Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Pre-existing interstitial lung disease in patients with coronavirus disease 2019: A meta-analysis

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ABSTRACT

Background: The impact of pre-existing interstitial lung disease (ILD) on the severity and mortality of COVID-19 remains largely unknown. The purpose of this meta-analysis was to investigate the prevalence of ILD among patients with COVID-19 and figure out the relationship between ILD and the poor clinical outcomes of COVID-19.
Methods: A systematic literature search was conducted in the PubMed, EMBASE, Web of Science and MedRxiv Database from 1 January 2020 to 26 May 2021.
Results: 15 studies with 135,263 COVID-19 patients were included for analysis of ILD prevalence. The pooled prevalence of comorbid ILD in patients with COVID-19 was 1.4% (95% CI, 1.1%-1.8%, $I^2 = 91\%$) with significant between-study heterogeneity. Moreover, the prevalence of ILD in non-survival patients with COVID-19 was 2.728-folds higher than that in corresponding survival patients (RR = 2.728, 95% CI 1.162–6.408, $I^2 = 54\%$, $p = 0.021$). Additionally, 2–3 studies were included for comparison analysis of clinical outcome between COVID-19 patients with and without ILD. The results showed that the mortality of COVID-19 patients with ILD was remarkably elevated compared with patients without ILD (RR = 2.454, 95% CI 1.111–5.421, $I^2 = 87\%$, $p = 0.026$). Meanwhile, the pooled RR of ICU admission for ILD vs. non-ILD cases with COVID-19 was 3.064 (95% CI 1.889–4.972, $I^2 = 0$, $p < 0.0001$). No significant difference in utilizing rate of mechanical ventilation was observed between COVID-19 patients with and without ILD.
Conclusions: There is great variability in ILD prevalence among patients with COVID-19 across the globe. Pre-existing ILD is associated with higher severity and mortality of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has posed huge challenges and health/economic burdens worldwide. As of 1 June 2021, more than 170 million confirmed COVID-19 cases including over 3.5 million deaths have been reported worldwide [1]. The clinical manifestation of COVID-19 varies from asymptomatic to severe acute respiratory distress syndrome (ARDS) and even death [2–4]. Identifying vulnerable populations with higher susceptibility and worse outcomes is of great importance for the control and prevention of COVID-19. Currently, elderly males with comorbidities including chronic respiratory diseases, chronic cardiovascular diseases and chronic kidney diseases are at a high risk of experiencing severe COVID-19 and poor prognosis [5,6].

Although several risk factors have been identified to be associated with the severity and mortality of COVID-19, the exact mechanisms underlying disease severity and progression remain unclear. In the current perspective, it is reported that the damage of alveolar (epithelial)-capillary (endothelial) barrier and cytokine storm participate in the pathogenesis and progression of COVID-19 [7–9]. SARS-COV-2 infection also seems to mount an attack and exacerbate endothelial damage in other vascular beds [8]. Additionally, the inflammatory cytokine cascade induces endothelial activation and capillary leak, leading to circulatory collapse and shock [7,8].

