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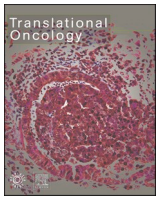

Original Research

Impact of coronavirus disease 2019 on lung cancer patients: A meta-analysis

Linlin Wang [a,1], Ye Wang [b,1], Xianbin Cheng [c], Xingzhao Li [a], Jun Li [d,*]

[a] Department of Ultrasound, China-Japan Union Hospital of Jilin University, Changchun, Jilin 130033, China
[b] Department of Pediatrics, China-Japan Union Hospital of Jilin University, Changchun, Jilin 130033, China
[c] Department of Gastrointestinal Colorectal and Anal Surgery, China-Japan Union Hospital of Jilin University, Changchun, Jilin 130033, China
[d] Department of Hematology and Oncology, China-Japan Union Hospital of Jilin University, Changchun, Jilin 130033, China

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) pandemic poses a great challenge to the treatment of lung cancer patients.
Materials and methods: The PubMed, Embase, and Web of Science databases were searched for studies published before March 15, 2022, and Stata 14.0 software was used to perform a meta-analysis with a random-effects model. The odds ratio (OR) along with the corresponding 95% confidence interval (CI) was reported.
Results: Our meta-analysis included 80 articles with 318,352 patients involved. The proportion of lung cancer patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was 2.4% (95% CI: 0.02–0.03) prior to the Omicron variant outbreak. Among COVID-19 patients, those with lung cancer showed a higher mortality rate than those with other types of malignant solid tumors (OR = 1.82, 95% CI: 1.61–2.06) and non-cancer patients (OR = 4.67, 95% CI: 3.61–6.05); however, no significant difference was observed in the mortality rate between patients with lung cancer and those with hematologic malignancies (OR = 1.07, 95% CI: 0.85–1.33). SARS-CoV-2 infection significantly increased the mortality rate in lung cancer patients (OR = 8.94, 95% CI: 6.50–12.31). By contrast, the all-cause mortality rate in lung cancer patients (OR = 1.04, 95% CI: 0.69–1.57) and the proportion of patients diagnosed with advanced lung cancer (OR = 1.04, 95% CI: 0.85–1.27) did not significantly change before and after the pandemic.
Conclusions: More attention should be paid on improving the health of lung cancer patients during the COVID-19 pandemic.

1. Introduction

The first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was detected in Wuhan, China, in December 2019; the coronavirus disease 2019 (COVID-19) quickly spread worldwide, subsequently posing considerable challenges to the health systems of numerous countries that were affected [1]. The epidemiology indicates that the pandemic will probably last for several years [2]. As of March 15, 2022, the cumulative number of confirmed cases worldwide exceeded 459 million, and the cumulative number of deaths exceeded 6.04 million [3]. Coronaviruses primarily infect birds and mammals. In recent decades, they have been shown to infect humans [4]. SARS-CoV-2 is a new virus strain belonging to the β-coronavirus group, which has not been previously detected in humans and is currently the seventh member of the human coronavirus family that infects humans. The nucleotide homology of SARS-CoV-2 and the genome of SARS-CoV that causes severe acute respiratory syndrome (SARS) reached 79.5% [5]. The SARS-CoV-2 that causes COVID-19 is less pathogenic than the virus that causes SARS and the Middle East respiratory syndrome (MERS) but is noticeably more contagious [6]. The initial symptoms typically include fever, cough, fatigue, anorexia, loss of smell, myalgia, sore throat, and headache. The symptoms, including tachypnea, severe hypoxemia, lymphopenia, and acute-onset bilateral infiltration, which is greater in the peripheral lung zones, may worsen after approximately a week. Eventually, it can progress to respiratory failure and death [7].

The COVID-19 outbreak has exerted an enormous impact on the

* Corresponding author.
E-mail address: ljun01@jlu.edu.cn (J. Li).
[1] Linlin Wang and Ye Wang have contributed equally to this work and share first authorship.

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global society and economy. According to a British study, around 12,000 new deaths unrelated to SARS-CoV-2 infection have been reported since the pandemic, compared with the previous year [8]. A considerable amount of attention should be paid to identifying other diseases during the epidemic. Patients with cancer, especially lung cancer, form a large group that deserves special attention [9]. Lung cancer is the second most common type of cancer, with approximately 1.8 million deaths and 2.2 million new cases in 2020 [10]. Angiotensin-converting enzyme 2 (ACE2), as the only experimentally confirmed SARS-CoV-2 receptor, can facilitate the entry of viruses into cells, and its expression level is considered to be a marker of susceptibility to COVID-19 [11]. COVID-19 is acquired through the inhalation of respiratory droplets containing SARS-CoV-2; in lung cancer patients, the expression levels of ACE2 are significantly increased, especially in the lower respiratory tract. This suggests that lung cancer patients have a higher risk of developing SARS-CoV-2 infection [12]. Lung cancer patients infected with SARS-CoV-2 tend to develop more severe symptoms, which may be due to the fact that the SARS-CoV-2 can modulate the lung tumor microenvironment and trigger a more severe cytokine response. Lung cancer can also induce an immunosuppressed state, leaving patients vulnerable to SARS-CoV-2 infection and complications [13]. The symptoms of lung cancer patients include cough, expectoration, difficulty of breathing, and fever. After the administration of antineoplastic therapy, patients may experience various treatment-related side-effects. In addition, the detection of COVID-19 on the imaging of lung cancer patients is atypical due to the influence of the tumor. Therefore, it becomes increasingly difficult to identify and diagnose COVID-19 pneumonia early in lung cancer patients [9].

Hence, it is necessary to take extensive efforts to study the association between lung cancer and COVID-19. Herein, this meta-analysis aimed to study the prevalence of COVID-19 in lung cancer patients and the impact of COVID-19 on the mortality rate of these patients.

2. Materials and methods

2.1. Eligibility criteria

(1) Studies that reported the characteristics of patients with lung cancer, (2) studies in which the literature used to evaluate the effect of COVID-19 on patients with advanced lung cancer defined advanced lung cancer as IV non-small cell lung cancer (NSCLC) or extensive small cell lung cancer (SCLC), and (3) regardless of the experimental or control groups, studies whose sample size was more than five patients were included in the meta-analysis.

Studies that discussed various thoracic malignancies without specifying the different tumor subtypes were not included. This meta-analysis evaluated patients with lung cancer, including SCLC and NSCLC, and excluded those with mesothelioma and thymic tumors.

2.2. Information sources

The PubMed, Embase, and Web of Science databases were searched to find articles related to COVID-19 and lung cancer published before March 15, 2022, and further screening was conducted based on the aims of the present study. No language restrictions were applied during the search, to collect comprehensive information on a global scale.

