PULMONOLOGY JOURNAL

Pulmonology

ISSN: 2531-0429 (Print) 2531-0437 (Online) Journal homepage: www.tandfonline.com/journals/tpul20

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To cite this article: Rémi Diesler, Laure Gallay, Yurdagül Uzunhan, Raphaël Borie, Martine Reynaud-Gaubert, Victor Valentin, Kaïs Ahmad, Romain Lazor, Lidwine Wemeau, Julie Traclet, Pierre Rigaud, Sylvain Marchand-Adam, Dominique Israël-Biet, Sandrine Hirschi, Philippe Bonniaud, Antoine Froidure, David Montani, Jean-Marc Naccache, Nicolas Romain-Scelle, Vincent Cottin & the OrphaLung Network (2025) Risk of hospitalisation and mortality among patients with interstitial lung disease and COVID-19: A French multicentre prospective cohort, Pulmonology, 31:1, 2598693, DOI: 10.1080/25310429.2025.2598693

To link to this article: https://doi.org/10.1080/25310429.2025.2598693

PULMONOLOGY
2025, VOL. 31, NO. 1, 2598693
https://doi.org/10.1080/25310429.2025.2598693

Risk of hospitalisation and mortality among patients with interstitial lung disease and COVID-19: A French multicentre prospective cohort

Rémi Diesler[a,b*], Laure Gallay[c*], Yurdagül Uzunhan[d], Raphaël Borie[e,f], Martine Reynaud-Gaubert[g,h], Victor Valentin[i], Kaïs Ahmad[a], Romain Lazor[j], Lidwine Wemeau[i], Julie Traclet[a], Pierre Rigaud[k], Sylvain Marchand-Adam[l], Dominique Israël-Biet[m], Sandrine Hirschi[n], Philippe Bonniaud[o], Antoine Froidure[p], David Montani[q], Jean-Marc Naccache[r], Nicolas Romain-Scelle[s], Vincent Cottin[a,b,t] and the OrphaLung Network

[a]National Reference Centre for Rare Pulmonary Diseases, Hôpital Louis Pradel, Hospices Civils de Lyon, Lyon, France; [b]ERN-LUNG, UMR 754, Université Claude Bernard Lyon 1, Lyon, France; [c]Service de Médecine Interne, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France; [d]Pneumology Department, Reference Centre for Rare Pulmonary Diseases, Hôpital Avicenne, APHP and Université Sorbonne Paris Nord, Bobigny, France; [e]Université Paris Cité, INSERM, PHERE, Paris, France; [f]Service de Pneumologie, AP-HP, Hôpital Bichat, Paris, France; [g]CHU de Marseille, Competence Centre for Rare Pulmonary Diseases, Marseille, France; [h]Aix Marseille University, Marseille, France; [i]CHU Lille, Constitutive Reference Centre for Rare Pulmonary Diseases, Lille, France; [j]Service de Pneumologie, Centre Hospitalier Universitaire Vaudois Et Université de Lausanne, Lausanne, Suisse; [k]Pulmonology Department, Centre Hospitalier de la Côte Basque, Bayonne, France; [l]CHU Tours, Constitutive Reference Center for Rare Pulmonary Diseases, Inserm, Tours, France; [m]Professeur émérite de Pneumologie, Université Paris Cité, Paris, France; [n]Pneumology, Competence Centre for Rare Pulmonary Diseases, Strasbourg University Hospital, Strasbourg, France; [o]Reference Constitutive Centre for Rare Pulmonary Diseases, Pulmonary Medicine and Intensive Care Unit Department, Dijon University Hospital, Burgundy University, Dijon, France; [p]Pulmonology Department, Cliniques Universitaires Saint-Luc, Institut de Recherche Expérimentale Et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium; [q]Université paris–Saclay, AP-HP, INSERM UMR_S 999, Department of Respiratory and Intensive Care Medicine, Hôpital de Bicêtre, Le Kremlin Bicêtre, France; [r]Service de Pneumologie-Allergologie-Oncologie Thoracique, Centre de compétence des Maladies Pulmonaires Rares, Hôpitaux Paris Saint-Joseph Et Marie-Lannelongue, France; [s]Biostatistics-Bioinformatics Unit, Hospices Civils de Lyon, Lyon, France; [t]Laboratory of Biometry and Evolutionary Biology, Université Claude Bernard Lyon 1, Lyon, France

ABSTRACT

Introduction and Objectives: Risk factors of poor outcomes associated with COVID-19 are not well identified in patients with interstitial lung disease (ILD).