Interstitial lung diseases (ILD) are a heterogenous group of diseases

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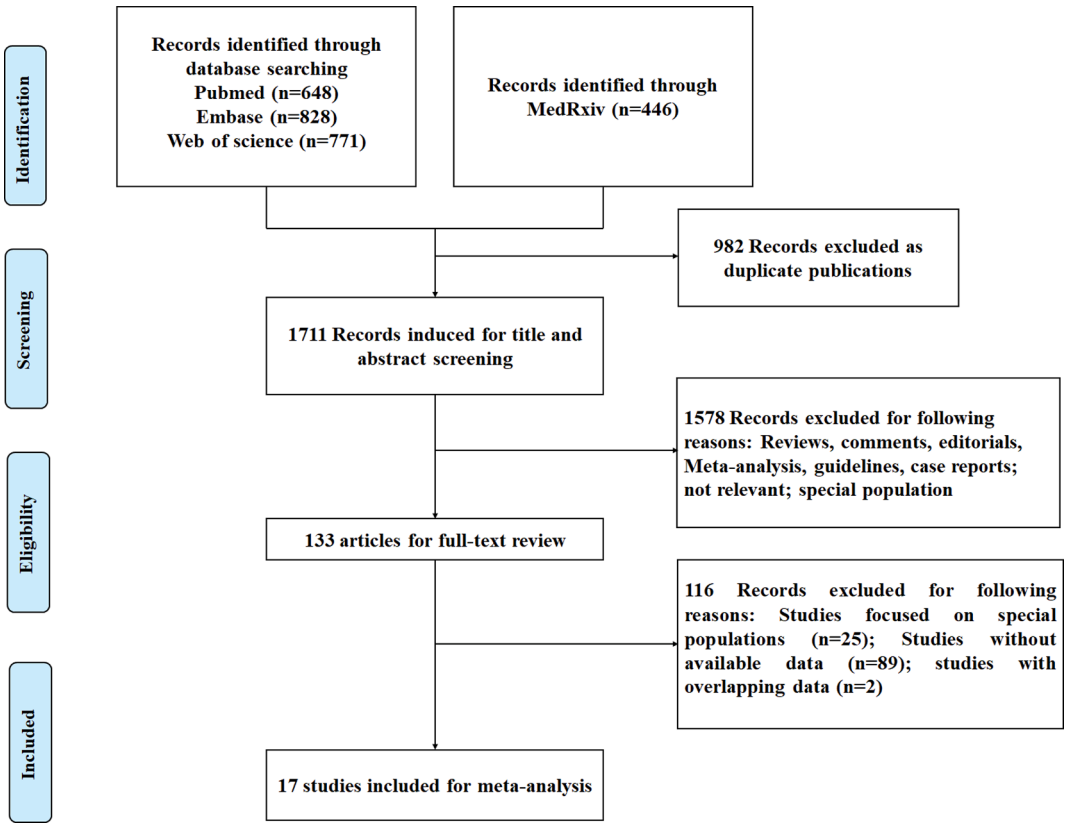

Fig. 1. PRISMA flowchart of included and excluded studies.

characterized by alveolar damage and interstitial thickening [10,11]. Patients with ILD have poor pulmonary reserve and impaired gas exchange [12]. Furthermore, ILD patients with viral infection can trigger acute exacerbations which are related to their poor prognosis [13]. Importantly, the functional impairment and injury of lung endothelial cells have been reported to contribute to the development and progression of ILD [14,15]. Thus, it is reasonable to speculate that ILD increases susceptibility and severity of COVID-19. This was supported by several studies from South Korea and the UK reporting the risk of COVID-19, severity and mortality were higher in patients with ILD compared with those without [16,17]. However, a study from Belgium demonstrated no increased occurrence of severe COVID-19 in ILD patients compared to the general population [18]. In view of the above-mentioned studies, the relationship between ILD and COVID-19 remains controversial. A *meta*-analysis with large clinical samples is warranted to draw a reliable conclusion.

In this study, we performed a systematic review and quantitative *meta*-analysis to report the prevalence of ILD among patients with COVID-19 and investigate the relationship between pre-existing ILD and poor outcomes of COVID-19.

2. Methods

This systematic review and meta-analysis were performed according to the

recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [19].

2.1. Search strategy

Articles published from 1 January 2020 to 26 May 2021 in Pubmed, EMBASE, Web of Science and MedRxiv Database were searched. To identify all the articles regarding the prevalence of ILD in COVID-19 and relationship between ILD and COVID-19, we used the following terms alone or in combination for literature search: “SARS-CoV-2”, “COVID-19”, “2019-nCoV”, “nCoV”, “coronavirus”, “severe acute respiratory syndrome coronavirus 2”, “interstitial lung disease”, “ILD” and “interstitial pneumonia”.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) Subjects: adult patients diagnosed with COVID-19 according to the guidelines for the diagnosis and treatment of novel coronavirus disease; (2) Outcomes: the number of ILD patients among COVID-19 patients; or comparison data of ILD prevalence between survival and non-survival COVID-19 patients; or comparison data of COVID-19 outcome (mortality and severity) between patients with ILD and those without.

Exclusion criteria included: (1) studies with special populations, such as children, elderly, pregnant women; (2) case reports, reviews, meta-analysis, guidelines, editorials and comments; (3) sample size is less than 20 patients; (4) publications with overlapping data and studies in non-English languages. The flowchart of the study selection has been drafted in accordance with the PRISMA principle.