2.3. Search strategy

To retrieve abundant useful literature, the search scope was not limited to studies with information on lung cancer. For COVID-19, only the title and abstract of the articles were searched. In PubMed, the search strategy used was as follows: ((((((((((((((Pulmonary Neoplasms) OR (Neoplasms, Lung)) OR (Lung Neoplasm)) OR (Neoplasm, Lung)) OR (Neoplasms, Pulmonary)) OR (Neoplasm, Pulmonary)) OR (Lung Cancer)) OR (Cancer, Lung)) OR (Cancers, Lung)) OR (Pulmonary Cancer)) OR (Thoracic Cancer)) OR (Thoracic Cancers)) OR (Pulmonary Cancers)) OR (Cancer of the Lung)) OR (Cancer of Lung)) AND (("COVID-19″ [*Mesh*]) OR (((((((((((((((((((((((((((((((((COVID 19[*Title/Abstract*]) OR (COVID-19 Virus Disease[*Title/Abstract*])) OR (COVID 19 Virus Disease [*Title/Abstract*])) OR (COVID-19 Virus Diseases[*Title/Abstract*])) OR (Disease, COVID-19 Virus[*Title/Abstract*])) OR (Virus Disease, COVID-19[*Title/Abstract*])) OR (COVID-19 Virus Infection[*Title/Abstract*])) OR (COVID 19 Virus Infection[*Title/Abstract*])) OR (COVID-19 Virus Infections[*Title/Abstract*])) OR (Infection, COVID-19 Virus[*Title/Abstract*])) OR (Virus Infection, COVID-19[*Title/Abstract*])) OR (2019-nCoV Infection[*Title/Abstract*])) OR (2019 nCoV Infection[*Title/Abstract*])) OR (2019-nCoV Infections[*Title/Abstract*])) OR (Infection, 2019-nCoV[*Title/Abstract*])) OR (Coronavirus Disease-19[*Title/Abstract*])) OR (Coronavirus Disease 19[*Title/Abstract*])) OR (2019 Novel Coronavirus Disease[*Title/Abstract*])) OR (2019 Novel Coronavirus Infection[*Title/Abstract*])) OR (2019-nCoV Disease[*Title/Abstract*])) OR (2019 nCoV Disease[*Title/Abstract*])) OR (2019-nCoV Diseases[*Title/Abstract*])) OR (Disease, 2019-nCoV[*Title/Abstract*])) OR (COVID19 [*Title/Abstract*])) OR (Coronavirus Disease 2019[*Title/Abstract*])) OR (Disease 2019, Coronavirus[*Title/Abstract*])) OR (SARS Coronavirus 2 Infection[*Title/Abstract*])) OR (SARS-CoV-2 Infection[*Title/Abstract*])) OR (Infection, SARS-CoV-2[*Title/Abstract*])) OR (SARS CoV 2 Infection [*Title/Abstract*])) OR (SARS-CoV-2 Infections[*Title/Abstract*])) OR (COVID-19 Pandemic[*Title/Abstract*])) OR (COVID 19 Pandemic[*Title/Abstract*])) OR (COVID-19 Pandemics[*Title/Abstract*])) OR (Pandemic, COVID-19[*Title/Abstract*]))))

2.4. Study selection process

The articles collected from the database were imported to the NoteExpress software to identify and remove duplicates. After deleting the duplicates, the titles and abstracts were screened, and irrelevant articles were eliminated. The articles that did not meet the requirements were further screened by reading the abstracts or full text. Articles that were fairly related were adopted for subsequent data selection.

2.5. Data selection process and items

Study and data extraction were performed independently by two authors. When disagreements occurred between the two authors, the conflict was resolved through discussion or by consulting a third author.

The following information was extracted from the literature included in the meta-analysis: author, country or region of the study, year of publication, date of the study conducted in experimental and control groups, characteristics of lung cancer patients, characteristics of lung cancer patients complicated by COVID-19, patients with other malignant solid tumors who developed COVID-19, characteristics of hematologic malignancy patients with COVID-19, characteristics of COVID-19 patients with non-cancer illness, and number of patients with advanced lung cancer. If the two groups of independent data could be extracted from the same literature, each group of data was represented by "-A" and "-B."

2.6. Quality assessment

The quality of the included studies was independently assessed using the Newcastle–Ottawa quality assessment scale. Studies with an overall score of 7 or higher were considered as high-quality studies.

2.7. Reporting bias assessment

Egger's test was used for quantitative analysis of reporting bias. A p value < 0.05 indicates the presence of bias.

2.8. Statistical analysis

The odds ratio (OR) was used for data analysis and evaluation, and the confidence interval (CI) was set at 95%. The I^2 statistic was used to quantify the heterogeneity between studies. $I^2 \leq 50\%$ indicated a low heterogeneity, $50\% < I^2 \leq 75\%$ indicated a moderate heterogeneity, and $I^2 > 75\%$ indicated a high heterogeneity between the included studies. The random-effects model was utilized for effect estimation. The Stata 14.0 software was used to perform all statistical analyses. A p value < 0.05 was considered significant.

3. Results

3.1. Study selection

A total of 8377 studies were found during the database search, and 3697 duplicates were deleted. After screening the titles and abstracts, 4248 studies irrelevant to this study were eliminated. Among the remaining 432 studies, 352 were excluded after further screening by reading the abstracts or full texts. Hence, only 80 articles were finally included in the meta-analysis (Fig. 1).

3.2. Study characteristics

After screening, 80 articles were included in this meta-analysis, covering 24 countries or regions. A total of 318,352 study patients were analyzed, including 74,228 with lung cancer, 21,263 with other types of malignant solid tumors, 3953 with hematologic malignancies, and 218,908 with non-cancer illness.