Patients or Materials and Methods: We analysed a multicentre prospective cohort of patients with ILD and COVID-19 from January 2020 to December 2022. Risk factor analysis for death at 90 days and hospitalisation was conducted using logistic regression, adjusted for age and sex.

Results: A total of 603 patients were included (66 years [54–74], 62% male). ILD diagnoses were autoimmune ILD ($n = 147$ [24%]), idiopathic pulmonary fibrosis (IPF, $n = 124$ [21%]), non-IPF fibrosing ILD ($n = 118$ [20%]), granulomatosis ($n = 115$ [19%]), exposure-related/secondary ILD ($n = 68$ [11%]), and other rare lung diseases ($n = 31$ [5%]). Hospitalisation due to COVID-19 was associated with cardiovascular disease, cancer or haematological disease, background glucocorticoid therapy, $DL_{CO} < 40\%$pred and $FVC < 70\%$pred. Death due to COVID-19 at day 90 was associated with the underlying ILD diagnosis, background glucocorticoid therapy, cardiovascular disease, cancer or haematological disease, and $DL_{CO} < 40\%$pred, whereas vaccination against SARS-CoV-2 was protective. COVID-19-related mortality occurred mainly in the first 90 days after SARS-CoV-2 infection.

Conclusions: Poor outcomes related to COVID-19 are associated with ILD subtype and severity, background glucocorticoid therapy and absence of vaccination. There is no evidence of late mortality.

ARTICLE HISTORY
Received 20 December 2024
Accepted 23 November 2025

KEYWORDS
Interstitial lung disease; SARS-CoV-2; prognosis; mortality; hospitalisation

Introduction

Coronavirus Disease 2019 (COVID-19) is a viral pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can present as an asymptomatic infection but can also lead to respiratory

CONTACT Rémi Diesler remi.diesler01@chu-lyon.fr; rdiesler@bwh.harvard.edu
*Authors contributed equally.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/25310429.2025.2598693

failure and death.[1] Interstitial lung diseases (ILD) are a large and heterogeneous group of diseases characterised by the infiltration of inflammatory cells and/or extracellular matrix components into the lung interstitium. Idiopathic interstitial pneumonias are a subset of ILD of unknown cause, among which idiopathic pulmonary fibrosis (IPF) is the most common and the most lethal.[2,3] A proportion of various ILD subtypes can present with a progressive fibrosing phenotype.[3,4]

Increasing age, male sex, and comorbidities (diabetes mellitus type 2, hypertension, ischaemic heart disease, and obesity) have been associated with increased COVID-19 severity in various populations,[5–7] patients with chronic lung diseases being particularly vulnerable.[8–10] Since ILD results in a reduced respiratory reserve as well as a frequent use of immunosuppressive therapy, and that patients with ILD commonly present with comorbidities associated with COVID-19 severity, they are particularly susceptible to COVID-19.[11–13] Moreover, patients with ILD (and especially fibrotic ILD) can present with acute exacerbation of the disease, with dismal prognosis and known triggering factors, including viral infections.[14] It is known that the risk of hospitalisation and mortality from SARS-CoV-2 infection is increased in patients with ILD,[11,15–19] but factors associated with higher hospitalisation and death rates are not well described. Moreover, the long-term consequences of COVID-19 are poorly understood in this population.[20,21] We therefore investigated the risk factors of hospitalisation and/or death, and the long-term outcomes of COVID-19 in a large nationwide cohort of patients with ILD.