2.3. Data extraction and quality assessment

Two investigators worked independently to decide which studies should be included, and conflicts were resolved by a third investigator. Data was extracted from selected studies including the first author, publication date, country, sex, mean age, number of COVID-19 patients, and study type. In addition, data regarding the number of ILD patients among COVID-19 patients, comparison data of ILD prevalence between survival and non-survival COVID-19 patients, or comparison data of COVID-19 outcome (mortality and severity) between patients with and

Table 1
Characteristics of the included studies.

Study	Country	Center	Type of study	Sample size, n	Male N.(%)	Age (mean)	Population	ILD prevalence (%)
Aveyard P [16]	UK	Multicenter	retrospective cohort	14,479	8038(55.5%)	69.9	Community	2
Drake TM [31]	UK	Multicenter	retrospective case-control	483	330(68.3%)	73.2	Hospital	/
Argenziano MG [32]	USA	Multicenter	retrospective case series	1000	596(59.6%)	62.6	Hospital	1.3
Beltramo G [33]	France	Multicenter	retrospective cohort	89,530	47,495 (53.05%)	65	Hospital	1.8
Huang H [34]	China	Single center	retrospective cross-section	3201	/	/	Hospital	0.9
Brenner DS [35]	USA	Multicenter	retrospective cohort	93	52(56%)	54.2	Hospital	1.1
Sapey E [36]	UK	Single center	retrospective cohort	2217	1290(58.2%)	71.6	Hospital	2.2
Hussain M [37]	Pakistan	Single center	retrospective cross-section	212	120(56.6%)	52	Community	6.6
Eman M [38]	Egypt	Multicenter	retrospective cohort	439	224(51%)	51.2	Hospital	0.7
Esposito AJ [39]	USA	Multicenter	retrospective case-control	138	48 (35%)	/	Hospital	/
Lee H [17]	South Korea	Multicenter	retrospective case-control	8070	3236 (40.1%)	/	Nationwide	0.8
Morgenthau AS [40]	USA	Multicenter	retrospective cohort	7337	4061(55.3%)	/	Hospital	0.5
Signes-Costa J [41]	Spain	Multicenter	retrospective cohort	5847	3432(58.7%)	65.1	Hospital	1.8
Awano N [42]	Japan	Single center	retrospective cohort	54	38(70.4%)	48.8	Hospital	3.7
Kokturk N [43]	Turkey	Multicenter	retrospective cohort	1500	850(57%)	51.89	Nationwide	1.5
Riou M [44]	France	Single center	retrospective cohort	124	75(60%)	62.7	Hospital	2.4
Memel ZN [45]	USA	Single center	retrospective cohort	1179	676 (57.3%)	/	Hospital	0.8

without ILD were also extracted. The data shown as median and interquartile range was transformed into mean and standard deviation (SD) according to the formula below (http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html). The prevalence of ILD was compared between survival and non-survival groups. The mortality and severity of COVID-19 were evaluated between ILD and non-ILD groups. The quality of included studies was evaluated according to the Newcastle-Ottawa scale (NOS) containing three aspects (selection, comparability and outcome) [20]. Scores range from 0 to 9, and the quality of the studies was regarded as low (0–3), moderate (4–6), or high (7–9), respectively.

2.4. Statistical analysis

All statistical analyses were performed using the "meta" package in R software (version 4.0.2) [21]. The "metaprop" command in R was performed to calculate the pooled prevalence estimates of ILD with 95% confidence in patients with COVID-19. The "metabin" function was used to calculate the risk ratio (RR) of comorbid ILD between survival and non-survival COVID-19 patients. The RR of COVID-19 outcomes (severity and mortality) between patients with and without ILD were also estimated using the "metabin" function. A random-effects model was applied to combine the data. The magnitude of heterogeneity between different studies was tested using I^2 statistics. Subgroup analysis and meta-regression based on geographical location, sample size, study type and quality score were performed to explore the origin of heterogeneity. Publication bias was evaluated by funnel plot and Egger test if the number of included studies > 10 [22]. P value<0.05 was regarded as statistically significant.

3. Results

3.1. Study selection

A total of 2693 articles were retrieved according to our search strategy. Firstly, duplicate articles (n = 982) were excluded. After reviewing the titles and abstracts, 1578 articles were ruled out. The 133 remaining articles were full-text reviewed for eligibility. 116 articles were excluded due to the following reasons: studies focused on special populations (n = 25); studies without available data (n = 89), studies with overlapped data (n = 2). Finally, 17 articles with 14,094 patients were included in our meta-analysis. Fig. 1 showed the flow diagram of the study selection.