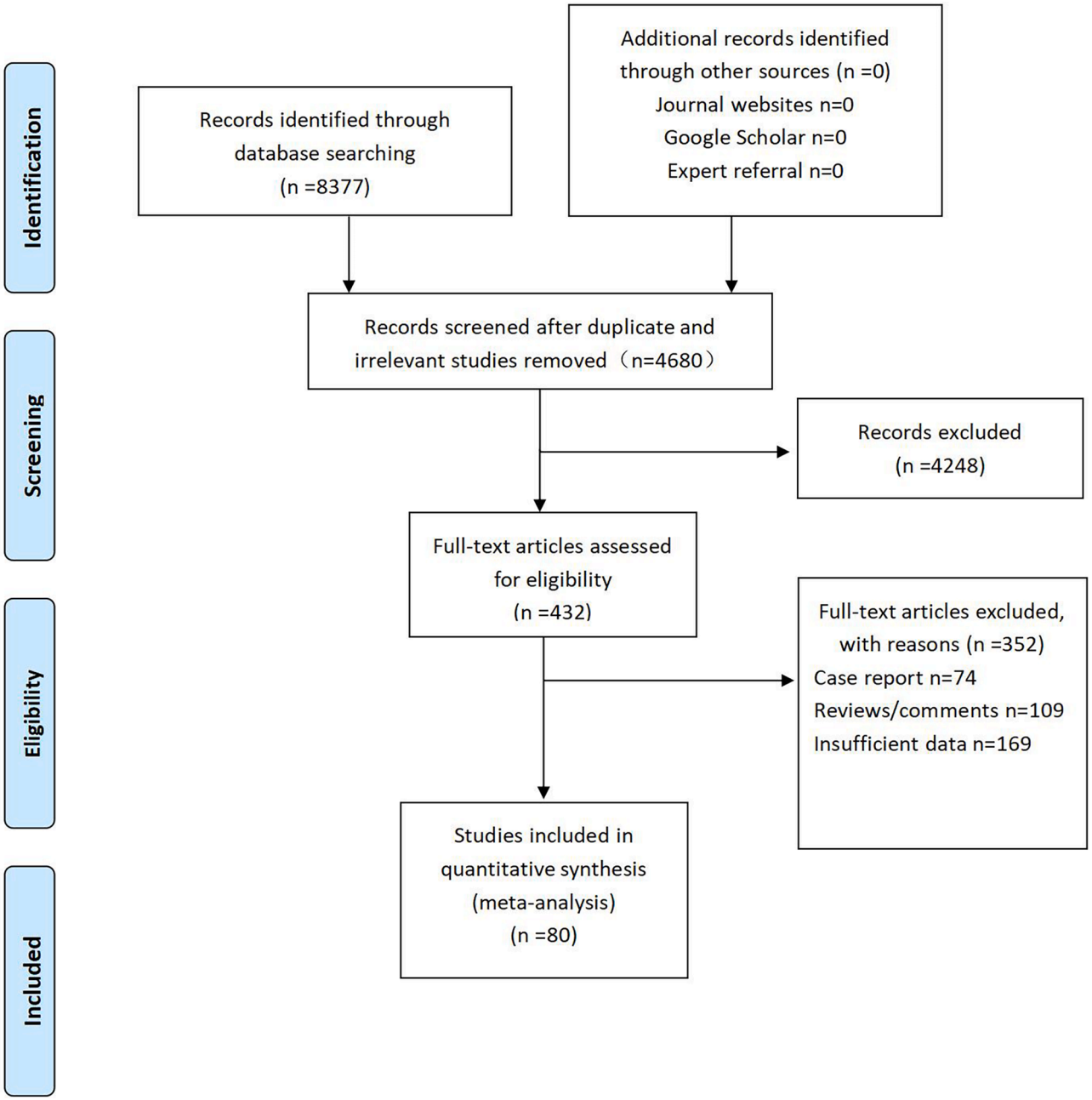

Fig. 1. Flow diagram of the study selection process.

3.3. Quality assessment

Results of the Newcastle–Ottawa quality assessment scale indicated that most studies were of high quality (Table 1).

3.4. Results of individual studies

Our study presents the results of individual studies in structured tables (Tables 2–5). Two meta-analyses specifically compared the mortality rate between lung cancer patients with COVID-19 and other

Table 1
Newcastle–Ottawa quality assessment scale.

Study	Publication year	Selection	Comparability	Outcome	Quality assessment result
Park et al.	2020	4	2	3	good
Cantini et al.	2022	4	1	2	good
Zhang et al.	2021	4	1	3	good
Fernandez et al.	2021	4	1	1	fair
Pages et al.	2021	4	2	3	good
Mynard et al.	2021	4	1	2	good
Reyes et al.	2021	4	1	1	fair
Leclere et al.	2021	4	1	3	good
Cantini et al.	2021	4	1	1	fair
Manas et al.	2021	4	1	1	fair
Nguyen et al.	2021	4	1	1	fair
Cudero et al.	2021	4	1	1	fair
Dai et al.	2020	4	1	3	good
Kasymjanova et al.	2021	4	1	3	good
Piwkowski et al.	2022	4	2	2	good
Fraser et al.	2021	4	2	3	good
Wang et al.	2021	4	1	3	good
Rogado et al.	2020	4	1	3	good
Leitao et al.	2021	4	1	1	fair
Liu et al.	2020	4	2	2	good
Antras et al.	2020	4	1	3	good
Song et al.	2020	4	1	3	good
Meng et al.	2020	4	1	2	good
Li et al.	2020	4	1	3	good
Melo et al.	2020	4	2	2	good
Cavanna et al.	2020	4	2	2	good
Mehta et al.	2020	4	2	3	good
Tian et al.	2020	4	1	2	good
Yang et al.	2020	4	1	2	good
Sorouri et al.	2020	4	2	3	good
Rogiers et al.	2021	4	2	2	good
Stroppa et al.	2020	4	1	2	good
Lee et al.	2020	4	1	3	good
Assaad et al.	2020	4	1	3	good
Lunski et al.	2020	4	2	3	good
Duarte et al.	2020	4	1	2	good
Zhang et al.	2020	4	1	3	good
Oliveira et al.	2020	4	1	3	good
Dai et al.	2020	4	1	2	good
Erdal et al.	2020	4	2	3	good
Roel et al.	2021	4	1	3	good
Caruso et al.	2021	4	2	2	good
Basse et al.	2021	4	1	3	good
Ozer et al.	2021	4	1	3	good
Liang et al.	2021	4	2	3	good
Guo et al.	2021	4	1	3	good
Benderra et al.	2021	4	1	3	good
Ozdemir et al.	2021	4	2	3	good
Zylberman et al.	2021	4	2	2	good
Bondeson et al.	2021	4	1	2	good
Farooque et al.	2021	4	1	3	good
Bernard et al.	2021	4	2	2	good
Martin et al.	2021	4	2	2	good
Linehan et al.	2021	4	2	3	good
Pinato et al.	2021	4	1	3	good
Fernandes et al.	2021	4	2	3	good
Ayhan et al.	2021	4	1	3	good
Demirci et al.	2021	4	1	3	good
Safari et al.	2021	4	1	3	good
Ospina et al.	2021	4	2	3	good
Trifanescu et al.	2022	4	2	3	good
Varnai et al.	2022	4	1	3	good
Guven et al.	2021	4	1	2	good
Chai et al.	2021	4	1	3	good
Preda et al.	2022	4	1	3	good
Rugge et al.	2022	4	2	3	good
Russell et al.	2022	4	1	2	good
Morais et al.	2021	4	1	3	good

Table 2
Prevalence of COVID-19 in lung cancer patients.

