Risk Factors for Mortality after COVID-19 in Patients with Preexisting Interstitial Lung Disease

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Interestingly, we successfully isolated infectious virus from five of five samples from patients with Tx (obtained 4–28 d after admission to the ICU), but, in line with data from Wölfel and colleagues (9), we were unable to detect infectious virus after Day 7 in immunocompetent control patients (zero of four patients).

Limitations. First, the sample size of our study is limited, but the significant findings with potential major impact on patient management are of great importance. Second, three patients remained under intensive care treatment on the day of data censoring, resulting in an unknown outcome. Third, some cases had incomplete documentation of clinical data, missing laboratory-testing results, or both.

Conclusions. To our knowledge, this is the first comprehensive report on COVID-19 in patients with a history of HSCT that focuses on virological parameters. In these patients, as compared with immunocompetent patients, prolonged shedding of infectious virus, viremia, and high viral loads in respiratory samples highlight the need of the immune system for viral control but also indicate virus-induced mortality and a higher risk for transmission to other patients and medical staff. ■

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Risk Factors for Mortality after COVID-19 in Patients with Preexisting Interstitial Lung Disease

To the Editor:

Patients with preexisting interstitial lung disease (ILD) may be at high risk for severe coronavirus disease (COVID-19) because of impaired lung function, propensity to develop acute exacerbation of pulmonary fibrosis, or immunomodulatory medications that may interact with viral clearance or pathogenesis (1, 2). Previous studies found that patients with ILDs had an increased risk of death compared with control subjects matched for age, sex, comorbidities, and/or race (3, 4). However, whether the type of ILD may influence the outcome of COVID-19 is unknown. Here, we aimed to compare mortality of COVID-19 between patients with fibrotic idiopathic ILD, including idiopathic pulmonary fibrosis (IPF), with those with other types of ILD.

In this multicentric observational survey of specialized centers, we analyzed the survival of COVID-19 in patients with ILDs and compared mortality rates among those with fibrotic idiopathic ILDs, including IPF, with those with other ILDs. Patients were eligible if they had preexisting ILD and if they had COVID-19 during the study period confirmed by RT-PCR or definite clinical manifestations (acute onset of fever, flu-like

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Table 1. Main Characteristics of the Study Population and Outcomes by ILD Diagnosis

	Fibrotic Idiopathic ILD ($n = 48$)	Other ILDs ($n = 75$)	All ($N = 123$)	*P* Value
Patient characteristics				
Sex, *n* (%)				**0.04**
F	11 (23)	31 (41)	42 (34)	
M	37 (77)	44 (59)	81 (66)	
Age, mean ± SD, yr	71 ± 11	60 ± 18	64 ± 16	**0.02**
Body mass index, mean ± SD, kg · m^{-2}	26 ± 4	27 ± 3	27 ± 5	0.29
Comorbidities, *n* (%)				
Obesity	8 (17)	16 (21)	24 (20)	0.55
Hypertension	24 (50)	29 (39)	53 (43)	0.26
Cardiovascular disease	16 (33)	12 (16)	28 (23)	**0.03**
Diabetes mellitus	17 (35)	19 (25)	36 (29)	0.27
Chronic kidney disease	4 (8)	7 (9)	11 (9)	0.81
Cancer or hemopathy	3 (6)	4 (5)	7 (6)	0.86
Pulmonary hypertension	7 (15)	8 (11)	15 (12)	0.50
Pulmonary characteristics				
mMRC, mean ± SD	1.9 ± 1.0	1.7 ± 1.1	1.7 ± 1.1	0.26
FVC% predicted, mean ± SD	76 ± 22	81 ± 25	79 ± 24	0.28
FVC% categories, *n* (%)				0.14
<50	7 (15)	4 (5)	11 (15)*	
50–70	8 (17)	19 (25)	27 (36)*	
>70	27 (56)	45 (60)	72 (96)*	
Corrected D_{LCO}% predicted, mean ± SD	46 ± 17	54 ± 21	51 ± 20	0.06
D_{LCO}% categories, *n* (%)				0.62
<40	12 (25)	15 (20)	27 (22)	
40–60	13 (27)	22 (29)	35 (28)	
>60	12 (25)	25 (33)	37 (30)	
Oxygen supplementation at home, *n* (%)	12 (25)	10 (13)	22 (18)	0.12
Treatment at baseline, *n* (%)				
Antifibrotic medication	12 (25)	0 (0)	12 (10)	**<0.01**
Glucocorticoids	11 (23)	36 (48)	47 (38)	**0.01**
Immunosuppressive drugs	10 (21)	35 (47)	45 (37)	**<0.01**
COVID-19–related medications, *n* (%)				
Any medication	18 (37)	25 (33)	43 (35)	0.64
Lopinavir/ritonavir	2 (4)	6 (8)	8 (7)	0.40
Azithromycine	8 (17)	6 (8)	14 (11)	0.14
Hydroxychloroquine	7 (15)	8 (11)	15 (12)	0.52
Glucocorticoids	5 (10)	9 (12)	14 (11)	0.79
Outcomes, *n* (%)				
Hospital admission				0.37
Not hospitalized	5 (10)	15 (20)	20 (16)	
Hospitalized, not in ICU	32 (67)	45 (60)	77 (63)	
Hospitalized in ICU	11 (23)	15 (20)	26 (21)	
Dead at Day 30	17 (35)	14 (19)	31 (25)	**0.04**