Methods

This observational, prospective, multicentre study was conducted within the French national network for rare adult lung diseases (OrphaLung), with the participation of one centre in Belgium and one in Switzerland. All consecutive patients with pre-existing ILD who presented with SARS-CoV-2 infection in the study period were prospectively declared to the coordinating site; queries were sent subsequently for missing data and mortality during follow-up. The first cases were included from 10 January 2020 (date of the outbreak in France) to 28 May 2020 (Study period 1) and were the subjects of a previous work;[19] the subsequent cases were included between 29 May 2020 and 21 December 2022 (Study period 2). Epidemic waves were defined as follows: first wave from the outbreak in France to 15 June 2020, second wave from 16 June 2020 to 3 December 2020, third wave from 4 December 2020 to 24 June 2021, and fourth wave from 25 June 2021 to 21 December 2022 (www.insee.fr). Patients who underwent lung transplantation before SARS-CoV-2 infection were excluded. Data collected comprised demographics, comorbidities, pulmonary function test results in stable condition prior to COVID-19, treatment received for ILD and COVID-19, and hospitalisation data (conventional care or intensive care unit [ICU], supplemental oxygen therapy, mechanical ventilation). The primary outcome was death, censored at 90 days post-COVID-19 diagnosis. No imputation was used for missing data. SARS-CoV-2 infection was confirmed by the presence of a positive polymerase chain reaction test result or the combination of clinical symptoms with typical features on chest computed tomography (CT) and a positive IgM serology result for SARS-CoV-2. Patients were classified according to the underlying ILD diagnosis: IPF, non-IPF fibrosing ILD (including idiopathic non-specific interstitial pneumonia, unclassifiable fibrosing ILD, combined pulmonary fibrosis and emphysema, smoking-related interstitial fibrosis, respiratory bronchiolitis with ILD), autoimmune ILD (including connective tissue disease-associated ILD, interstitial pneumonia with autoimmune features, vasculitis-associated ILD), exposure-related/secondary ILD (pneumoconiosis including silicosis and asbestosis, hypersensitivity pneumonitis, drug-related ILD, pleuroparenchymal fibroelastosis, desquamative interstitial pneumonia), granulomatosis (including sarcoidosis and pulmonary Langerhans cell histiocytosis), and other rare lung diseases (including eosinophilic lung diseases, pulmonary amyloidosis, lymphangioleiomyomatosis, Birt-Hogg-Dubé syndrome, alveolar proteinosis and alveolar microlithiasis). ILD diagnoses were reported by the declaring physicians, based on the conclusion of local multidisciplinary discussions. Descriptive data were expressed as median (interquartile range [IQR]) or counts (percentage), whichever was appropriate. Statistical testing was conducted using the Kruskal-Wallis rank-sum test for continuous variables and the Pearson's Chi^2 test or Fisher's exact test, as appropriate. Risk factor analysis for death at 90 days and hospital admission was conducted using a two-step logistic regression, including age at diagnosis and sex as potential confounders. Putative risk factors were selected before analysis based on expert opinion. The estimated effect size was calculated using risk ratios with their 95% confidence interval (95% CI). Survival analyses were performed according to the Kaplan-Meier

method, using the log-rank test to compare survival across strata. The crude mortality rate for the first 90 days was estimated using penalised splines in the R *survPen* package[22]. The 'other rare lung diseases' category was not included in the survival analysis according to ILD diagnosis due to the considerable diagnostic heterogeneity within this category. The statistical analysis was conducted using R (version 4.3.3) with package *marginaleffects* for risk ratios computation. The study was approved by the Hospices Civils de Lyon institutional review board and was registered within the French data protection authority (*Commission Nationale de l'Informatique et des Libertés*, number 20–059). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Results

Patient characteristics

Overall, 603 patients were included (Table 1, Figure A1 in the Supplementary Appendix). The median age was 66 years (54–74) and 62% were male. The ILD diagnoses were IPF ($n = 124$ [21%], median age 73 years [66–79]), non-IPF fibrosing ILD ($n = 118$ [20%], median age 69 years [60–77]), autoimmune ILD ($n = 147$ [24%], median age 62 years [52–70]), exposure-related ILD ($n = 68$ [11%], median age 69 years [62–76]), granulomatoses ($n = 115$ [19%], median age 53 years [43–62]), and other rare lung diseases ($n = 31$ [5.1%], median age 53 years [41–66]). COVID-19 diagnosis was performed using positive RT-PCR in 565 patients (94%). Comorbidities previously associated with poor outcomes in patients with SARS-CoV-2 infection were frequent (Table 1). The vaccination against SARS-CoV-2 was only reported in 63 patients (10%), and missing data was considered as no vaccination.

