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The impact of COVID-19 infection on idiopathic pulmonary fibrosis mortality: a systematic review and meta-analysis

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Informed consent: not applicable.

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Availability of data and materials: the data used to support the findings of this study are available from the corresponding author upon request.

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Abstract

COVID-19 has a negative impact on the survival of respiratory patients, especially those with interstitial lung disease. This review aims to better understand the effect of COVID-19 on patients with idiopathic pulmonary fibrosis (IPF). A systematic search of MEDLINE, PubMed, Embase, and Scopus performed from December 2019 up to July 2024 identified relevant studies. Eligibility criteria included English language, sample size 10 patients, COVID-19 infection and outcome measures. Two independent reviewers assessed studies using the Newcastle-Ottawa Scale for bias and extracted data. Meta-analysis employed a random-effects model, and the Grading of Recommendations Assessment, Development and Evaluation assessed evidence quality. Outcomes considered were hospitalization, intensive care unit admission, and mortality.

Of the 1541 initially identified articles, 6 high-quality studies were included. Meta-analysis revealed a 34% mortality rate [95% confidence interval (CI): 21-48%], 36% hospitalization rate (95% CI: 10-75%), and 31% ICU admission rate (95% CI: 7-71%) among IPF patients with COVID-19. The certainty of evidence was low or very low due to publication bias and heterogeneity.

This study underscores the elevated risk of hospitalization and death in IPF patients with COVID-19, emphasizing the vulnerability of this population. Prompt and tailored care is crucial to mitigate the impact of COVID-19 on IPF patients, necessitating proactive measures, vaccination, and comprehensive management.

Key words: idiopathic pulmonary fibrosis, SARS-CoV-2, mortality, hospitalization, interstitial lung disease, COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), emerged in China in late 2019 [1,2]. Most COVID-19 infections are either asymptomatic or result in only mild disease. However, in a substantial proportion of persons, the infection leads to a respiratory illness requiring hospital care, which can progress to critical illness with hypoxemic respiratory failure and lead to prolonged ventilatory support [3,4].

Individuals of all ages are at risk for infection and severe disease, but COVID-19 has disproportionately affected frail older people, with high rates of mortality and symptom persistence in the long-term period [5,6]. Mortality is more than three and six times higher among patients aged 70 to 79 years and 80 years or older, respectively [7]. Moreover, underlying medical conditions, such as chronic lung disease, cardiovascular disease, obesity, chronic kidney disease, diabetes, smoking, cancer, solid organ or hematopoietic stem cell transplant, increase the risk of developing severe COVID-19 infection [8-10]. Even if the management of COVID-19 has made quick and considerable steps forward with the vaccines development and proven therapeutic options, namely antiviral medications, monoclonal antibodies and immunomodulatory agents [11], the presence of various comorbidities may limit the therapeutic potential of these medications [12].

Interstitial lung diseases (ILDs) include a heterogeneous group of pulmonary parenchymal disorders and are classified into those with an underlying disorder, such as autoimmune rheumatic diseases, with a known exposure, such as hypersensitivity pneumonitis, asbestosis, silicosis, and interstitial idiopathic pneumonias, of which idiopathic pulmonary fibrosis (IPF) is considered the archetypal [13]. IPF is a chronic respiratory disease, characterised by progressive lung scarring and loss of lung function [14], affecting elderly, frail individuals with a median age at diagnosis of 65 years [15]. The prognosis is poor, with a median survival of 3–5 years after diagnosis [16], and IPF is often accompanied by comorbidities that negatively impact survival [17].

The prognosis of COVID-19 patients with pre-existing ILD has been significantly worse than those without ILD [17-20]. Ouyang et al. showed that pre-existing ILD is associated with higher mortality and severe COVID-19 [21], according to Stokes et al. COVID-19 patients with pre-existing medical conditions were hospitalised six times higher than those without (45.4% vs. 7.6%) [22], and approximately 30-40% of the IPF patients die due to other comorbidities, such as infectious diseases [23,24].

Even if different studies have focused on the impact of COVID-19 on ILD patients, only a few data are available about the impact of COVID-19 on IPF mortality.

