), with a high heterogeneity (I^2 = 84.9%; P < 0.001).

In the subgroup analysis, psychological distress showed a significant correlation between depression and shorter MST in patients with lung cancer (0.296, 0.222–0.371). Only one reported Clinically diagnosed disorders, so the combined results could not be reported. The correlation between depression and shorter MST was more significant after diagnosis and before treatment (0.287, 0.211–0.362). Low-quality studies showed a more significant association (0.292, 0.203–0.382). In addition, consistent with the mortality risk, the association was more pronounced among Asian participants (0.407, 0.149–0.666).

Table 2
The effect of depression on MST: results of the subgroup analyses

Subgroup analysis	No. of studies	Combined effect size			*P* value for heterogeneity	*P* value between groups
		RR (95%CI)	*P* Value	I^2 Value		
Overall analysis	13	0.362 (0.169–0.554)	<0.001	84.9%	<0.001	NA
Measure of mental status						<0.001
Symptom scale	12	0.296 (0.222–0.371)	<0.001	66.4%	0.001	
Clinical diagnosis	1	-0.111 (-0.201-0.021)	0.016	-	-	
Diagnosis time of mental status						<0.001
Pre to treatment	11	0.287 (0.211–0.362)	<0.001	66.5%	0.001	
Following treatment	2	-0.084 (-0.173-0.005)	0.063	90.5%	0.001	
Study quality						<0.001
≥ 8	9	0.019 (-0.056-0.094)	0.618	84.9%	<0.001	
<8	4	0.292 (0.203–0.382)	<0.001	44.2%	0.146	
Geographical region						0.100
Europe	1	0.182 (-0.229 0.593)	0.385	-	-	
North America	8	0.118 (0.059–0.178)	<0.001	90.1%	<0.001	
Asia	3	0.407 (0.149–0.666)	0.002	37.7%	0.201	

CI confidence interval, RR risk ratio

3.4 Mortality rate

Eight studies yielded a pooled RR of 1.054 (1.003–1.107) for the association between overall depression and all-cause mortality based on a fixed-effect model (Fig. 4). Low heterogeneity was observed with an $I^2 = 44.3\%$ ($Chi^2 = 12.57$, $P = 0.083$). However, there was no clear distinction between all-cause or lung-specific death in any of the eight included studies.

In the subgroup analysis, only the subgroup analysis of Measure of mental status found differences between groups, among which psychological distress was significantly correlated with the mortality risk of lung cancer patients (1.114, 1.037–1.197). Although significant intergroup differences were observed in all other subgroups, the association of having depression identified prior to treatment initiation (1.107, 1.029–1.190) and Asian participants (1.170, 1.031–1.328) were more significant.

Table 3
The effect of depression on mortality rate: results of the subgroup analyses

Subgroup analysis	No. of studies	Combined effect size			*P* value for heterogeneity	*P* value between groups
		RR (95%CI)	*P* Value	I^2 Value		
Overall analysis	8	1.054 (1.003–1.107)	0.038	44.3%	0.083	NA
Measure of mental status						0.034
Symptom scale	7	1.114 (1.037–1.197)	0.003	25.6%	0.233	
Clinical diagnosis	1	1.001 (0.934–1.072)	0.982	-	-	
Diagnosis time of mental status*						0.063
Pre to treatment	5	1.107 (1.029–1.190)	0.006	43.8%	0.130	
Following treatment	2	1.007 (0.941–1.078)	0.841	41.4%	0.191	
Study quality						0.645
≥ 8	2	1.072 (0.982–1.170)	0.119	0	0.623	
<8	6	1.045 (0.984–1.110)	0.147	58.7%	0.033	
Geographical region						0.173
Europe	1	1.211 (0.738–1.988)	0.448	-	-	
North America	4	1.032 (0.978–1.090)	0.252	63.1%	0.043	
Asia	3	1.170 (1.031–1.328)	0.015	0	0.629	

*One study did not report on time of diagnosis, so only seven studies were included in the subgroup analysis. CI confidence interval, RR risk ratio

