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Interstitial lung disease independently associated with higher risk for COVID-19 severity and mortality: A meta-analysis of adjusted effect estimates

**ARTICLE INFO**

**Objective:** The aim of this study was to address the association between interstitial lung disease and the risk for severity and mortality among patients with coronavirus disease 2019 (COVID-19).

**Methods:** The electronic databases of PubMed, Web of Science and EMBASE were systematically searched. The pooled effect size with 95% confidence interval (CI) was computed by a random-effects meta-analysis model. Heterogeneity test, sensitivity analysis, subgroup analysis, meta-regression analysis, Begg’s test and Egger’s test were performed.

**Results:** A total of sixteen eligible studies with 217,260 COVID-19 patients were enrolled in this meta-analysis. The findings based on adjusted effect estimates indicated that pre-existing interstitial lung disease was significantly associated with higher risk for COVID-19 severity (pooled effect = 1.34 [95% CI: 1.16–1.55]) and mortality (pooled effect = 1.26 [95% CI: 1.09–1.46]). Consistent results were observed in the subgroup analysis stratified by sample size, age, the percentage of male patients, study design, setting, the methods for adjustment and the factors for adjustment. The results of meta-regression demonstrated that sample size, age and region might be the potential sources of heterogeneity. Sensitivity analysis exhibited that our results were stable and robust. No publication bias was observed in Egger’s test and Begg’s test.

**Conclusion:** This meta-analysis on the basis of adjusted effect estimates demonstrated that pre-existing interstitial lung disease was independently associated with significantly higher risk for COVID-19 severity and mortality.

Previous individual studies on the association between pre-existing interstitial lung disease and the risk for severity and mortality of patients with coronavirus disease 2019 (COVID-19) yielded inconsistent results [1–4]. Recently, Ouyang et al have performed a meta-analysis to address the impact of pre-existing interstitial lung disease on the severity and mortality among COVID-19 patients in the journal of International Immunopharmacology [5]. Their data suggested that pre-existing interstitial lung disease was associated with higher risk for severity and mortality of COVID-19 patients. This study is extremely interesting. However, the number of included studies (3 articles) and the sample sizes (8691 participants) were relatively small, and the stability of the overall results was not evaluated, moreover, the pooled effect size was calculated on the basis of un-adjusted effect estimates in Ouyang et al’s study [5]. As the authors mentioned, sex, age and certain comorbidities were known risk factors for severe COVID-19 and poor prognosis [5], which indicates that these factors might confound the association between interstitial lung disease and COVID-19 severity and mortality. Taken together, we performed this updated meta-analysis on the basis of risk factors-adjusted effect estimates to clarify the association between interstitial lung disease and COVID-19 severity and mortality.

We systematically screened the electronic databases of PubMed, Web of Science and EMBASE to identify all relevant articles published from January 1, 2020 to July 5, 2022, by using the following keywords: “interstitial lung disease”, “interstitial pneumonia”, “COVID-19”, “2019-nCoV” and “SARS-CoV-2”. We also searched the reference lists of the included articles to obtain more eligible literature. The outcome of interest was severity (reported as severity, severe or critical illness, admission to intensive care unit, need for mechanical ventilation or mortality in original articles). The peer-reviewed articles in English were included if they reported the association between interstitial lung disease and COVID-19 severity or mortality in the setting, the methods for adjustment and the factors for adjustment.

We performed study selection and data extraction, and any disagreement was resolved by a third investigator. Two independent investigators performed study selection and data extraction, and any disagreement was resolved by a third investigator.

R software with the “meta” package was used to perform all statistical analyses [8,9]. The inter-study heterogeneity was examined by using standard Cochran’s Q test and I² statistics [10,11]. The pooled effect size with 95% confidence interval (CI) was computed by a random-effects meta-analysis model [12,13]. Leave-one-out sensitivity analysis was used to evaluate the stability of the overall results [7,14]. Subgroup analysis and meta-regression analysis of the following potential variables were conducted to explore the cause of heterogeneity: sample size, age, the percentage of male patients, region, study design, setting, the methods for adjustment and the factors for adjustment. Publication bias was assessed by Egger’s linear regression analysis and Begg’s rank correlation analysis. A two-sided P value < 0.05 was
considered to be statistically significant.