Table 2
Quality assessment of included studies by Newcasttle-Ottawa scale (NOS).

Study	Newcastle Ottawa Scale score			Total (/9)	Quality
	Selection (/4)	Comparability (/2)	Outcome (/3)		
Aveyard P	4	2	2	8	High
Drake TM	3	2	2	7	High
Argenziano MG	4	1	2	7	High
Beltramo G	3	2	2	7	High
Huang H	4	0	1	5	Moderate
Brenner DS	2	2	2	6	Moderate
Sapey E	4	2	2	8	High
Hussain M	3	0	0	3	Low
Eman M	4	2	2	8	High
Esposito AJ	4	2	2	8	High
Lee H	4	2	2	8	High
Morgenthau AS	4	2	2	8	High
Signes-Costa J	4	2	2	8	High
Awano N	3	2	1	6	Moderate
Kokturk N	4	2	1	7	High
Riou M	3	2	2	7	High
Memel ZN	4	2	2	8	High

3.2. Study characteristics

The main characteristics of the included studies are shown in Table 1. Most of the included studies were retrospective cohort studies. 11 studies were conducted in multicenter and 6 studies in single-center. The studies were from various countries across the globe, of which 6 were from Europe, 5 from Americas, 5 from Asia, and 1 from Africa. The quality of the studies was evaluated using the Newcastle-Ottawa scale. As shown in Table 2, 13 studies were of high quality, 3 studies of moderate quality, and the remaining 1 study of low quality.

3.3. The pooled prevalence of ILD in COVID-19 patients

Among 17 studies, 15 studies from 10 countries with 135263 COVID-19 patients reported prevalence of ILD. The pooled prevalence of comorbid ILD in patients with COVID-19 was 1.4% (95% CI, 1.1%-1.8%, I^2 = 91%, random-effects model; Fig. 2). Considering the significant between-study heterogeneity, we performed subgroup analysis and meta-regression to explore the possible factors based on geographical location, sample size, study type and quality score (Table 3, supplemental Figs. 1–4). Subgroup analysis based on geographical location

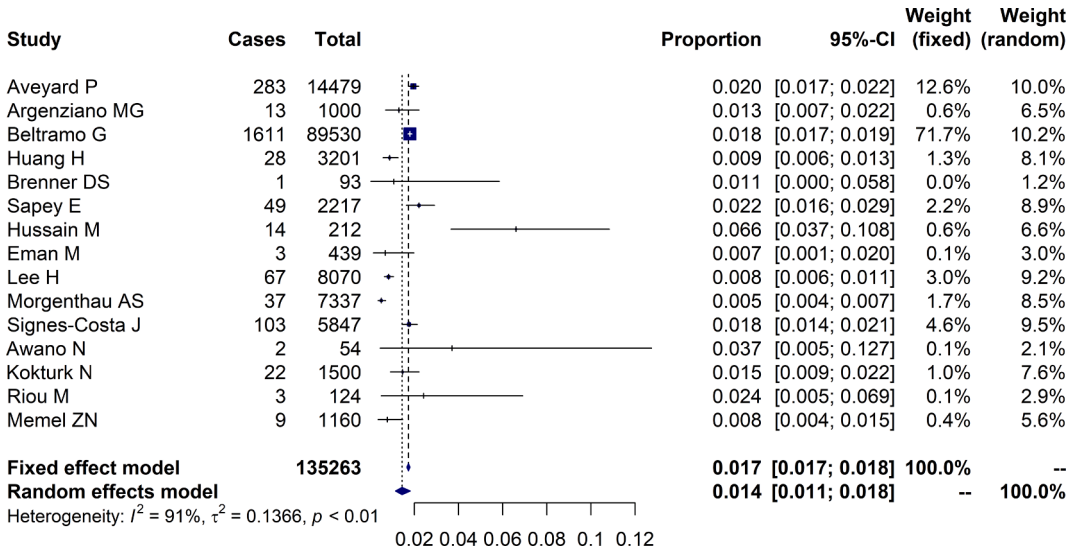

Fig. 2. Forest plot of the pooled prevalence of ILD in patients with COVID-19. CI, confidence interval.