Lung function

The pulmonary function test results are presented in Table 2. Overall, 186 (31%) patients had a forced vital capacity (FVC) < 70%pred, and among them, 64 (11%) patients had FVC < 50%pred. A total of 367 (61%) patients had a reduced diffusing lung capacity for carbon monoxide (DL_{CO}), of whom 247 (41%) patients had a DL_{CO} < 50%pred.

ILD treatment

Prior to SARS-CoV-2 infection, patients were treated with glucocorticoids ($n = 238$, 40%), immunosuppressive therapy ($n = 179$, 30%), and antifibrotic medication ($n = 100$, 17%). Regarding immunosuppressive therapy, 65 (11%) patients received mycophenolate mofetil (MMF), 40 (6.6%) rituximab, 39 (6.5%) methotrexate, 18 (3.0%) hydroxychloroquine, 17 (2.8%) azathioprine, 11 (1.8%) tacrolimus or sirolimus, and 9 (1.5%) cyclophosphamide. There were 4 (0.7%) patients who received intravenous immunoglobulins.

Table 1. Patient characteristics.

	Overall ($n = 603$)	IPF ($n = 124$)	Non-IPF fibrosing ILD ($n = 118$)	Autoimmune ILD ($n = 147$)	Exposure-related ILD ($n = 68$)	Granulomatosis ($n = 115$)	Other rare lung diseases ($n = 31$)
Median (IQR) age, years	66 (54–74)	73 (66–79)	69 (60–77)	62 (52–70)	69 (62–76)	53 (43–62)	53 (41–66)
Obesity, n (%)	147 (24.4)	25 (20.2)	27 (22.9)	39 (26.5)	17 (25)	35 (30.4)	4 (12.9)
Diabetes, n (%)	143 (23.7)	34 (27.4)	28 (23.7)	35 (23.8)	18 (26.5)	25 (21.7)	3 (9.7)
Systemic hypertension, n (%)	188 (31.2)	41 (33.1)	36 (30.5)	44 (30)	25 (36.8)	35 (30.4)	7 (22.6)
Cardiovascular disease, n (%)	157 (26)	45 (36.3)	42 (35.6)	31 (21.1)	23 (33.8)	13 (11.3)	3 (9.7)
Cancer or haematological disease (active or in remission), n (%)	48 (8)	13 (10.5)	16 (13.6)	7 (4.8)	8 (11.8)	3 (2.6)	1 (3.2)
Chronic kidney disease, n (%)	43 (7.1)	11 (8.9)	9 (7.6)	12 (8.2)	5 (7.4)	5 (4.3)	1 (3.2)

IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; IQR, interquartile range.

Table 2. Last available pulmonary function tests before COVID-19.

	Overall ($n = 603$)	IPF ($n = 124$)	Non-IPF fibrosing ILD ($n = 118$)	Autoimmune ILD ($n = 147$)	Exposure-related ILD ($n = 68$)	Granulomatosis ($n = 115$)	Other rare lung diseases ($n = 31$)
Median (IQR) FVC % pred	79 (60–93)	77 (62–90)	74 (58–92)	78 (57–95)	74 (55–87)	85 (65–97)	85 (83–100)
FVC > 70%pred, n (%)	295 (48.9)	62 (50)	47 (39.8)	68 (46.3)	33 (48.5)	68 (59.1)	17 (54.8)
70%pred ≥ FVC ≥50% pred, n (%)	132 (21.9)	37 (29.8)	25 (21.2)	34 (23.1)	14 (20.6)	20 (17.4)	2 (6.5)
FVC < 50%pred, n (%)	64 (10.6)	8 (6.5)	15 (12.7)	22 (15)	10 (14.7)	7 (6.1)	2 (6.5)
Median (IQR) FEV1	76 (60–92)	80 (63–95)	75 (61–90)	73 (55–92)	73 (56–91)	78 (67–92)	78 (51–92)
Median (IQR) DLco	47 (33–62)	41 (31–55)	45 (30–59)	45 (32–61)	43 (38–57)	60 (47–76)	52 (44–83)
DLco > 70%pred, n (%)	78 (12.9)	10 (8.1)	8 (6.8)	20 (13.6)	5 (7.4)	28 (24.3)	7 (22.6)
70%pred ≥ DLco ≥50%pred, n (%)	120 (19.9)	20 (16.1)	26 (22)	27 (18.4)	14 (20.6)	29 (25.2)	4 (12.9)
DLco < 50%pred, n (%)	247 (41)	63 (50.8)	43 (36.4)	68 (46.3)	33 (48.5)	32 (27.8)	8 (25.8)

IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; FVC, forced vital capacity; IQR, interquartile range, FEV1, forced expiratory volume in 1 second; DL_{CO}, diffusing lung capacity of carbon monoxide.

Treatment of COVID-19

Regarding the medications reported for the treatment of SARS-CoV-2 infection, 253 (42%) patients received glucocorticoids, 131 (22%) anticoagulants, 38 (6.3%) azithromycin, 8 (1.3%) tocilizumab, and 4 (0.7%) remdesivir.

Outcomes

Hospitalisation

A total of 390 (65%) patients were hospitalised for COVID-19 and 121 (20%) were admitted in an ICU. On univariable logistic analysis, the probability of hospitalisation was associated with male sex, increasing age, background glucocorticoid therapy, cardiovascular disease, cancer or haematological disease, DL_{CO} < 40% pred, and FVC < 70%pred (Table 3). In the multivariable logistic analysis, cardiovascular disease, cancer or haematological disease, background glucocorticoid therapy, DL_{CO} < 40%pred, and FVC < 70%pred remained independently predictive of the hospitalisation risk (Table 3). In the multivariable model adjusted for age and sex, ICU hospitalisation was associated with cardiovascular disease (RR 1.48, 95% CI [1.02–2.14], $p = 0.039$) and background glucocorticoid therapy (RR 1.73, 95% CI [1.17–2.56], $p = 0.006$).

Mortality

On day 30, 106 (18%) patients had died, while on day 90, 130 (22%) had died. Figure 1 shows the crude death rates during the first 90 days after COVID-19 diagnosis. $N = 494$ cases were complete for the analysis of the death at day 90, with 15 missing data on the outcome and notably 89 for obesity status. On univariable logistic analysis, the probability of death at day 90 was associated with increasing age, antifibrotic therapy, absence of vaccination against SARS-CoV-2, background glucocorticoid therapy, cardiovascular disease, cancer or haematological disease, DL_{CO} < 40%pred, and FVC < 70%pred (Table 3). In the multivariable logistic analysis, a diagnosis of IPF or non-IPF fibrosing ILD, background glucocorticoid therapy, cardiovascular disease, cancer or haematological disease, and DL_{CO} < 40%pred were independently associated with higher mortality at day 90, whereas vaccination against SARS-CoV-2 remained protective (Table 3). When exploring outcomes regarding the ILD category in the univariable model, the association between lower FVC, lower DL_{CO}, and death remained significant only in patients with IPF and non-IPF fibrosing ILD (IPF patients, RR = 1.99 [1.33–2.98], $p < 0.001$ for FVC%pred and RR = 2.10 [1.41–3.12], $p < 0.001$ for DLCO%pred; non-IPF fibrosing ILD patients, RR = 2.12 [1.17–3.82], $p = 0.013$ for FVC%pred and RR = 3.14 [1.74–5.65], $p < 0.001$ for DLCO%pred). As survival did not differ between the different epidemic waves (log-rank test for survival difference between the four waves = 0.5; Figure A2 in the Supplementary Appendix), this ecological variable (i.e not related to intrinsic characteristics of the patient) was not included in the analysis.

Table 3. Logistic univariable and multivariable analyses of the risk of hospitalisation and the risk of death at day 90 in patients with Interstitial Lung Disease (ILD) and SARS-CoV-2 infection.