A total of sixteen eligible studies with 217,260 COVID-19 patients were enrolled in this meta-analysis (Table 1). And the results of the risk of bias assessment are displayed in Supplementary Table S1. The adjustment methods used in detail for each study as well as the adjustment factors in Supplementary Table S2. The results based on adjusted effect estimates indicated that pre-existing interstitial lung disease was significantly associated with higher risk for COVID-19 severity (pooled effect = 1.34 [95% CI: 1.16–1.55], Fig. 1A). When the outcome of interest was only limited to mortality, pre-existing interstitial lung disease was still associated with significantly higher risk for COVID-19 mortality (pooled effect = 1.26 [95% CI: 1.09–1.46], Fig. 1B). Sensitivity analysis exhibited that our results were stable and robust (Fig. 1C and D). We observed consistent results on the association of interstitial lung disease with significantly higher risk for COVID-19 severity in the subgroup analysis stratified by sample size (pooled effect = 2.17 [95% CI: 1.42–3.33] for <5000 cases and 1.15 [95% CI: 1.02–1.30] for ≥5000 cases), age (pooled effect = 3.98 [95% CI: 1.67–9.50] for <60 years and 1.30 [95% CI: 1.11–1.52] for ≥60 years), the percentage of male patients (pooled effect = 1.28 [95% CI: 1.05–1.56] for <50% and 1.43 [95% CI: 1.16–1.76] for ≥50%), study design (pooled effect = 1.34 [95% CI: 1.15–1.57] for retrospective study and 2.24 [95% CI: 1.15–4.39] for the others), setting (pooled effect = 1.30 [95% CI: 1.09–1.54] for hospitalized patients and 1.93 [95% CI: 1.23–3.02] for all COVID-19 patients), the methods for adjustment (pooled effect = 1.34 [95% CI: 1.14–1.57] for multiple logistic regression and 1.54 [95% CI: 1.01–2.33] for others), and the factors for adjustment (pooled effect = 1.18 [95% CI: 1.04–1.34] for including respiratory diseases and 1.97 [95% CI: 1.24–3.14] for without respiratory diseases) (Table S3).

Subgroup analysis by region revealed that pre-existing interstitial lung disease was associated with significantly higher risk for COVID-19 severity in Asia (pooled effect = 3.38 [95% CI: 1.16–7.07]) and Europe (pooled effect = 1.50 [95% CI: 1.07–2.10]), but not in North America (pooled effect = 1.17 [95% CI: 0.99–1.39]). The results of meta-regression demonstrated that sample size (P = 0.046), age (P = 0.008), region (P = 0.004) might be the potential sources of heterogeneity and the percentage of male patients (P = 0.363), study design (P = 0.193), setting (P = 0.600), the methods for adjustment (P = 0.681) and the factors for adjustment (P = 0.082) might not be the potential sources of heterogeneity (Table S4). No publication bias was observed in Egger’s test (P = 0.077, Fig. 1E) and Begg’s test (P = 0.322, Fig. 1F).

Interstitial lung disease is a group of fibroinflammatory diseases affecting the alveolar interstitium, characterized by alveolar damage and interstitial thickening, which can lead to shortness of breath, cough, and eventual death from respiratory failure [15]. Studies have shown that viral infection is an important cause of interstitial lung disease and interstitial lung disease exacerbation, because respiratory virus infection can cause inflammation in lung tissue, although the mechanism by which the virus involved is triggered during disease progression is unclear [16]. More importantly, functional impairment and injury of pulmonary endothelial cells have been reported to be involved in the onset and development of interstitial lung disease, as well as in the pathogenesis and progression of COVID-19 [17–20]. Therefore, it is reasonable to speculate that interstitial lung disease increases the susceptibility and severity of COVID-19. Furthermore, our results indirectly support this hypothesis.