Table 3
Subgroup analysis and Meta-regression.

Variables	No. of studies	Univariate meta-regression *P* value	Subgroup analysis	Heterogeneity	
			Pooled prevalence of ILD (%, 95% CI)	I^2 (%)	*P* value
Geographical location		0.0009			
Europe	5		1.8(1.8–1.9)	0	0.42
Americas	4		0.8(0.5–1.4)	67	0.03
Asia	5		1.8(0.9–3.6)	93	<0.01
Africa	1		0.7(0.2–2.1)	–	–
Sample size		0.0069			
More than 500	10		1.3(1.0–1.6)	93	<0.01
<500	5		2.4(0.9–6.2)	75	<0.01
Study type		0.171			
Cohort	11		1.5(1.2–1.8)	87	<0.01
Case-control	1		0.8(0.7–1.1)	–	–
Cross-sectional	2		2.4(0.3–16)	97	<0.01
Case-series	1		1.3(0.8–2.2)	–	–
Quality		0.0008			
High	11		1.3(1.0–1.7)	91	<0.01
Moderate	3		1.3(0.5–3.3)	49	0.14
Low	1		6.6(3.9–10.8)	–	–

showed that the pooled prevalence of ILD in COVID-19 patients was 1.8% (95% CI 1.8%-1.9%, $I^2 = 0$) in Europe, 0.8% (95% CI 0.5%-1.4%, $I^2 = 67\%$) in the Americas, 1.8% (95% CI 0.9%-3.6%, $I^2 = 93\%$) in Asia, respectively. Only 1 study was from Africa, and the prevalence of ILD in patients with COVID-19 was 0.7% (95% CI, 0.2%-2.1%). Univariate meta-regression demonstrated that geographical location ($P = 0.0009$), sample size ($P = 0.0069$), quality score ($P = 0.0008$) might be factors leading to heterogeneity, whereas no significant differences were found in study type ($P = 0.171$).

3.4. The association of poor outcomes of COVID-19 patients with ILD

To figure out the association of ILD and clinical outcome of patients with COVID-19, we compared the estimated prevalence of ILD between survival and non-survival patients with COVID-19. As shown in Fig. 3, only two studies were included and combined. The prevalence of ILD was significantly higher in the non-survival group compared to the survival group (RR = 2.728, 95% CI 1.162–6.408, $I^2 = 54\%$, $p = 0.021$; Fig. 3A). Furthermore, we also compared clinical outcomes of COVID-19 between patients with and without ILD. The mortality rate was significantly higher in patients with ILD than those without (RR = 2.454, 95% CI 1.111–5.421, $I^2 = 87\%$, $p = 0.026$; Fig. 3B). Considering the significant between-study heterogeneity, we performed subgroup analysis to explore the origin of heterogeneity. As shown in Fig. 3 and Table 1, the sex ratio difference of cohort in studies may contribute partly to the heterogeneity. In addition, the rate of ICU admission was higher in patients with ILD than those without (RR = 3.064, 95% CI 1.889–4.972, $I^2 = 0$, $p < 0.0001$; Fig. 3D). However, no significant difference in utilizing rate of mechanical ventilation was observed between patients with and without ILD (RR = 1.863, 95% CI 0.362–9.582, $I^2 = 93\%$, $p = 0.456$; Fig. 3C).

3.5. Publication bias

No significant publication bias was found by funnel plot and Egger test (P = 0.274).

4. Discussion

To our knowledge, this meta-analysis is the first to report the pooled estimated prevalence of ILD in patients with COVID-19 as well as the relationship between ILD and COVID-19 based on a large COVID-19 population. Our results showed that the prevalence of ILD in COVID-19 patients across the globe was 1.4% with significant between-study heterogeneity. The following subgroup analysis and meta-regression demonstrated that geographical location, sample size and quality score might be potential sources of heterogeneity. The ILD prevalence was significantly higher in non-survival COVID-19 patients compared to their survival counterparts. In addition, a higher risk of death and ICU admission was found in COVID-19 patients with ILD compared to those without. Taken together, our results suggest that ILD is associated with poor outcomes of COVID-19.