Outcome	Variable	Univariable* analysis		Multivariable analysis	
		RR (95% CI)	*P* value	RR (95% CI)	*P* value
Hospitalisation	Sex (M/F)	1.23 (1.06 – 1.43)	**0.008**	–	–
	Age (each additional year)	1.01 (1.01 – 1.02)	**<0.001**	–	–
	Vaccination	0.95 (0.77 – 1.19)	0.7	0.91 (0.72 – 1.16)	0.5
	IPF or non-IPF fibrosing ILD	1.01 (0.86 – 1.18)	>0.9	1.13 (0.94 – 1.35)	0.2
	Antifibrotic therapy	0.99 (0.81 – 1.20)	>0.9	0.85 (0.66 – 1.09)	0.2
	Background glucocorticoids	1.31 (1.12 – 1.53)	**<0.001**	1.26 (1.06 – 1.50)	**0.007**
	Background immunosuppressive therapy	1.13 (0.96 – 1.33)	0.14	1.14 (0.95 – 1.36)	0.2
	Cardiovascular disease	1.26 (1.09 – 1.46)	**0.002**	1.27 (1.08 – 1.48)	**0.003**
	Cancer or haematological disease	1.33 (1.09 – 1.61)	**0.004**	1.31 (1.04 – 1.65)	**0.023**
	Obesity	0.96 (0.82 – 1.12)	0.6	0.97 (0.82 – 1.15)	0.7
	DLCO < 40%pred	1.54 (1.36 – 1.74)	**<0.001**	1.44 (1.24 – 1.68)	**<0.001**
	FVC < 70%pred	1.43 (1.25 – 1.64)	**<0.001**	1.20 (1.02 – 1.41)	**0.032**
Death on day 90	Sex (M/F)	1.31 (0.89 – 1.93)	0.2	–	
	Age (each additional year)	1.06 (1.04 – 1.07)	**<0.001**	–	
	Vaccination	0.19 (0.06 – 0.57)	**0.004**	0.15 (0.05 – 0.51)	**0.002**
	IPF or non-IPF fibrosing ILD	1.39 (0.95 – 2.02)	0.087	1.64 (1.03 – 2.61)	**0.039**
	Antifibrotic therapy	1.59 (1.07 – 2.37)	**0.022**	1.42 (0.90 – 2.24)	0.13
	Glucocorticoids	1.89 (1.26 – 2.82)	**0.002**	2.05 (1.3 – 3.23)	**0.002**
	Immunosuppressive therapy	0.94 (0.60 – 1.48)	0.8	1.03 (0.63 – 1.69)	>0.9
	Cardiovascular disease	1.53 (1.04 – 2.24)	**0.03**	1.64 (1.08 – 2.49)	**0.021**
	Cancer or haematological disease	1.74 (1.09 – 2.78)	**0.021**	1.91 (1.13 – 3.21)	**0.016**
	Obesity	1.15 (0.78 – 1.7)	0.5	1.32 (0.86 – 2.03)	0.2
	DLCO <40%pred	2.34 (1.65 – 3.3)	**<0.001**	1.89 (1.26 – 2.85)	**0.002**
	FVC <70%pred	2.16 (1.52 – 3.07)	**<0.001**	1.44 (0.95 – 2.19)	0.086

RR, relative risk; CI, confidence interval; FVC, forced vital capacity; DL_{CO}, diffusing lung capacity of carbon monoxide. *Risk ratios are age-sex adjusted in both the univariable and multivariable analyses, except for the univariable age- and sex-associated RRs (crude risk ratios).