Several potential limitations exist in our meta-analysis. First, there is heterogeneity in our meta-analysis. Thus, we undertook subgroup analysis and meta-regression analysis to explore the cause of heterogeneity. The results of meta-regression suggested that sample size, age and region might contribute to the initial heterogeneity. Second, our combined effect size was calculated on the basis of adjusted effect estimates, all included studies were adjusted for demographic characteristics such as age and sex, and most also adjusted for underlying comorbidities such as hypertension, diabetes, cardiovascular diseases, and chronic respiratory diseases and so on, the factors for adjustment and methods for adjustment were not entirely consistent among the included studies. But further subgroups by the factors for adjustment and methods for adjustment yielded consistent results. Third, most of the studies we included were retrospectively designed, which may contain bias. Therefore, the interpretation of our results should be taken with caution.

In conclusion, this meta-analysis on the basis of adjusted effect estimates demonstrated that pre-existing interstitial lung disease was independently associated with significantly higher risk for COVID-19 severity and mortality. Further prospective cohort studies with bigger sample size should be done to confirm the results in the future. We hope that the current data will contribute to more accurate elaboration and substantiation of the findings reported by Ouyang et al [5].

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.

Table 1

| Author     | Country | Case (n) | Male (%) | Age (Mean/median) | Study design | Adjusted effect (95% CI) | Outcomes | Setting |
|------------|---------|----------|----------|-------------------|-------------|-------------------------|----------|---------|
| Esposito AJ| USA     | 138      | 34.8     | 69                | Retrospective study | 4.3 (1.4–14) | Mortality | Hospitalized patients |
| Drake TM   | UK      | 483      | 68.3     | 72.8              | Retrospective study | 1.6 (1.17–2.18) | Mortality | Hospitalized patients |
| Ji W       | Korea   | 7341     | 40.5     | 47.05             | Retrospective study | 5.332 (0.978–29.082) | Severity | All COVID-19 patients |
| Izzy S*    | USA     | 5190     | 46       | 52                | Cohort       | 1.36 (0.35–5.30) | Intensive care | Unit All COVID-19 patients |
| Izurieta HS| France  | 694      | 33.4     | 56.1              | Retrospective study | 2.87 (1.06–7.8) | Severity | All COVID-19 patients |
| Oh TK      | Korea   | 27,961   | 48.8     | 75                | Retrospective study | 1.08 (0.97–1.2) | Mortality | All COVID-19 patients |
| Mollado A* | USA     | NR       | NR       | NR                | NR          | 1.00 (0.68–1.46) | Mortality | All COVID-19 patients |
| Lee H      | Korea   | 8070     | 40.1     | NR                | Retrospective study | 2.23 (1.24–4.01) | Severity | All COVID-19 patients |
| Kokturk N  | Turkey  | 1500     | 57       | 51.89             | Retrospective study | 5.27 (1.17–23.8) | Mortality | All COVID-19 patients |
| Beltramo G | France  | 89,530   | 53.05    | 65                | Retrospective study | 1.2 (1.05–1.38) | Mortality | Hospitalized patients |
| Lu Y       | USA     | 63,201   | 42.2     | NR                | Retrospective study | 1.11 (0.99–1.11) | Mortality | Hospitalized patients |
| Sinvani L  | USA     | 4783     | 55.9     | 77.4              | Retrospective study | 3.35 (1.28–1.42) | Mortality | Hospitalized patients |
| Shields AM | UK      | 310      | NR       | NR                | Retrospective study | 0.54 (0.02–6.12) | Mortality | All COVID-19 patients |
| Boglione L | Italy   | 137      | 71       | 77                | Retrospective study | 7.223 (0.839–62.139) | Mortality | All COVID-19 patients |
| Bajpai J   | India   | 142      | 64.8     | 56                | Retrospective study | 52.839 (3.896–716.274) | Mortality | All COVID-19 patients |
Data availability

The data that support the findings of this study are included in this article and available from the corresponding author upon reasonable request.

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**Appendix A. Supplementary material**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2022.109088.

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