ILD refers to a large, heterogeneous group of more than 300 different entities with known or unknown etiology, most of which are classified as non-common diseases [23]. Among the ILDs, the most common is sarcoidosis, while idiopathic pulmonary fibrosis (IPF) is the most severe [23]. Other major ILDs consisted of hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis (EAA), connective tissue disease associated ILD (CTD-ILD), and drug-induced ILD [24]. It is reported that the prevalence estimates of ILD with fibrosis ranges from 42.7 to 63 per 100.000 population in the USA and 1.25–23.4 per 100.000 population in Europe [25]. Our results revealed that the pooled prevalence of ILD in

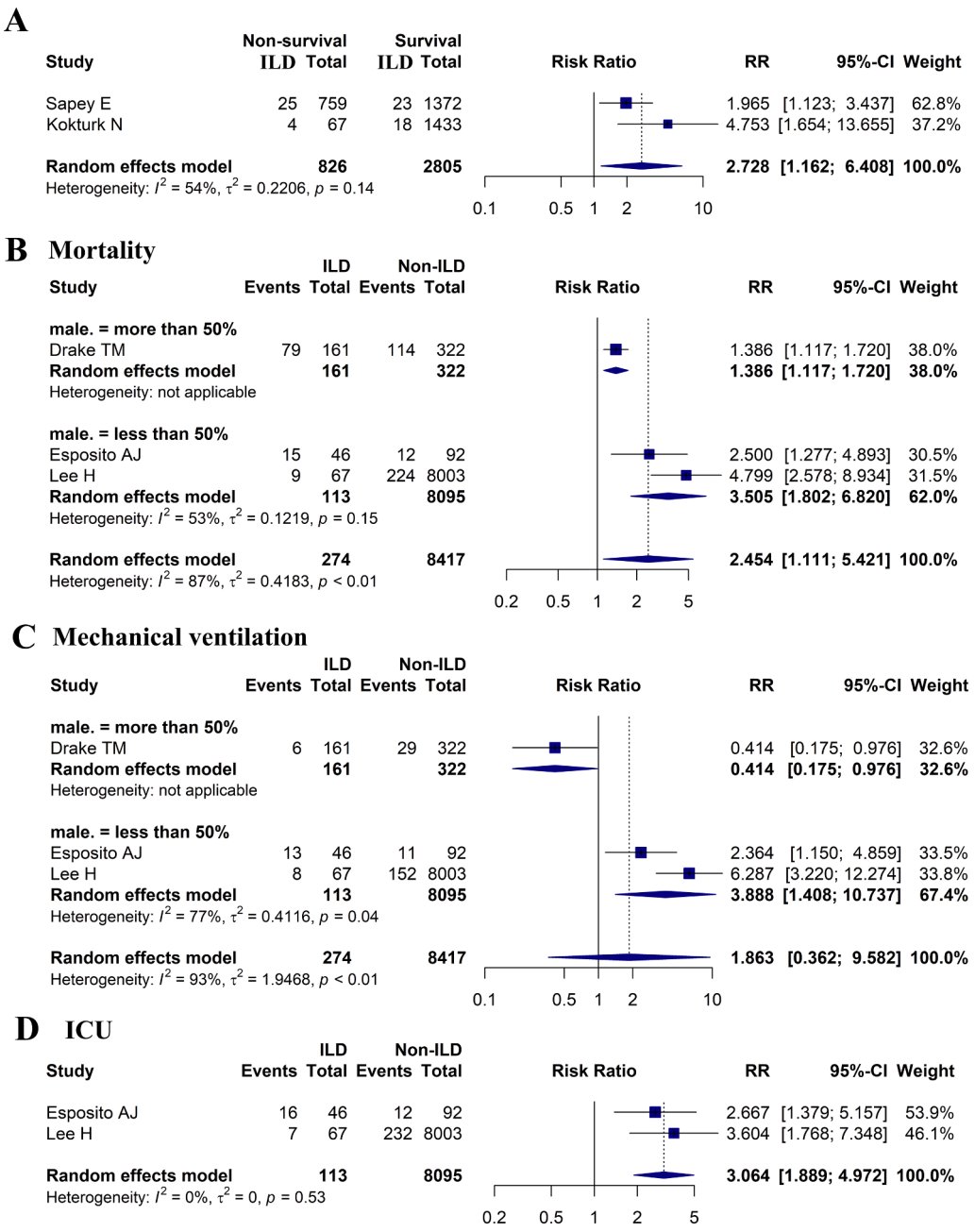

Fig. 3. (A) Forest plot of the prevalence of comorbid ILD in non-survival and survival patients with COVID-19; (B) Forest plot of mortality in COVID-19 patients with and without ILD; (C) Forest plot of utilization rate of mechanical ventilation in COVID-19 patients with and without asthma; (D) Forest plot of proportion of ICU admission in COVID-19 patients with and without asthma.