Definition of abbreviations: COVID-19 = coronavirus disease; ILD = interstitial lung disease; mMRC = modified Medical Research Council.
Comparisons used χ^2 or Student's *t* test when appropriate. Bold indicates $P < 0.05$.
*These percentages were calculated from available data.

symptoms, headache, and anosmia), typical features on chest computed tomography and positive serology for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with lung transplantation were excluded. Consecutive cases were collected using a deidentified case report form through the French rare lung disease network (OrphaLung) between the onset of the outbreak in France to May 28, 2020. Data collected included demographics, medical history, comorbidities, last available lung function in stable condition, and treatment received at the time of COVID-19. The primary outcome was death, censored at Day 30 of COVID-19. No imputation was applied for missing data. Univariable and multivariable Cox regression analyses were used to investigate predictors of mortality. For multivariable analysis, we included into the model variables that were associated with mortality in univariable analysis with a *P* value of less than 0.10, as well as glucocorticoid therapy used to treat COVID-19, as it was considered clinically relevant. Medications to treat ILD were excluded from the prediction model to limit collinearity with the underlying diagnosis. This study was formally approved by the institutional review boards of the French learned society for respiratory medicine (Comité d'Ethique Pour la Recherche Observationnelle 2020-036; August 25, 2020) and the Hospices Civils de Lyon (May 13, 2020), which waived the need for written informed consent (April 14, 2020).

Table 2. Association with Mortality of Clinical Characteristics, Comorbidities, Lung Function, and Treatment by Cox Regression Analysis

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sex, M/F	4.22 (1.47–12.06)	**0.01**	3.90 (1.17–13.04)	**0.03**
Age, yr	1.07 (1.03–1.10)	**<0.01**	1.07 (1.04–1.11)	**<0.01**
Body mass index, kg · m^{-2}	1.02 (0.96–1.09)	0.51	—	—
Underlying ILD, fibrotic/other	2.15 (1.06–4.35)	**0.04**	—	—
Comorbidities, yes/no				
Obesity	1.01 (0.41–2.47)	0.99	—	—
Hypertension	2.48 (1.18–5.21)	**0.02**	—	—
Cardiovascular disease	3.20 (1.55–6.59)	**<0.01**	—	—
Diabetes mellitus	1.46 (0.69–3.06)	0.32	—	—
Chronic kidney disease	1.81 (0.63–5.20)	0.27	—	—
Cancer or hemopathy	3.21 (1.12–9.21)	**0.03**	5.82 (1.88–18.08)	**<0.01**
Pulmonary hypertension	2.88 (1.22–6.83)	**0.02**	—	—
Pulmonary characteristics				
FVC% predicted	0.98 (0.96–0.99)	**0.02**	—	—
Corrected D_{LCO}% predicted	0.96 (0.94–0.99)	**<0.01**	—	—
Oxygen supplementation at home	4.25 (2.02–8.91)	**<0.01**	4.56 (2.13–9.78)	**<0.01**
Treatment at baseline, yes/no				
Antifibrotic medication	3.09 (1.27–7.55)	**0.01**	—	—
Glucocorticoids	1.06 (0.51–2.18)	0.88	—	—
Immunosuppressive drugs	0.58 (0.26–1.30)	0.19	—	—
COVID-19–related medications, yes/no				
Any	1.43 (0.70–2.92)	0.32	—	—
Lopinavir/ritonavir	1.61 (0.49–5.30)	0.43	—	—
Azithromycine	0.23 (0.03–1.72)	0.15	—	—
Hydroxychloroquine	1.58 (0.60–4.11)	0.35	—	—
Glucocorticoids	1.15 (0.40–3.28)	0.80	—	—

Definition of abbreviations: CI = confidence interval; COVID-19 = coronavirus disease; HR = hazard ratio; ILD = interstitial lung disease.
Bold indicates $P < 0.05$.