3.5 Sensitivity analysis and publication bias

Applying the leave-one-out sensitivity analysis did not significantly alter the pooled RRs from above cohorts, indicating that no individual study influenced the results. Contour-enhanced funnel plots for cancer incidence, cancer-specific mortality, and all-cause mortality are shown in Supplementary figures. 1-2. We used funnel plot, Egger test and Begg test to test publication bias. The plot for survival revealed asymmetry. Egger's test for studies assessed the outcomes of mortality risk in lung cancer patients was nonsignificant ($P = 0.304$), but the outcomes of MST and mortality rate (0.036 and 0.004, respectively). Begg's test of mortality risk and MST was nonsignificant ($P = 0.656$ and 0.393), however, the mortality rate was still significant ($P = 0.035$). The discrepancy between these two test might derived from the correlation between the lnRRs and their variances and the level of heterogeneity across studies on MST. In fact, type I error rates (the proportion of false-positive results) for Egger's test are higher than those for Begg's test when the summary estimates are RRs or HRs, particularly when there is considerable between-study heterogeneity [54,55]. The Begg's test, however, is more robust and has the appropriate type I error rates regardless of the size of the underlying risk estimates, the number of included studies, and the level of heterogeneity.

4. Discussion

In recent years, the incidence of tumours has risen and the biomedical model has shifted to a bio-psycho-social medical model, so research on tumour-related psychological diseases has received increasing attention. The National Comprehensive Cancer Network summarized a series of psychological problems that occur in cancer patients as cancer-related psychological pain and tumour-related depression and anxiety greatly affect the quality of life of cancer patients[56,57]. CRD is an emotional pathological reaction caused by the diagnosis, treatment, and comorbidities of malignant tumours, which leads to the loss of the individual's mental normality[15]. After the diagnosis of a malignant tumour, most patients often develop negative emotions such as anxiety and depression. Data showed that about 20-40% of patients newly diagnosed with malignant tumours had significant emotional disorders, [58] but fewer than 10% of patients had received a diagnosis and psychological intervention [59]. A meta-analysis on depression and anxiety about malignant tumours in the Chinese population showed that the level of depression and anxiety of malignant tumours was significantly higher than that of the healthy control group (54.90% vs. 17.50%, P 0.05) [60]. Psychosocial factors, directly or indirectly affecting the occurrence and development of tumours, are related to the human nervous, immune, and endocrine systems. CRD can suppress the body's immune function to increase the risk of tumour recurrence and metastasis, thereby shortening the survival of patients. [61]

The incidence and mortality rate of lung cancer, which continue to rise, both rank first among malignant tumours. The prevalence of depression in cancer patients varies according to diagnostic criteria, but studies have shown that the incidence of depression in lung cancer patients is higher than for other types of cancers[62,63]. Studies have shown that the severity of depression is related to many factors in cancer patients, for example, prolonged hospitalization, poor treatment compliance, reduced quality of life, physical discomfort, and increased death wish [64]. About half of the cohort studies showed that patients with lung cancer developed depressive symptoms at some points during the observation period, and most patients had persistent depressive symptoms. Persistent depression symptoms in cancer patients are associated with poor treatment compliance and cognitive dysfunction, which may lead to increased mortality [65]. Currently, there is no meta-analysis to systematically review the correlation between depression and lung cancer survival outcomes.

Meta-analyses based on RE or FE models suggest that depression is be in connection with higher mortality risk in lung cancer patients and is associated with shorter survival and increased mortality. That indicated that the early clinical diagnosis and intervention of depression in lung cancer patients had positive significance for the prognosis of patients, which could provide the scientific basis for the development of a comprehensive treatment plan for lung cancer patients. At present, society and clinicians are paying more and more attention to the role played by the psychological status of cancer patients. Some research results suggested that psychological intervention may not only affect the patients' emotional disorders, such as depression, but also improve their physical symptoms, such as fear, fatigue, sleep disturbance, and pain, and may have a potential impact on immune function [66,67,68]. Subgroup analysis found that depression was more closely associated with mortality risk in patients with stage I-II lung cancer. Depression found after diagnosis of lung cancer and before treatment was significantly associated with reduced survival. In all three outcomes, Asian participants showed a higher correlation.

4.1 Strengths and limitations

This meta-analysis focused only on lung cancer patients, filling in a gap in the research. The primary outcomes included mortality risk, MST and mortality of lung cancer, which complemented the mortality risk and survival data not available in previous meta-analyses. And adds to existing evidence of all-cause mortality reported in previous meta-analyses, which may help to directly reveal the effect of depression on cancer outcomes.