Author	Rigion	Publication year	Study period	Lung cancer	Lung cancer with COVID-19
Calles et al. [16].	Spain	2020	2020.2.20–2020.6.20	242	11
Park et al. [18].	America	2020	2020.1.31–2020.6.1	696	24
Pages et al. [22].	France	2021	2020	11,634	51
Leclere et al. [25].	France	2021	2020.3.14–2020.5.11	115	6
Manas et al. [27].	Spain	2021	2020.1–2020.6	96	9
Nguyen et al. [28].	America	2021	2020.1.1–2020.7.1	59	9
Cudero et al. [29].	Spain	2021	2020.1.1–2020.7.31	70	11
Fraser et al. [33].	England	2021	2020.3.1–2020.6.1	352	7
Mandala et al. [34].	Italy	2021	2020.3.5–2020.5.18	100	22
Banfill et al. [35].	England	2022	2020.4.2–2020.10.2	1553	33
Teixeira et al. [39].	Brazil	2021	2020.6–2021.1	32	1
Peer et al. [40].	Israel	2022	2020.2–2020.12	113	2
Wang et al. [62]	America	2020	By 2020.8.14	34 830	100
Roel et al. [63].	Spain	2021	2020.3.1–2020.5.6	7569	140
Kwon et al. [75].	America	2021	2020.2.1–2020.12.31	1404	33
Ayhan et al. [80].	Turkey	2021	2020.3.11–2020.6.11	229	27
Basse et al. [85].	France	2021	2020.3.23–2020.4.17	314	3
Fillmore et al. [92].	America	2021	2010.1.1–2020.5.4	2806	121
Zorzi et al. [93].	Italy	2021	2020.2.22–2020.7.31	1934	45
Russell et al. [94].	England	2022	2020.3.1–2020.5.31	275	6

COVID-19: coronavirus disease 2019, NA: not applicable.

malignant tumor patients with COVID-19. Peravali et al. published a meta-analysis based on 12 studies. They concluded that the mortality rate of lung cancer patients with COVID-19 was higher than that of other types of cancer patients with COVID-19 (OR = 1.62, 95% CI: 1.06–2.48) [14]. However, after reviewing 13 studies, the meta-analysis of Lei et al. yielded an opposite conclusion; no significant difference was found in the mortality rate between lung cancer patients with COVID-19 and other types of cancer patients with COVID-19 (OR = 1.47, 95% CI: 0.98–2.20) [15]. The lower range value of the 95% CI of the above two meta-analyses was extremely close to the critical value. The results were not stable, and the conclusions were likely to be reversed after the inclusion of new literature. Due to the significant differences between malignant solid tumors and hematologic malignancies, we studied the mortality rate of SARS-CoV-2 infection in the above two types of patients, which were not uniformly classified as "other types of cancer patients"; forty-five articles that reported this topic were included in the analysis.

3.5. Results of meta-analysis

Data were extracted from 20 studies to calculate the prevalence of COVID-19 in lung cancer patients, and the results showed that 2.4% of lung cancer patients were infected with SARS-CoV-2 (95% CI: 0.02–0.03, $I^2 = 95.5\%$, Fig. 2). Among cancer patients with COVID-19, the mortality rate in lung cancer patients was notably higher than that in other malignant solid tumor patients (OR = 1.82, 95% CI: 1.61–2.06, $I^2 = 16.3\%$, $p < 0.001$, Fig. 3A). However, no significant difference was observed in the mortality rate between patients with lung cancer and those with hematologic malignancies (OR = 1.07, 95% CI: 0.85–1.33, $I^2 = 45.8\%$, $p = 0.575$, Fig. 3B); the OR value was nearly 1, indicating that the mortality rate of the two groups was considerably close. Among COVID-19 patients, the mortality rate of lung cancer patients was significantly higher than those without cancer (OR = 4.67, 95%CI: 3.61–6.05, $I^2 = 45.3\%$, $p < 0.001$, Fig. 4A).

Among lung cancer patients, a higher mortality rate was possibly associated with SARS-CoV-2 infection (OR = 8.94, 95% CI: 6.50–12.31, $I^2 = 0$, $p < 0.001$, Fig. 4B). Certain characteristics of lung cancer patients were also compared before and after the COVID-19 pandemic. Results showed that after the outbreak of COVID-19, the proportion of patients diagnosed with advanced lung cancer did not significantly increase (OR = 1.04, 95% CI: 0.69–1.57, $I^2 = 92.7\%$, $p = 0.854$, Fig. 5A). Additionally, no obvious difference was observed in the all-cause mortality rate among patients between the two time periods (OR = 1.04, 95% CI: 0.85–1.27, $I^2 = 41.1\%$, $p = 0.727$, Fig. 5B).

3.6. Reporting biases

Results of the Egger's test indicated that there was no publication bias in all the studies (Supplementary File 1).

4. Discussion

Among all patients with various types of cancer, particular concerns should be raised among those with lung cancer during this pandemic as the respiratory tract, which is the primary site of viral infection, is compromised by the tumor. Lung cancer patients are exceptionally vulnerable compared with those with other cancer types when outbreaks of respiratory viruses occur because their damaged respiratory epithelium probably accelerates the invasion of virus into the lungs [96]. Approximately 80.0% of primary lung cancer cases worldwide are caused by smoking [97] Structural lung damage and reduced lung function caused by smoking, and lung damage caused by lung cancer treatment (surgery and radiotherapy) leads to additionally severe symptoms and consequences of SARS-CoV-2 infection in patients with lung cancer compared with other malignant solid tumors [98]. Therefore, the mortality rate of lung cancer patients with COVID-19 is higher than that of other malignant solid tumor patients with COVID-19.

Our study showed that patients with hematologic malignancies who developed COVID-19 had a high mortality rate, which was not significantly different from that of patients with lung cancer who developed COVID-19. Cooksley et al. found a similar pattern when they examined the clinical differences in influenza virus infection among patients with various types of cancer. Compared with patients with other types of cancer, those with lung cancer or hematologic malignancies tended to have a longer average length of hospital stay, frequently required ventilatory support, had higher hospitalization costs, and had a higher case fatality rate [99]. The immune system protects the human body from viruses by producing antibodies, while health recovery relies on both humoral (antibody) and cell-mediated immune responses [100]. Anti-CD20 therapy is widely used to treat hematologic malignancies; however, one significant side-effect is persistent impairment of the patient's immune function. For example, both T-cell dependent and independent responses are severely impaired after rituximab treatment, lasting for at least 6 months [101]. Respiratory viruses usually successfully invade and reproduce in the body of individuals with low immune function, and the severity of disease caused by infection is closely

Table 3
Characteristics of lung cancer patients with COVID-19, other malignant tumor patients with COVID-19, and non-cancer patients with COVID-19.