Our systematic review and meta-analysis aim to describe the probability of hospitalization, ICU admission and mortality of IPF patients with concomitant COVID-19 infection.

Methods

The study was conducted in accordance with a prespecified protocol (PROSPERO registration number CRD42023339808) and has been reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data guidelines [25].

Search strategy and selection criteria

We performed a systematic search of literature indexed on MEDLINE, PubMed, Embase and Scopus (from 1st December 2019 to 31st July 2024), and citations were screened using EndNote x8 (Clarivate Analytics). Searches were carried out using patient-related, exposure-related and outcomes-related terms. The complete search strategy is provided in *Supplementary Material – Appendix A.*

Two reviewers (UZ and DC) independently screened the records' titles and abstracts retrieved through database searches. No article-type restrictions were applied. We considered only articles in English. We also performed a manual search to include additional relevant articles using the reference lists of key articles. Full texts of records recommended by at least one reviewer were screened independently by the same two reviewers and assessed for inclusion in the systematic review. Disagreements between reviewers were solved by consensus. Data from the selected articles were extracted independently by reviewers and mutually confirmed to ensure accuracy and consistency.

Data extraction and quality assessment

Extracted data included the first author's name, publication date, country of origin, study design, gender distribution, and average age. We extracted the number of patients with outcomes of hospitalization, ICU admission, and death among patients diagnosed with both IPF and COVID-19, encompassing all levels of infection severity.

To assess the risk of bias, we followed the Newcastle-Ottawa scale (NOS). The NOS encompasses three fundamental aspects: selection, comparability, and outcome assessment [26]. Each study was assigned a score ranging from 0 to 9, with higher scores indicating superior quality. Based on these scores, we categorized the studies as low (0–3), moderate (4–6), or high (7–9) quality, respectively.

The quality of the evidence for each overall rate estimate was evaluated using the GRADE guidance [27]. Analytical and publication risks of bias, inconsistency, indirectness, and

imprecision in reporting were assessed. An overall judgement of ‘high’, ‘moderate’, ‘low’, or ‘very low’ was provided for the quality of the cumulative evidence for review outcomes.

Statistical analysis

We included in the meta-analysis studies that utilised the same outcome measures. In order to support the precision of our meta-analysis, we excluded studies with a sample size of less than 10 patients. We also used exact or Clopper-Pearson confidence limits for binomial proportions (probabilities) to address the nature of the data. A random-effects model was employed to combine the data, and the pooled estimate was calculated using the DerSimonian-Laird method based on the transformed values and their variances. Heterogeneity was assessed using the I-squared statistic, with an I-squared value exceeding 50% indicative of substantial heterogeneity. We employed a funnel plot and conducted an Egger test to evaluate publication bias. All statistical analyses were conducted using the "meta" package in the R software. R's "metaprop" command was used to calculate pooled proportion estimates for different outcomes with a 95% confidence interval. A p-value below 0.05 was considered statistically significant in all analyses.

Results

The keywords described in the appendix were used for the database searches. We purposively chose broad keywords in order to include all reports potentially useful for the purpose of this review. SCOPUS, PubMed, Embase, and ISI WOS were used simultaneously for the search.

Initially, the search process yielded 1541 articles. After removing 780 duplicates, 761 articles remained. These were then evaluated based on their titles, resulting in the exclusion of 657 articles. The remaining 104 articles were subjected to a thorough screening of their abstracts, where 55 were deemed inadequate for these review purposes and excluded. Further screening of the full texts of the remaining 49 articles resulted in the exclusion of 42 studies due to irrelevant outcome or lack of data.

After rigorous screening, seven manuscripts were included in the qualitative analysis, while only six of them were included in the meta-analysis, as one of these was excluded due to the low sample size [28]. Among the six articles included in the meta-analysis, five were retrospective cohort studies [29-33] and one was a prospective cohort study [34]. For a more detailed overview of the screening process, please refer to Figure 1.