Some limitations of the literature and our meta-analysis should be considered. First, we found significant heterogeneity on the study of lung cancer mortality rate, which may be due to differences in treatment measures, pathologic types, measures of depression, and confounders adjustment. Heterogeneity persists despite the use of appropriate random-effects model meta-analysis techniques. Therefore, the mean meta-analysis effect size of the effect of depression on cancer outcomes should be interpreted with caution. Second, our meta-analysis is limited to publications published in English, and it is possible for unidentified articles to appear in other databases. In addition, we did not include unpublished literature. So they may also be the main cause of publication bias. However, a comprehensive search of studies published in English on PubMed, EMBASE and Scopus should cover the majority of all available reports. Including unpublished literature may lead to potential bias. Third, the studies included were mainly from Europe, North America and Asia, which reduced the global universality. Fourth, factors such as the duration of depression, antidepressant use, and time interval between lung cancer diagnosis and depression measurement were generally not provided in the included studies, limiting further analysis. In addition, the scales used to assess depressive symptoms have different cut off points and ways of dividing severity. However, the reliability and validity of those scales have been tested to support the accuracy of the measurement. Finally, as a common limitation of observational meta-analyses, our results cannot show a cause-and-effect relationship between depression and anxiety and cancer outcomes.

5. Conclusion

In summary, current evidence suggests that depression may have a negative impact on survival in lung cancer patients, and the association is more significant for Asian participants. Therefore, when standardizing lung cancer treatment, we should pay close attention to the emotional status of lung cancer patients to ensure the maximum benefit of anti-tumor therapy. However, Some caution in interpreting the results, because the results of our study found significant heterogeneity. But due to the limitations of the current study, we were unable to analyze the source of heterogeneity, thus affecting the results of this study. Therefore, these conclusions still need to be confirmed by large-sample, multi-center, high-quality prospective studies.

Declarations

Availability of data and material All data generated or analyzed during this study are included in this published article and its supplementary information fles.

Code availability Codes generated or used during the study appear in the submitted article and its supplementary information fles.

Author contribution All authors participated in the design of the study, interpretation, and analysis of the data and review of the manuscript. Study design: Guanghui Zhu; data collection and appraisal: Guanghui Zhu, Juan Li; data analysis: Guanghui Zhu, Minghao Dai; study supervision: Jie Li; manuscript writing: Guanghui Zhu, Ruike Gao; critical revisions: Heping Wang. All authors revised and accepted the final draft.

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Ethics approval This study involved the analysis of previously published papers and did not involve studies with animals or people; therefore, the approval of an ethics committee was not needed.

Consent to participate N/A

Consent for publication N/A

Competing interests The authors declare no competing interests.