Author	Rigion	Publication year	Study period	Lung cancer with COVID-19		Other malignant solid tumors with COVID-19		Hematologic malignancies with COVID-19		COVID-19 without cancer	
				Number	Death	Number	Death	Number	Death	Number	Death
Dai et al. [30].	China	2020	2020.1.1–2020.3.1	31	8	NA	NA	NA	NA	186	15
Wang et al. [36]	China	2021	2020.2.4–2020.4.11	13	1	NA	NA	NA	NA	52	0
Rogado et al. [37].	Spain	2020	2020.2–2020.4	17	9	NA	NA	NA	NA	1861	183
Liu et al. [41].	China	2020	2020.12.17–2020.3.18	49	14	144	23	NA	NA	NA	NA
Antras et al. [42].	Spain	2020	2020.2.21–2020.5.8	14	5	59	13	NA	NA	NA	NA
Song et al. [43].	China	2020	2020.1.1–2020.3.25	61	16	187	24	NA	NA	NA	NA
Meng et al. [44].	China	2020	2020.1.18–2020.3.27	17	3	76	21	16	8	2556	261
Li et al. [45].	China	2020	2020.1.20–2020.4.4	5	2	45	12	9	2	1794	191
Melo et al. [46].	Brazil	2020	2020.4.30–2020.5.26	7	4	138	48	34	8	NA	NA
Cavanna et al. [47].	Italy	2020	2020.4.4–2020.5.4	12	7	30	13	5	2	NA	NA
Mehta et al. [48].	America	2020	2020.3.18–2020.4.8	11	6	153	35	54	20	NA	NA
Tian et al. [49].	China	2020	2020.1.13–2020.3.18	23	9	197	32	12	5	519	46
Yang et al. [50].	China	2020	2020.1.13–2020.4.20	24	6	159	25	22	9	NA	NA
Sorouri et al. [51].	Iran	2020	2020.2.25–2020.4.21	5	0	24	10	24	17	106	17
Rogiers et al. [52].	North America, Europe and Australia	2021	2020.3.5–2020.5.15	17	4	93	14	NA	NA	NA	NA
Stroppa et al. [53].	Italy	2020	2020.2.21–2020.3.18	8	2	14	5	NA	NA	31	5
Lee et al. [54].	England	2020	2020.3.18–2020.5.8	111	43	706	172	227	80	NA	NA
Lunski et al. [56].	America	2020	2020.3.1–2020.4.30	26	8	225	39	42	19	4833	418
Duarte et al. [57].	Brazil	2020	By 2020.9.28	51	38	475	308	155	96	681	217
Zhang et al. [58].	China	2020	2020.1.5–2020.3.18	21	5	77	16	9	2	NA	NA
Oliveira et al. [59].	Brazil	2020	2020.3–2020.7	5	4	72	60	NA	NA	NA	NA
Dai et al. [60].	China	2020	2020.1.1–2020.2.24	22	4	74	5	9	3	NA	NA
Erdal et al. [61].	Turkey	2020	2020.3.15–2020.5.15	7	1	52	12	12	4	NA	NA
Roel et al. [63].	Spain	2021	2020.3.1–2020.5.6	140	37	4740	883	513	117	93,558	4153
Caruso et al. [64].	Brazil	2021	2020.2–2020.11	20	14	194	108	60	33	NA	NA
Basse et al. [65].	France	2021	2020.3.13–2020.5.1	18	6	104	15	19	5	NA	NA
Ozer et al. [66].	America	2021	2020.3–2020.10	8	4	52	17	8	4	NA	NA
Liang et al. [67].	China	2021	2020.1.18–2020.3.20	14	2	83	16	12	5	2951	229
Guo et al. [68].	China	2021	2019.12.31–2020.2.20	50	11	215	12	17	2	5176	344
Benderra et al. [69].	France	2021	2020.3.3–2020.5.19	85	37	799	253	264	93	NA	NA
Ozdemir et al. [70].	Turkey	2021	2020.3.11–2020.5.20	157	18	1366	59	NA	NA	NA	NA
Zylberman et al. [71].	Argentina	2021	2020.5–2020.11	14	7	51	17	9	0	NA	NA
Bondeson et al. [72].	Sweden	2021	2020.3.1–2020.8.14	11	1	96	12	NA	NA	NA	NA
Farooque et al. [73].	Pakistan	2021	2020.4–2020.9	159	7	1360	65	NA	NA	NA	NA
Bernard et al. [74].	France	2021	2020.3–2020.4	873	359	3460	1024	1389	470	83,329	13,057
Martin et al. [76].	France	2021	2020.2–2020.5	32	10	180	53	NA	NA	NA	NA
Linehan et al. [77].	Ireland	2021	2020.3–2020.5	7	6	18	3	NA	NA	NA	NA
Pinato et al. [78].	Europe	2021	2020.2.27–2020.9.10	176	74	991	277	142	83	NA	NA
Fernandes et al. [79].	Brazil	2021	2020.4.2–2020.8.31	18	6	346	35	47	10	NA	NA
Ayhan et al. [81].	Turkey	2021	2020.3.11–2020.5.31	26	4	66	18	NA	NA	NA	NA
Safari et al. [83].	Iran	2021	2020	7	2	46	18	13	5	NA	NA
Ospina et al. [84].	Columbia	2021	2020.4.1–2020.10.31	37	20	418	110	NA	NA	NA	NA
Trifanescu et al. [86].	Rumania	2022	2020.5–2020.12	8	2	81	3	NA	NA	NA	NA
Varnai et al. [87].	England	2022	2020.3.18–2020.8.1	265	131	1646	573	604	262	NA	NA
Chai et al. [89].	China	2021	2020.1.1–2020.3.18	25	4	124	22	17	8	498	42

(*continued on next page*)

Table 3 (*continued*)

Author	Rigion	Publication year	Study period	Lung cancer with COVID-19		Other malignant solid tumors with COVID-19		Hematologic malignancies with COVID-19		COVID-19 without cancer	
				Number	Death	Number	Death	Number	Death	Number	Death
Preda et al. [90].	Rumania	2022	2020.4–2021.2	66	5	250	17	25	4	NA	NA
Rugge et al. [91].	Italy	2022	2020.2.22–2020.7.31	62	23	1541	358	184	54	20,777	2008
Russell et al. [94].	England	2022	2020.3.1–2020.5.31	6	1	36	5	NA	NA	NA	NA

COVID-19: coronavirus disease 2019, NA: not applicable.

Table 4
Characteristics of lung cancer patients with and without COVID-19.

Author	Rigion	Publication year	Study period	Experimental group		Control group	
				Lung cancer with COVID-19	Death	Lung cancer without COVID-19	Death
Pages et al. [22].	France	2021	2020	51	11	11,583	232
Leclere et al. [25].	France	2021	2020.3.14–2020.5.11	6	0	109	1
Nguyen et al. [28].	America	2021	2020.1.1–2020.7.1	9	4	50	8
Fraser et al. [33].	England	2021	2020.3.1–2020.6.1	7	2	345	5
Assaad et al. [55].	France	2020	2020.3.1–2020.4.25	7	3	35	5
Roel et al. [63].	Spain	2021	2020.3.1–2020.5.6	140	37	7429	314

COVID-19: coronavirus disease 2019, NA: not applicable.

Table 5
Characteristics of lung cancer patients before and after the COVID-19 pandemic.