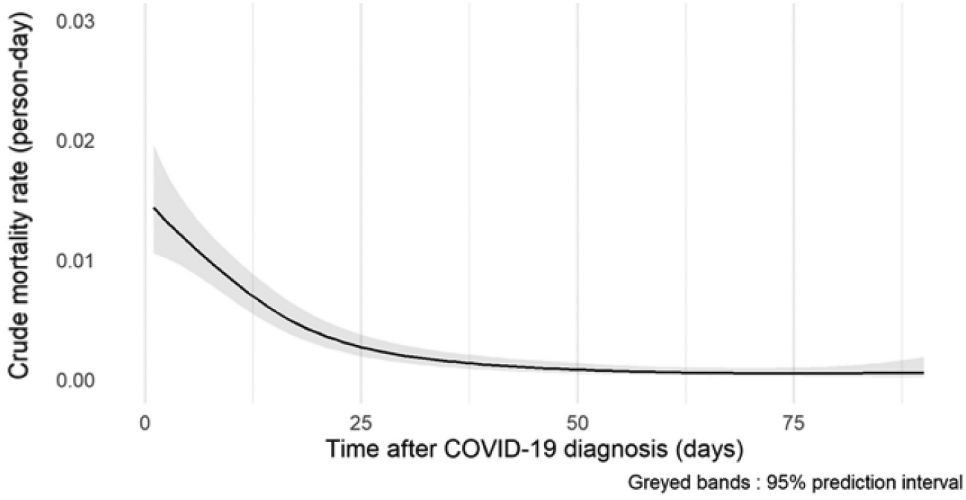

Figure 1. Crude mortality rates (person-days) during the first 90 days after COVID-19 diagnosis. The shaded area indicates the 95% confidence interval.

Long-term survival

The median follow-up duration was 751 days (362–834). Overall, 163 patients (27%) had died during follow-up. Survival differed between the different ILD subgroups; patients with IPF had the worst prognosis (Figure A3 in the Supplementary Appendix). The median time between COVID-19 diagnosis and death was 11 days (6–35), and the crude mortality rate decreased to approximately zero within the 90 days after COVID-19 diagnosis (Figure 1). Regarding lung function, survival was worse in patients with FVC < 70%pred compared to patients with FVC > 70%pred and in those with DL_{CO} < 40%pred compared to patients with DL_{CO} > 40% pred (Figure A4 in the Supplementary Appendix).

Discussion

In this prospective and multicentre study, we found that ILD diagnosis, lung function, background glucocorticoid therapy, cardiovascular, and oncologic comorbidities were independently associated with increased mortality at day 90 in patients with COVID-19 and pre-existing ILD, whereas vaccination against SARS-CoV-2 (which became available from January 2021 in France) was protective. These results confirmed the risk factors previously identified in a study performed by our group that included patients from this cohort.[19]

One of the main questions asked during the outbreak of this large-scale transmissible infectious disease was the additional risk of lung function deterioration and long-term consequences for patients with chronic lung diseases, especially those with ILD.[20] Concerns were also expressed regarding the risk of COVID-19-induced acute exacerbation of ILD.[19,21,23] The results of the present study do not support the hypothesis of late increased mortality rates related to acute SARS-CoV-2 infection. Our results highlight the impact of impaired DL_{CO} in patients with ILD on the outcomes of COVID-19. In these patients low DL_{CO} probably recapitulates overall severity of ILD. FVC < 80%pred has previously been associated with COVID-19 mortality in patients with ILD.[17,24] Herein, FVC < 70%pred was not predictive of the risk of death from COVID-19 on day 90 in the multivariable model. However, survival throughout the study period was lower in patients with FVC < 70%pred.

Patients with ILD often receive immunosuppressive therapy, including several treatments associated with a higher probability of severe COVID-19.[25] In the present study, background immunosuppressive therapy was not associated with hospitalisation or mortality, which is in line with earlier studies.[16,17] These results support the positive risk/benefit ratio of immunosuppressive therapy in patients with ILD during the pandemic. However, in some studies, only certain immunosuppressive therapies, such as rituximab, were associated with poorer outcomes in COVID-19[25] and the present study does not provide details regarding each immunosuppressive regimen. Moreover, background glucocorticoid therapy was associated with poorer outcomes, consistent with data from cohorts of patients with autoimmune diseases.[26,27] However, glucocorticoid therapy is widely used to treat patients with COVID-19 and hypoxaemia.[28] One hypothesis to explain this discrepancy is that the initial inflammatory phase of the immune response to SARS-CoV-2 is required for effective infection control but is deleterious when prolonged. Background glucocorticoid therapy might impair this initial inflammatory phase and facilitate the onset of a severe form of COVID-19.