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Figures

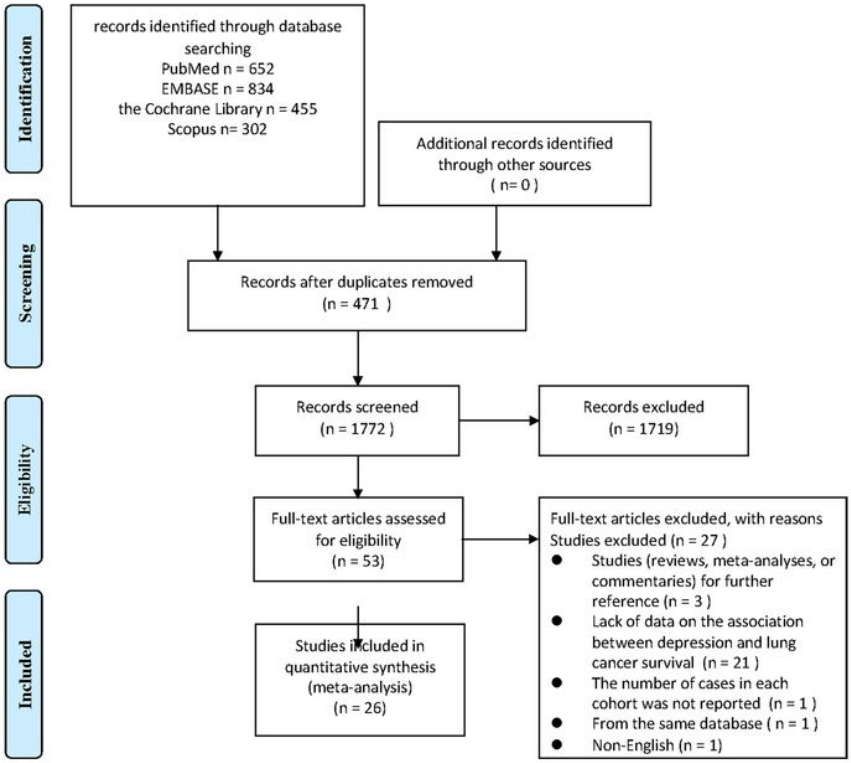

Figure 1

Flow chart of identification of eligible studies

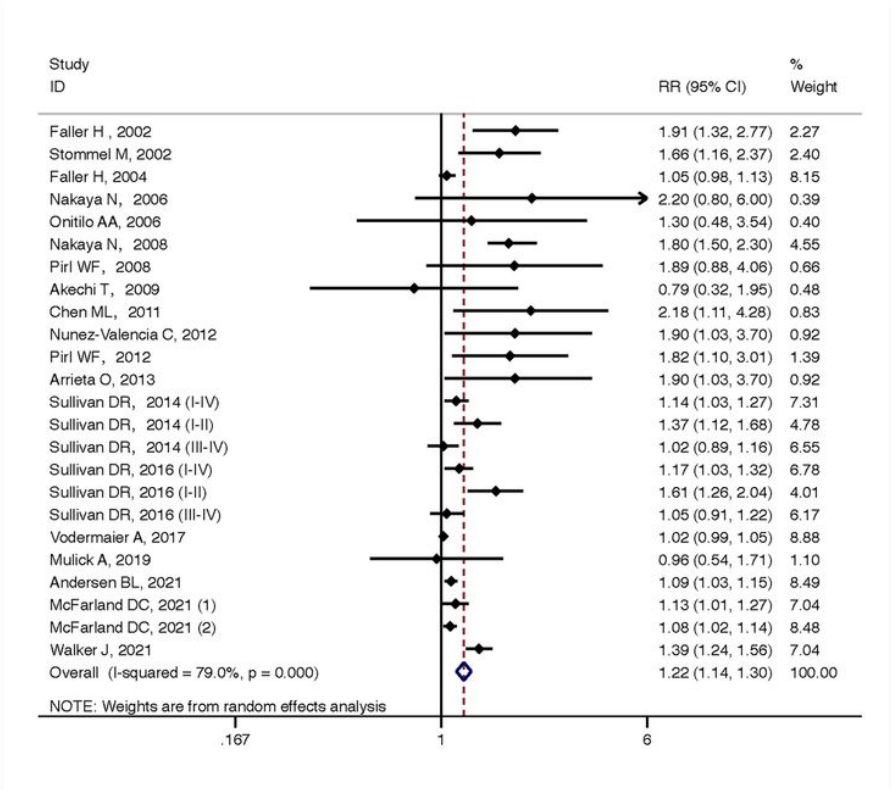

Figure 2

The effect of depression on mortality risk