The main characteristics of the included studies regarding the specific outcomes are shown in Table 1. Table 2 shows the analysis of the risk of bias based on the Newcastle-Ottawa Scale (NOS). According to NOS, all the studies analysed were of moderate quality. Given the absence of a non-exposed cohort in the research question, the maximum score obtainable by

a single study would be 6 points. All studies confirmed that the exposed group was adequately represented and the exposure assessment was appropriate. All studies demonstrated that the outcome of interest was absent at the start of the study. Outcome assessment and follow-up duration were deemed satisfactory, but a lack of consistency in follow-up was observed.

We identified a risk of publication bias based on funnel plot analysis and Egger's test. There was high heterogeneity for each outcome assessed, although the test was not statistically significant (*Supplementary Figure 1*).

All studies conducted in 5 different countries were included in the analysis for the death and the hospitalization, as shown in Table 1, while 3 studies were used for ICU admission. According to the research findings, the probability of mortality among patients with COVID-19 and IPF was 34% (95% CI: 21%-48%, I^2=90%, random-effects model; Figure 2). 36% (95% CI 10%-75%, I^2=100%, random-effects model; Figure 2) of the patients analyzed were hospitalized. Among the hospitalized patients, 31% (95% CI 7%-71%, I2=95%, random-effects model; Figure 2) needed intensive care.

Despite a consistent direction of effect across studies, all the outcomes showed high heterogeneity in the pooled results. Most studies indicate a large or moderate effect size with a wide confidence interval, indicating imprecision.

Certainty of evidence

We used the GRADE to assess the certainty of evidence (Table 3). The outcomes of interest were reported by six studies, consisting of five retrospective and one prospective cohort. The overall quality ratings for the impact of SARS-CoV2 on IPF patients' mortality, hospitalization, and ICU admission were low or very low.

Discussion and Conclusions

This systematic review and meta-analysis highlighted that patients with IPF who were affected by SARS-CoV-2 have a higher risk of death compared to the general population and has a significant impact on their prognosis. The study also showed that a significant number of IPF patients who tested positive for SARS-CoV-2 required intensive medical care, with more than one in three experiencing hospitalization that resulted in a notable impact on their respiratory health and mortality. Almost one in three patients required ICU admission, indicating the severity of their clinical status. These findings highlight the pressing need for prompt and appropriate care for IPF patients affected by COVID-19, as their condition can rapidly worsen and become life-threatening.

Our review focusing on IPF aligns with the current body of evidence on other ILDs, reinforcing the findings of Ouyang et al., who observed a significant trend in patients with ILD affected by

SARS-CoV-2, reporting a mortality rate that exceeds twice that of individuals without ILD [21]. While the general population mortality rates varied across countries, they ranged from 0.1% to 4.9%, which is markedly lower than what we found in our meta-analysis. Additionally, even if compared with the general population over 60 with COVID-19, the mortality rates in our meta-analysis are markedly higher, emphasizing IPF's impact on infection [35,36]. Notably, our data also suggests that patients with IPF are particularly prone to SARS-CoV-2 infection and experienced an even higher mortality rate, that can be attributed to their comorbidities, such as older age, heart failure or diabetes, and reduced respiratory function associated with ILD [7,8].

According to our results, ICU admission due to SARS-CoV-2 in IPF patients is higher compared to the border population over 60 years old hospitalized with COVID-19 infection [37]. It is well-known that patients admitted to ICU showed a higher mortality rate compared to those who do not require advanced care. According to a study conducted by Auld and colleagues, the global mortality rate of ICU patients is 29%, with older patients and those with comorbidities appeared to be the most affected [38]. Among the reported comorbidities in COVID-19 patients hospitalized in ICU, IPF was found to be a significant proportion [38]. While the IPF prevalence in ICU patients with SARS-CoV-2 infection was lower than that of hypertension or diabetes, it was still higher than in kidney diseases, congestive heart failure, and cerebrovascular disease [39]. Therefore, it is crucial to identify SARS-CoV2 infection in IPF patients and provide appropriate care. In fact, several studies underlined that prompt antiviral therapy improved outcomes in patients infected by SARS-CoV- 2 [40-42], as shown by Ganatra et al. who reported that patients treated with nirmatrelvir-ritonavir were associated with a lower rate of emergency department visits, hospitalization, and death compared to controls matched for age, gender, race, and comorbidities [43]. Access to ICUs and the management of COVID-19 can significantly vary by region, impacting outcomes for IPF patients. Disparities in ICU access and management strategies for IPF patients with COVID-19, influenced by healthcare policies and the pandemic's impact, could affect mortality rates. Understanding these variations is crucial for tailoring interventions to improve patient outcomes [44].