Our results and work from other authors suggest an increased mortality from COVID-19 in patients with IPF and other fibrotic ILDs.[11,17,29] Vaccination against SARS-CoV-2 has been proven beneficial for patients with ILD[25] but one study reported a reduced vaccinal response to the SARS-CoV-2 mRNA vaccine BNT162b2 in patients with IPF.[30] Taken together, these results highlight the importance of booster doses of SARS-CoV-2 vaccines in patients with fibrotic ILD, as confirmed in the study by Shao et al.[31]

Obesity has been associated with worse outcomes of SARS-CoV-2 infection in patients with ILD[17] but this was not the case in our study. In a recent study, a higher baseline BMI was associated with a lower mortality risk in two prospective cohorts of patients with fibrosing ILD.[32] This finding could explain the absence of significantly increased obesity-related risk of death observed herein. Previous studies have identified the ILD subtype as a factor associated with increased mortality from SARS-CoV-2.[15,17,19] Our study showed the importance of the underlying ILD subtype, particularly with a fibrotic phenotype, in the risk of hospitalisation or death from COVID-19. However, during the French SARS-CoV-2 outbreak and especially during the first wave, insufficient numbers of ICU beds sometimes resulted in decisions not to admit frail patients in the ICU. For example, elderly patients with IPF were often treated in standard care units, without possibility to benefit from mechanical ventilation, which can result in higher mortality.[33]

As the COVID-19 pandemic proved that no physical border could prevent the global propagation of emerging infectious agents, airborne transmission appears to be one of the key factors facilitating rapid spreading of the pandemic. Airborne transmission being associated with the onset of primarily respiratory diseases, it appears logical to consider patients with chronic lung disease as high-risk of dire outcomes. The identification of risk factors is therefore not only useful in the case of COVID-19 but can also help identify high-risk patients in the case of other potential emerging viruses targeting the lung.[34]

Our study prospectively included a large nationally representative cohort of patients with ILD. Compared with earlier studies,[11,15] ours provides the detailed clinical characteristics and pulmonary function testing results of the patients. However, it is limited by data collection in an urgent setting as illustrated by the missing data for obesity which was not systematically collected during the first wave of the pandemic. Considering the cause of missingness being independent of death, an anecdotic missing rate for the outcome and the fact that about 500 cases remained available for the logistic regression, this likely induced larger confidence intervals but a small bias at worst in the estimated relative risks. Also of note among limitations are the low rates of available data regarding SARS-CoV-2 vaccination, and the absence of detailed descriptions of background immunosuppressive therapy.

Conclusion

In patients with ILD, a higher COVID-19 mortality is associated with a diagnosis of IPF or non-IPF fibrosing ILD, lower lung function, background glucocorticoid therapy but not background immunosuppressive therapy, and absence of vaccination. There is no evidence of increased late mortality in this population.

Acknowledgments

We thank Shanez Haouari (*Direction de la Recherche en Santé, Hospices civils de Lyon, France*) for help in manuscript preparation.

Disclosure statement

Yurdagul Uzunhan declares grants from Oxyvie; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, Boehringer Ingelheim and CSL Vifor; support for attending meetings and/or travel from Oxyvie and Boehringer Ingelheim; participation on a Data Safety Monitoring Board or Advisory Board from Boehringer Ingelheim. Raphaël Borie declares consulting fees from Boehringer Ingelheim, Ferrer and Sanofi and support for attending meetings and/or travel from Boehringer Ingelheim. Victor Valentin declares personal fees from Boehringer Ingelheim and research grants from Santelys. David Montani declares research grants to his institution from Acceleron, Janssen, Merck MSD; consulting fees from Acceleron, Janssen, Merck MSD and Ferrer and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bayer, Janssen, Boehringer Ingelheim, Chiesi, GSK, Ferrer and Merck MSD.

ORCID

Rémi Diesler http://orcid.org/0000-0003-0746-357X

Data availability statement

The data that support the findings of this study are available from the corresponding author, RD, upon reasonable request.

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