COVID-19 patients was 1.8% in Europe and 0.8% in the Americas, which is higher than the reported prevalence of ILD in the general population. A possible reason is that ILD patients, especially IPF patients, tend to be older and have multiple comorbidities which is suggested to increase the risk of COVID-19[26]. These evidence indicate that ILD patients are susceptible to COVID-19.

In our study, we found that the prevalence of ILD was significantly higher in non-survival groups than that in survival groups. Furthermore, the risk of death and ICU admission in COVID-19 patients was higher in patients with ILD compared to those without. These results suggest that ILD might be a risk factor for poor clinical outcomes of patients with COVID-19. The reasons underlying it are complicated and possibly multifactorial. Firstly, it is suggested that ILD renders the host susceptible to respiratory viral infection which is recognized as the main trigger for exacerbations of ILD and related with severe adverse outcomes [27], although the exact mechanism underlying the event is unknown. Given the impaired lung reserve and gas exchange of ILD patients, the SARS-COV-2 infection of ILD patients could be the proverbial straw that breaks the camel's back. ILD patients with SARS-COV-2 infection may be more likely to develop severe ARDS, respiratory failure, or even death. Secondly, ILD patients, especially patients with CTD-ILD are often treated with corticosteroids and/or immunosuppressive agents [28]. Although the robust data regarding the impact of corticosteroids/immunosuppressive agents on severity and mortality of COVID-19 are still lacking, previous data have suggested that ILD patients receiving immunomodulatory agents have an increased risk of viral infections such as influenza, rhino- and adenovirus [29]. Corticosteroid treatment is also suggested to lead to increased viremia, delayed clearance of viral, and an increased length of hospital stay in studies of coronavirus infections [30]. Therefore, it could be another explanation

of poor outcomes in ILD patients.

To the best of our knowledge, this meta-analysis is the first to evaluate the relationship between ILD and COVID-19 outcome (mortality and severity). Pre-existing ILD is a risk factor influencing the progression and prognosis of COVID-19. However, this study is descriptive and the underlying mechanisms behind the results are poorly understood. Further research is needed to investigate the effect of the endothelial dysfunction associated with ILD on the cytokine storm caused by SARS-COV-2. Several limitations inevitably exist in our meta-analysis. First, due to the limited studies regarding the prevalence of ILD in patients with COVID-19, the quantity of included studies in our meta-analysis might not be sufficient. The results of this study should be considered with caution and be re-analyzed when emerging literature across the globe becomes available to provide a reliable conclusion. Second, most included studies were based on inpatients, while few were based on national population. Therefore, the pooled prevalence of ILD might be overestimated in our study. Third, the non-English articles were excluded during study selection which might introduce a potential bias. Fourth, most selected studies were retrospective, which might lead to potential bias. Re-evaluation is needed when more prospective studies are available. Fifth, only 2–3 studies were available to retrieve data regarding the relationship between ILD and COVID-19, which might not be sufficient. Further update of meta-analysis is needed when data becomes sufficient. Finally, ILD is characterized as a heterogeneous disease. The component of ILD in different studies might be variable. We fail to compare clinical outcomes of COVID-19 among different types of ILD due to the lack of data.

In conclusion, this meta-analysis provides evidence that pre-existing ILD is associated with a higher risk of poor clinical outcomes in patients with COVID-19. Therefore, it is necessary for respiratory doctors to pay more attention to COVID-19 patients with pre-existing ILD and implement optimized interventions and treatments for them during a COVID-19 epidemic.

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Author contributions

Lichen Ouyang designed the search strategy, screened studies for eligibility, conducted the data analysis, and wrote the first draft of the manuscript. Muqing Yu conceived the study, screened studies for eligibility, and critically revised the manuscript. Jie Gong addressed discrepancies in screening and data extraction, and critically revised the manuscript. All co-authors were involved in final editing of the manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2021.108145.

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