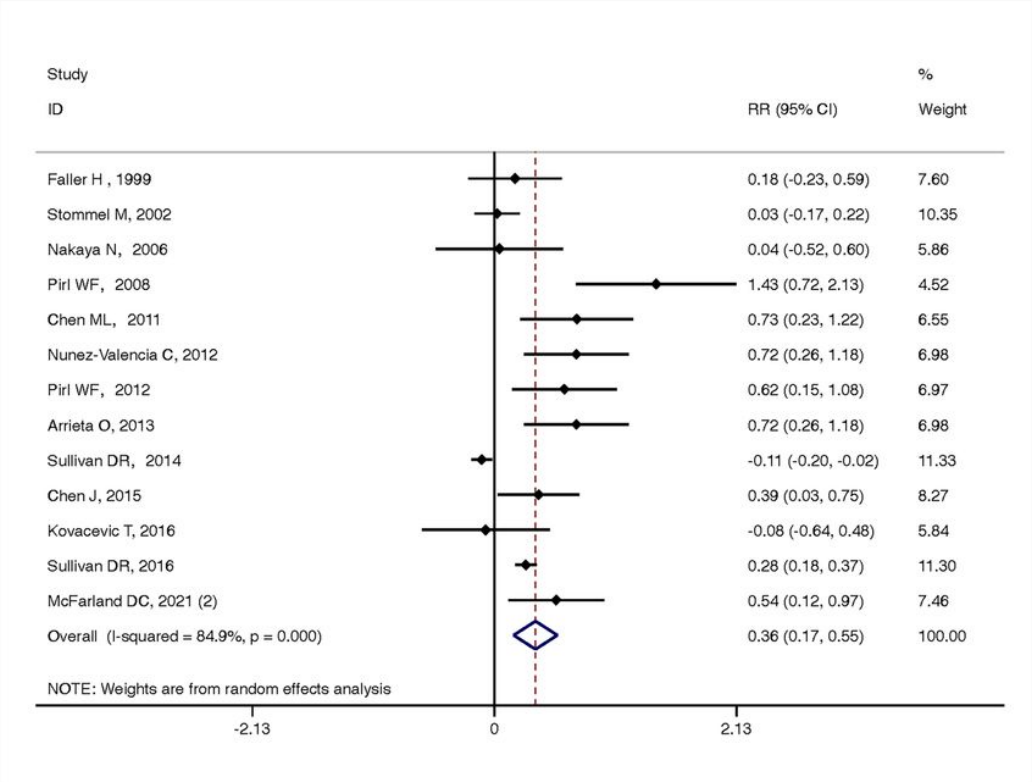

Figure 3

The effect of depression on MST

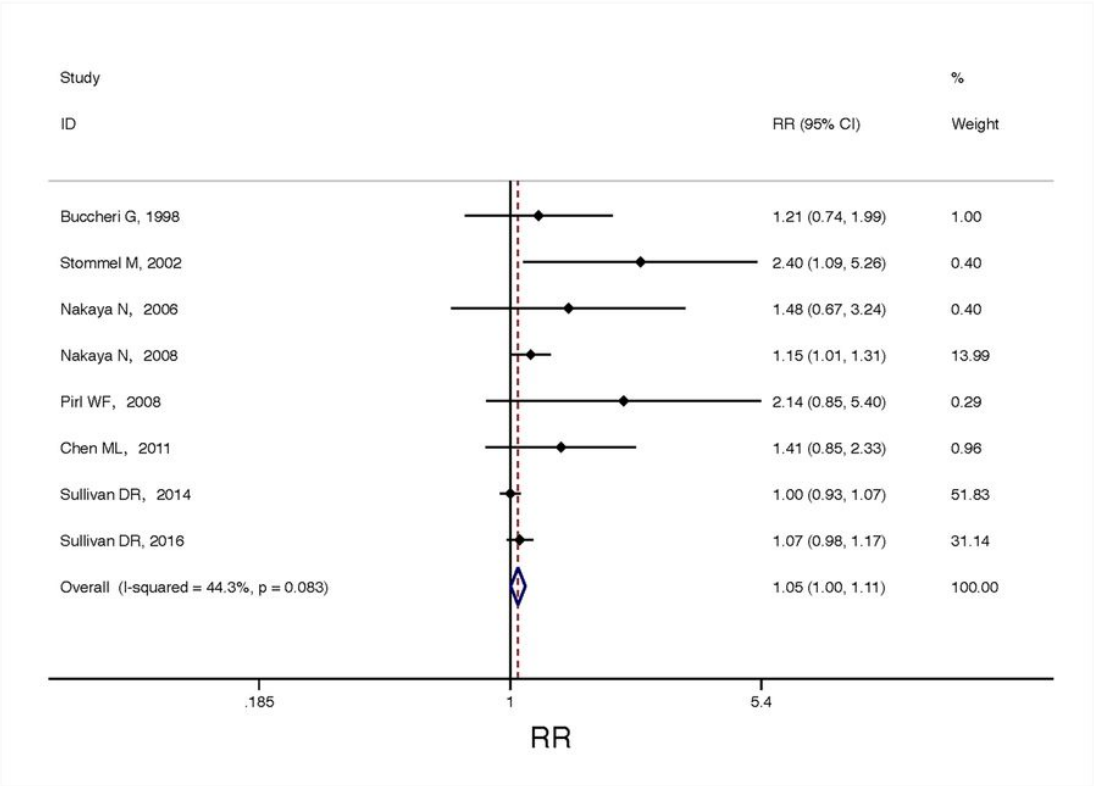

Figure 4

The effect of depression on mortality rate

Supplementary Files

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