Author	Rigion	Publication year	Experimental group period	Control group period	Experimental group			Control group		
					Lung cancer	Death	Advanced	Lung cancer	Death	Advanced
Park et al. [17].	Korea	2020	2020.2–2020.6	2017.2–2017.6 2018.2–2018.6 2019.2–2019.6	169	NA	93	443	NA	208
Cantini et al. [19].	Italy	2022	2020.3–2020.12	2019.3–2019.12	1399	NA	1084	1486	NA	1125
Zhang et al. [20].	China	2021	2020.2–2020.7	2019.2–2019.7	231	NA	9	156	NA	8
Fernandez et al. [21].	Spain	2021	2020.2–2020.6	2019.2–2019.6	40	NA	28	20	NA	15
Pages et al. [22].	France	2021	2020	2018–2019	11,634	244	NA	24,380	561	NA
Mynard et al. [23].	America	2021	2020.7–2021.3	2019.7–2020.3	241	NA	81	269	NA	74
Reyes et al. [24].	Spain	2021	2020.1–2020.6	2019.1–2019.6	62	27	35	100	23	43
Cantini et al. [26].	Italy	2021	2020.3–2020.12	2020.3–2020.12	1381	NA	594	1443	NA	996
Manas et al. [27].	Spain	2021	2020.1–2020.6	2020.1–2020.6	96	25	82	133	27	114
Cudero et al. [29].-A	Spain	2021	2020.1.1–2020.7.31	2019.1.1–2019.7.31	70	NA	58	132	NA	88
Cudero et al. [29].-B	Spain	2021	2020.1.1–2020.7.31	2019.1.1–2019.7.31	91	NA	49	101	NA	56
Kasymjanova et al. [31].	Canada	2021	2020.3.1–2021.2.28	2019.3.1–2020.2.29	103	NA	59	130	NA	68
Piwkowski et al. [32].	Poland	2022	2020.1.1–2020.12.31	2019.1.1–2019.12.31	3236	33	NA	4066	46	NA
Leitao et al. [38].	Portugal	2021	2020.9–2020.10	2019.9–2019.10	80	NA	49	94	NA	61
Demirci et al. [82].	Turkey	2021	2019.12.1–2020.5.31	2017.12.1–2018.5.31 2018.12.1–2019.5.31	259	56	NA	502	118	NA
Guven et al. [88].	Turkey	2021	2020.3–2020.12	2019.3–2019.12	120	101	88	159	132	115
Morais et al. [95].	Portugal	2021	2020.3.2–2020.7.1	2019.3.2–2019.7.1	164	58	NA	204	73	NA

COVID-19: coronavirus disease 2019, NA: not applicable.

related to the degree of the impaired immune function [100]. Patients with hematologic malignancies are generally at a higher risk of developing an infection, which is the primary cause of death in patients with hematologic malignancies, and COVID-19 has been proven to cause various hematologic abnormalities. Hence, compared with most COVID-19 patients with malignant solid tumors, COVID-19 patients with blood cancer have a higher mortality rate [102,103].

Although the mortality rate of lung cancer patients with COVID-19 was higher than that of patients without COVID-19, no significant difference was found in the mortality rate among lung cancer patients before and after the pandemic. In response to this situation, our study presents the following findings: 1. The prevalence of COVID-19 among lung cancer patients is 2.4%, which has a limited impact on the all-cause mortality rate of lung cancer patients. 2. Lung cancer can be cured if it is detected at an early stage [104]. One of the reasons for the high mortality rate in lung cancer patients is that approximately 57% of patients are diagnosed at a later stage [105]. COVID-19 has caused a tremendous amount of social panic. A survey conducted in Italy reported that 21% of lung cancer patients were more concerned about having COVID-19 than having lung cancer [106]. Duong et al. reported that this excessive fear of COVID-19 would discourage potential lung cancer patients from participating in lung cancer screening, possibly leading to the increase in

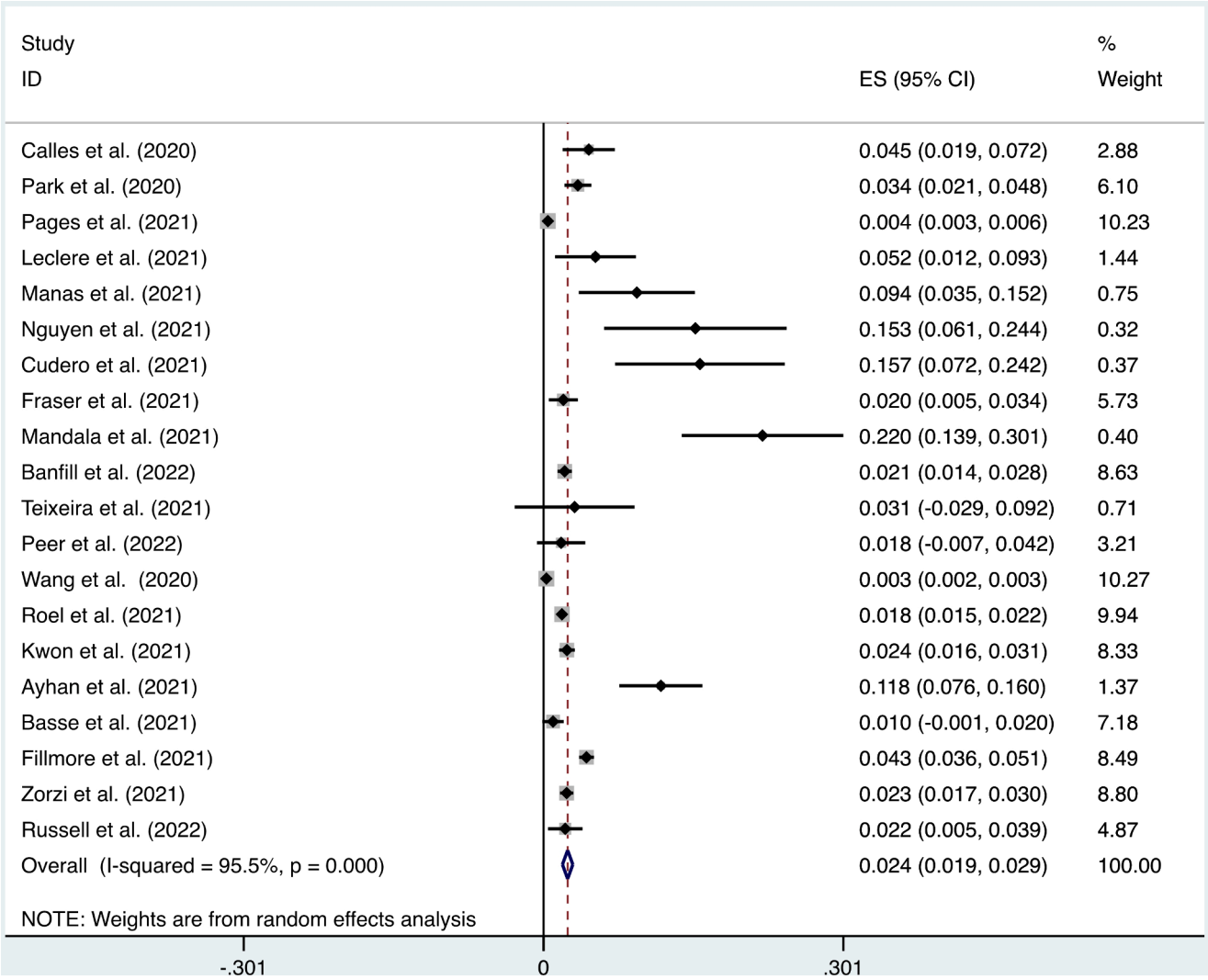

Fig. 2. Forest plot of the proportion of lung cancer patients infected with SARS-CoV-2.

the proportion of patients with more advanced cases [107]. Our findings revealed that after the outbreak of COVID-19, the proportion of patients diagnosed with advanced lung cancer did not notably increase, which may probably explain why the mortality rate of lung cancer did not significantly change after the outbreak.