Furthermore, our findings highlight on the impact of COVID-19 on IPF, particularly in terms of hospitalization rates. According to Stokes et al., patients with comorbidities such as respiratory diseases showed hospitalization rates six times higher than those without comorbidities [22]. This emphasizes the need for strict follow-up and management of IPF patients to prevent disease progression and improve outcomes. By implementing proactive measures, healthcare providers can reduce the number of people with respiratory conditions admitted to hospitals. Improved monitoring and intervention protocols can lower the risk of

hospitalization, slow the progression of diseases, and ultimately result in better patient outcomes. A personalized and comprehensive approach to caring IPF patients is critical in the management of COVID-19, protecting public health, and minimizing hospital admissions.

Some limitations should be considered. First of all, the studies were conducted in different countries and years, and this could be a source of bias for the incidence of IPF, data collection, and the standard of therapy. The limited number of studies and their heterogeneity could be explained by the recent onset of the pandemic and the rare incidence of IPF among the overall population. Additionally, our study period coincided with the introduction of COVID-19 vaccines and the emergence of new variants, factors which could influence outcomes. Unfortunately, another limitation is that it was impossible to thoroughly assess the impact of therapies received by the enrolled IPF patients as the necessary information was largely absent in the reference papers available at the time. We identified an area that needs improvement, which was the low or very low-quality rating of the outcomes analyzed through the GRADE assessment. Despite the poor rating, we conducted a thorough revision of the outcomes based on the latest literature available.

In conclusion, this systematic review and meta-analysis underline the relevant impact of COVID-19 on IPF patients, leading to a higher risk of death in IPF patients compared to the general population, in consideration of the vulnerability of IPF patients to SARS-CoV-2 infection. Healthcare providers should consider the management of IPF patients, implementing measures to prevent the spread of the virus among them and improve patient outcomes through vaccination and other good clinical practices aimed to preventing respiratory infections. Further research and clinical studies are needed to better understand the influence of SARS-CoV-2 and other respiratory infections may have on IPF patients and, more generally, on patients affected by interstitial lung disease.

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Online supplementary material:
Supplementary Figure 1. Funnel plot of the systematic review and meta-analysis of hospitalization, intensive care unit admission, and mortality.
Appendix A. Queries used for the search.

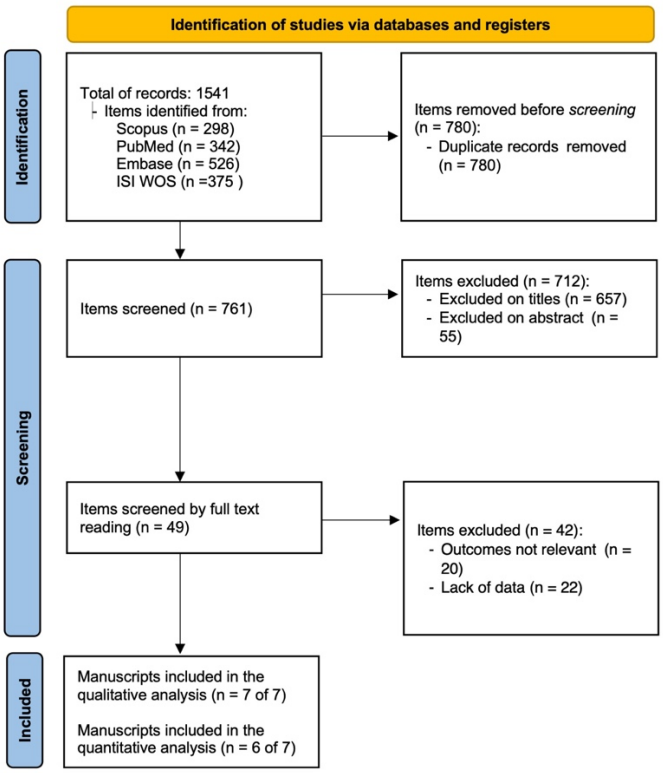

Figure 1. PRISMA flowchart of included and excluded studies.