A total of 123 patients were included (Table 1), with a median age of 64 years (interquartile range, 58–74 yr), and 66% were of male sex. Forty-eight patients (39%) had fibrotic idiopathic ILD, including IPF ($n = 20$; median age, 72 yr), idiopathic nonspecific pneumonia ($n = 8$; median age, 66.5 yr), and other fibrotic idiopathic ILDs ($n = 20$; median age, 73.5 yr). Other diagnostic categories included connective tissue disease–associated ILD ($n = 27$; median age, 57 yr), systemic vasculitis ($n = 7$; median age, 61 yr), sarcoidosis ($n = 16$; median age, 56 yr), and other ILDs ($n = 25$; median age, 64.5 yr). Patients were receiving antifibrotic drugs (10%), glucocorticoids (38%), or other immunosuppressive drugs (37%). COVID-19 was confirmed by RT-PCR in 91% of patients and by symptoms, computed tomography scan, and serology in 9% of patients. COVID-19–related medications were prescribed for COVID-19 in 35% of cases.

Hospital admission was required in 84% of patients (90% of those with fibrotic idiopathic ILD and 80% of those with other ILDs), including 21% in ICUs. According to the reporting physician, admission modalities were appropriate in all cases (i.e., no patient was denied admission because of bed unavailability). At Day 30 of COVID-19, 17 of 48 (35%) patients with fibrotic idiopathic ILD had died compared with 14 of 75 (19%) of those with other ILDs ($P = 0.04$). The median time between diagnosis and death was 8 days (interquartile range, 4–15 d). Death was related to COVID-19 in all cases, including four in whom COVID-19 triggered an acute exacerbation of IPF.

On univariable Cox regression analysis, mortality was significantly associated with male sex, increasing age, an underlying diagnosis of fibrotic idiopathic ILD compared with other ILDs, comorbidities (hypertension, cardiovascular disease, cancer or hemopathy, and pulmonary hypertension), lower FVC, lower D_{LCO}, chronic use of oxygen supplementation at home (at rest or exercise), and treatment with antifibrotic drugs (Table 2). On Cox multivariable analysis, increasing age, male sex, history of cancer/hemopathy, and the chronic use of oxygen supplementation at home remained independently predictive of mortality (Table 2).

Here, we report a series of 123 patients with ILD who had COVID-19 and were followed in the French network of rare pulmonary disease expert centers. This relatively low number likely reflects that patients with ILD stayed at home during the lockdown period and rigorously adopted preventive measures to protect themselves from infection (5).

The case fatality rate was 35% among subjects with idiopathic fibrotic ILD and was 19% in those with another ILD. Of note, the mortality among subjects with an ILD other than fibrotic idiopathic ILD was comparable with that reported in the global French population hospitalized for COVID-19 (18.1%) (6). Multivariable analysis indicated that the greater mortality among subjects with fibrotic idiopathic ILD was attributable to age and

comorbidities already identified as risk factors of severity in COVID-19 (7, 8).

Chronic home oxygen supplementation was also associated with greater mortality, reflecting the severity of the underlying ILD, independently of the ILD diagnostic subgroup. This finding is consistent with that of a large prospective observational cohort study, in which peripheral oxygen saturation on room air lower than 92% was significantly associated with in-hospital mortality (7), and with a study of patients with ILD before developing COVID-19, in which an FVC of <80% predicted was associated with mortality (4). Mortality in our cohort was directly related to COVID-19 and followed an acute exacerbation of fibrotic ILD triggered by the viral infection in four cases. However, distinguishing an infection from a triggered acute exacerbation can be challenging (9). Long-term treatment with glucocorticoids or immunosuppressive drugs was not associated with a worse prognosis, in contrast to previous suggestions (10).

This study has limitations, including the small sample size, retrospective design, and absence of model validation. Individuals who were not hospitalized may have been missed; however, this does not influence the case fatality rate among patients who were admitted. A longer follow-up is required to assess potential irreversible pulmonary fibrosis secondary to COVID-19 (11) because delayed improvement may occur (12).