The government's recommendations for increasing social distancing and isolation have heightened the fear of COVID-19 among lung cancer patients, who may avoid the screening and treatment for lung cancer to prevent infection [107]. Fujita et al. found that during the COVID-19 epidemic, 9.1% of lung cancer patients experienced anxiety and consequently requested to delay their treatment [108]. The concerns of lung cancer patients are reasonable. Lung cancer patients need to visit multiple medical institutions frequently and undergo blood extraction, imaging examinations, bronchoscopy, radiotherapy, chemotherapy, targeted therapy, and other procedures, which increase the risk of acquiring SARS-CoV-2 infection. In Italy, the lung cancer diagnosis rate in 2020 decreased by 6.9% compared with that reported in the previous year [19]. From June to September 2020, the rate of lung cancer-related surgical procedures performed in Italy decreased by 36% compared with those performed in the same period in 2019 [109]. A similar trend occurred during the SARS outbreak in 2003. In Taiwan, 64% of lung cancer patients participating in clinical trials were reluctant to visit the hospital when the international spread of SARS became evident, and about 4% decided to discontinue all treatments [110]. In many countries, the wards used to treat lung cancer patients were designated as isolation and treatment areas for COVID-19 patients during the outbreak [111]. In a hospital in Madrid, Spain, which had 1350 beds, more than 1100 were occupied by patients with COVID-19 during the outbreak [112]. The sudden shortage of medical resources has further delayed the treatment of an increasing number of lung cancer patients. Delayed cancer treatment may increase the 5-year mortality rate by 4.8%–16.6% (depending on the cancer type), which exceeds the mortality rate of COVID-19 [113]. The American College of Surgeons found that a delay of over 8 weeks in the treatment of NSCLC is an independent risk factor for disease progression [114]. The treatment for lung cancer patients, including chemotherapy, immunotherapy and targeted therapy, should be selected based on the individual symptoms, biomarkers, and comorbidities; however, the reduction of side-effects and the risk of COVID-19 infection should be considered. The most important guiding principle in lung cancer treatment is the timely provision of appropriate medical coverage rather than unreasonable delays in treatment [7]. When medical resources are restricted due to the admission of COVID-19 patients, the government should open new temporary hospitals instead of occupying the pulmonary department as specialized units for COVID-19 patients, which may result in serious consequences for lung cancer patients [32].

5. Limitations

Our study has certain limitations. 1. Since November 2021, the

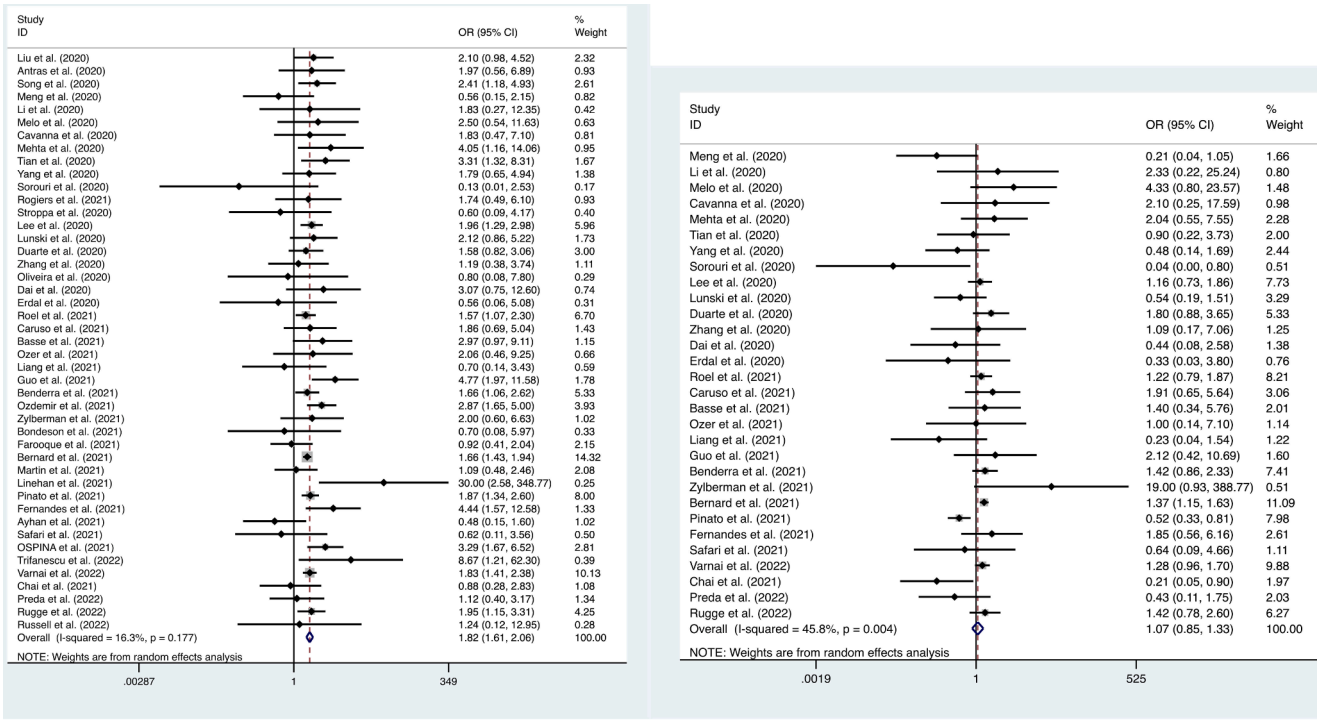

Fig. 3. A: Forest plot of the difference in the mortality rate between lung cancer patients with COVID-19 and other types of malignant solid tumor patients with COVID-19.
B: Forest plot of the difference in the mortality rate between lung cancer patients with COVID-19 and hematologic malignancy patients with COVID-19.