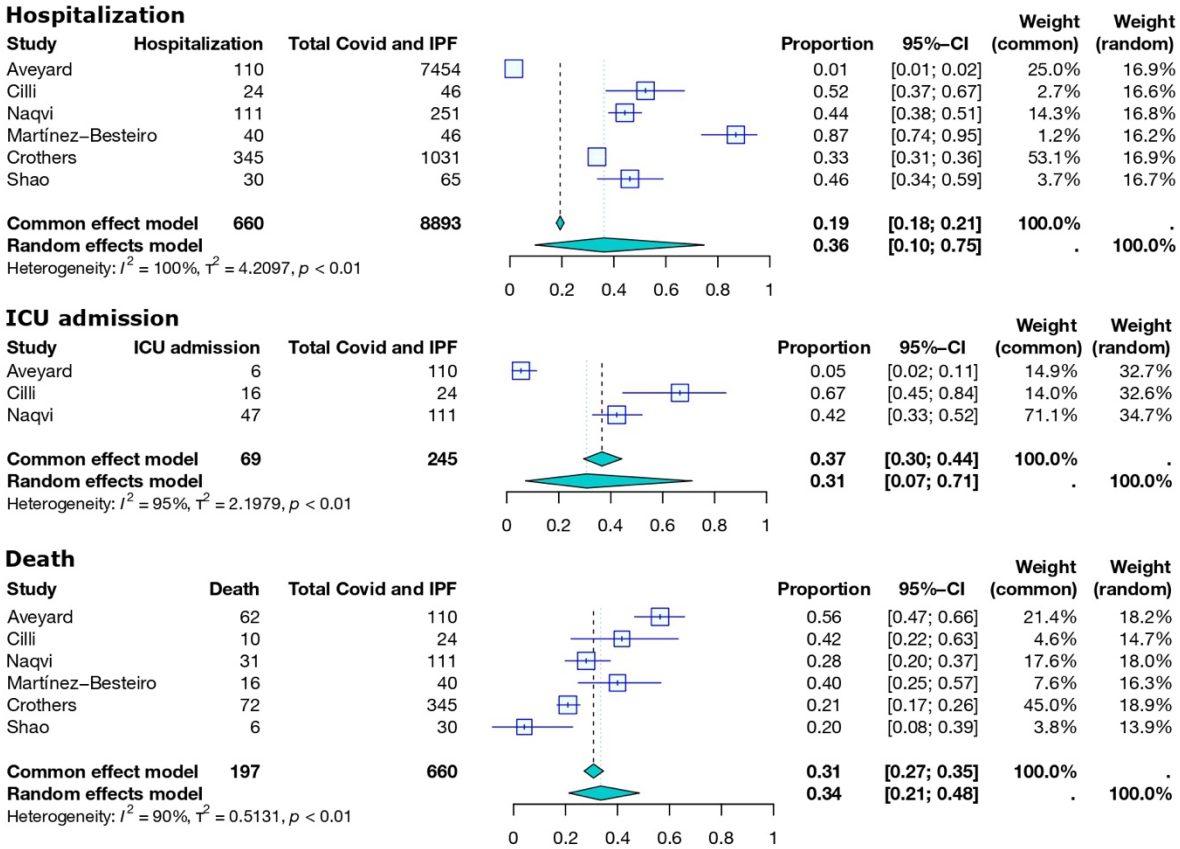

Figure 2. Analysis of the systematic review and meta-analysis of hospitalization, intensive care unit admission, and mortality. IPF, idiopathic pulmonary fibrosis; ICU, intensive care unit; CI, confidence interval.

Table 1. Summary of the studies selected in the systematic review and meta-analysis.

Authors	Year	Study design	Country	Population	Patients with outcomes	Sample size	Female n, (%)	Age (years), mean (SD)	Comorbidity n, (%)	
									Hypertension	Diabetes mellitus
Aveyard *et al.*	2021	Prospective Cohort	England	Community	110^{H}-6^{I}-62^{D}	7454 (110)*	-	-	-	-
Cilli *et al.*	2022	Retrospective Cohort	Turkey	Hospital	24^{H}-16^{I}-10^{D}	46 (24)*	13 (28.3)	65	19 (41.30)	9 (19.56)
Naqvi *et al.*	2021	Retrospective Cohort	USA	Hospital	111^{H}-47^{I}-31^{D}	251 (111)*	108 (43.03)	68.3	200 (79.68)	127 (50.60)
Kondoh *et al.*	2021	Retrospective Cohort	Japan	Hospital	3^{D}	5	1 (20)	74.6	-	-
Martinez-Besteiro *et al.*	2023	Retrospective Cohort	Spain	Hospital	40^{H}-16^{D}	46 (40)*	10 (21.7)	71	24 (52.2)	13 (28.3)
Crothers *et al.*	2024	Retrospective Cohort	USA	Hospital	345^{H}-72^{D}	1031 (345)*	-	73	-	-
Shao *et al.*	2023	Retrospective Cohort	China	Hospital	30^{H}-6^{D}	65 (30)*	-	-	-	-

SD, standard deviation. Quantitative synthesis, outcomes reported: H, hospitalized among idiopathic pulmonary fibrosis (IPF) and Covid-19 patients; I, intensive care unit admission among IPF and COVID-19 patients; D, death among IPF and COVID-19 patients. *Hospitalized population affected by COVID and IPF.

Table 2. Evaluation of the risk of bias according to the Newcastle-Ottawa scale.

Study	Items&score								
	Representativeness of the exposed cohort (1)	Selection of the non exposed cohort (1)	Ascertainment of exposure (1)	Demonstration that outcome of interest was not present at start of study (1)	Comparability of cohorts on the basis of the design or analysis (2)	Assessment of outcome (1)	Was follow-up long enough for outcomes to occur (1)	Adequacy of follow up of cohorts (1)	Total
Aveyard	1	NA	1	1	NA	1	1	NA	5 (moderate)
Cilli	1	NA	1	1	NA	1	1	NA	5 (moderate)
Naqvi	1	NA	1	1	NA	1	1	NA	5 (moderate)
Martinez-Besteiro *et al.*	1	NA	1	1	NA	1	1	NA	5 (moderate)
Crothers *et al.*	1	NA	1	1	NA	1	1	NA	5 (moderate)
Shao *et al.*	1	NA	1	1	NA	1	1	NA	5 (moderate)

NA, not applicable.

Table 3. Grading of recommendations assessment, development and evaluation summary of findings table.

Summary of findings							Quality rating
Design (number of studies)	**Limitations (risk of bias)**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Pooled estimates (95% CI)**	
Hospitalization							
6 studies: • 5 retrospective cohort studies • 1 prospective cohort study	-Few studies demonstrated that the outcome of interest was absent at the start of the study.	High heterogeneity observed (as measured by the I 2=100% statistic for pooled results)	Highly variable in the population included in the studies (respiratory diseases, including IPF, vs IPF).	Moderate effect size with wide confidence interval seen across most studies	Potential publication bias present as measured by funnel plot	36% (10-75%)	⊕◯◯◯ Very Low
ICU admission							
3 studies: • 2 retrospective cohort studies • 1 prospective cohort study	-Few studies demonstrated that the outcome of interest was absent at the start of the study.	High heterogeneity observed (as measured by the I 2=95% statistic for pooled results)	Highly variable in the population included in the studies (respiratory diseases, including IPF, vs IPF).	Moderate effect size with wide confidence interval seen across most studies	Potential publication bias present as measured by funnel plot	31% (7-71%)	⊕◯◯◯ Very Low
Mortality							
6 studies: • 5 retrospective cohort studies • 1 prospective cohort study	-Few studies demonstrated that the outcome of interest was absent at the start of the study.	High heterogeneity observed (as measured by the I 2=90% statistic for pooled results)	Highly variable in the population included in the studies (respiratory diseases, including IPF, vs IPF).	Large effect size with narrow confidence interval seen across most studies	Potential publication bias present as measured by funnel plot	34% (21-48%)	⊕⊕◯◯ Low

CI, confidence interval; IPF, idiopathic pulmonary fibrosis.