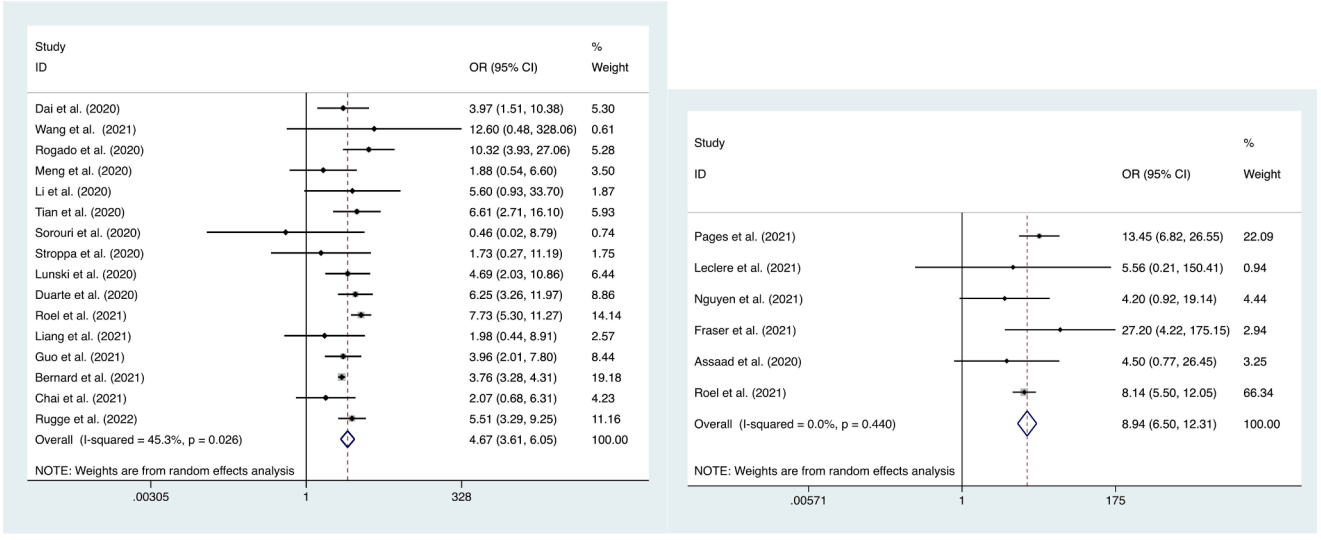

Fig. 4. A: Forest plot of the difference in the mortality rate between lung cancer patients with COVID-19 and non-cancer patients with COVID-19.
B: Forest plot of the difference in the mortality rate between lung cancer patients with and without COVID-19.

Omicron variant of SARS-CoV-2 has rapidly spread worldwide. This variant may be 10-fold more contagious than the original virus and is approximately 2.8-fold more infectious than the Delta variant [115]. It has led to a dramatic increase in the number of COVID-19 patients. In the United Kingdom, Omicron cases accounted for more than 99% of all sequential cases a week after January 10, 2022 [116]. When the prevalence of COVID-19 in lung cancer patients was calculated in our study, all the cases involved had occurred prior to the Omicron outbreak. Therefore, the prevalence of COVID-19 in lung cancer patients may presumably increase afterward. 2. Patients infected with the Omicron variant had a significantly decreased hospitalization rate, disease severity, and mortality rate than of those infected with the previous variant [117]. Whether infection with the Omicron variant has a significant effect on the mortality of lung cancer patients should be investigated further by incorporating more studies in the future. 3. The acquisition of immunity through vaccines is regarded as one of the best

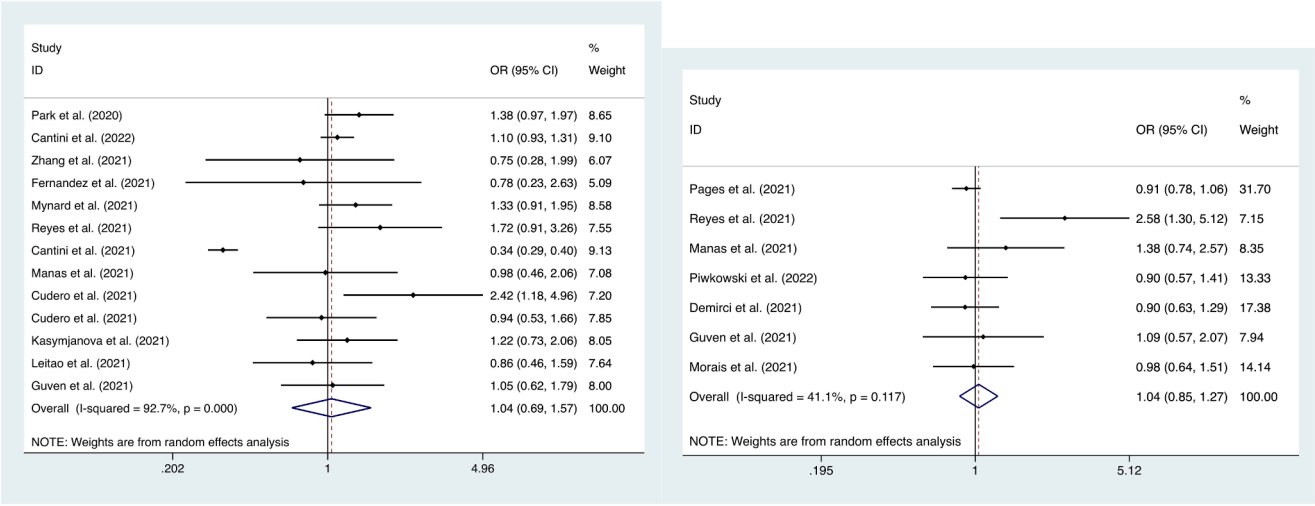

Fig. 5. A: Forest plot of the proportion of patients diagnosed with advanced lung cancer before and after the COVID-19 pandemic.
B: Forest plot of the all-cause mortality rate of lung cancer patients before and after the COVID-19 pandemic.

countermeasures against COVID-19 [118]. Trontzas et al. showed that lung cancer patients could demonstrate sufficient antibody response if they were vaccinated with two-dose regimens [119]. Vaccination may affect the prevalence and mortality rate of COVID-19 in lung cancer patients, but we were unable to conduct a study on this because we could not determine whether the lung cancer patients in our sample had received COVID-19 vaccines.

6. Conclusions

Despite the unchanged all-cause mortality rate, our findings suggested an increased mortality rate in lung cancer patients infected with SARS-CoV-2, whose health deserves more attention, particularly during the COVID-19 pandemic.

Author contributions statement

All authors have full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CRediT authorship contribution statement

Linlin Wang: Writing – original draft, Investigation. **Ye Wang:** Writing – original draft, Investigation. **Xianbin Cheng:** Writing – review & editing. **Xingzhao Li:** Writing – review & editing. **Jun Li:** Conceptualization, Data curation, Investigation.

Declaration of Competing Interest

None.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2022.101605.

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