In conclusion, this study found a high mortality rate due to COVID-19 in patients with preexisting fibrotic idiopathic ILD compared with those with other ILDs, which was mostly attributable to age, male sex, history of cancer, and severity of the underlying ILD as reflected by the chronic use of supplemental oxygen. The potential long-term impact of COVID-19 on the course of ILD remains to be determined. ■

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In Search of "Hepatic Factor": Lack of Evidence for ALK1 Ligands BMP9 and BMP10

To the Editor:

Considerable evidence suggests that the liver produces or modifies a circulating factor critical for preventing pulmonary arteriovenous malformations (PAVMs). In hepatopulmonary syndrome, liver dysfunction is associated with hypoxemia secondary to PAVMs, and PAVMs are reversed by liver transplantation (1). Additionally, portosystemic shunts that allow gut venous effluent to bypass the liver lead to PAVMs, which resolve when the shunt is closed (2). Further evidence comes from single-ventricle patients who undergo a three-staged surgery to relieve hemodynamic burden on the heart and correct oxygen desaturation. The second-stage surgery, the bidirectional Glenn, directs passively draining venous return from the superior vena cava (SVC) to the pulmonary circulation, with venous return from the inferior vena cava (IVC) pumped to the systemic circulation. Although the Glenn effectively decreases ventricular hemodynamic stress, intrapulmonary arteriovenous shunting is pervasive, and up to 25% of Glenn patients develop clinically significant hypoxemia secondary to diffuse PAVMs (3, 4). Although early theories of PAVM development focused on the absence of pulsatile flow or increased lower lobe perfusion (3), later evidence implicated the exclusion of a liver-derived substance from the pulmonary vasculature. This "hepatic factor" was postulated based on correlation between laterality of PAVMs and laterality of exclusion of hepatic venous effluent (5), and its existence is strongly supported by evidence that the third-stage Fontan procedure (completion of the total cavopulmonary anastomosis), which reroutes IVC flow to the lungs without restoring pulsatility, is strongly associated with PAVM regression (6). Despite the strong evidence for hepatic factor, its identity remains unknown.

Approximately 80% of PAVMs are associated with hereditary hemorrhagic telangiectasia, a genetic disorder caused primarily by mutations in BMP (bone morphogenetic protein) receptors *ENG* (endoglin) and *ACVRL1* (activin A receptor like type 1, which encodes ALK1) (7). This pathway is active in lung endothelium, and ligands include BMP9 and BMP10 homodimers and BMP9/10 heterodimer (8, 9). Both *BMP9* and *BMP10* are transcribed in hepatic stellate cells (9). Given the strong relationship between PAVMs and hereditary hemorrhagic telangiectasia, the hepatic origins of *BMP9* and *BMP10*, and evidence of decreased plasma BMP9 in hepatopulmonary syndrome (10), we hypothesized that ALK1 ligands may be the hepatic factor required for PAVM prevention. We expect that hepatic factor is either labile or actively removed from circulation on first pass through the systemic circulation, making it unavailable to the lung vasculature in Glenn circulation. Accordingly, in normal circulation, we hypothesized that concentrations of ALK1 ligands would be higher in the right atrium and pulmonary artery compared with the SVC and infrahepatic IVC. Some of the results of these studies have been previously reported in the form of an abstract (11), and some have been previously reported in the form of a preprint (https://doi.org/10.1101/2020.07.09.20148320).

Methods

This study was approved by the University of Pittsburgh Institutional Review Board. Participants undergoing clinically indicated cardiac catheterization were recruited between September 2015 and February 2017 and provided informed child assent and/or parental consent. Patients with bidirectional Glenn, prior to Fontan, were compared with two-ventricle control subjects. Excluded diagnoses among control subjects included single ventricle physiology, unrepaired complex congenital heart disease, and large shunt lesions. Patients with liver disease, anemia (Hb <8 g/dl), cardiac surgery within 30 days, or transfusion within 48 hours were excluded from both cohorts.

We collected 1 ml blood in K_2EDTA tubes from five sites: the right atrium, pulmonary artery, aorta, SVC, and infrahepatic IVC. We measured ligands in duplicate in 30 μl of plasma via sandwich ELISAs (R&D Systems) using DY3209 (BMP9), MAB2926 and BAF3956 (BMP10), and MAB2926 and BAF3209 (BMP9/10), with in-house generated recombinant proteins for the latter two standard curves. We fit data to a four-parameter logistic curve and performed statistical analysis using GraphPad Prism. We ran all samples from an individual on a single plate, and the operator was blinded to sample identity. Sample volume limitations prevented us from assaying all ligands in every individual.

Results

Diagnoses in 38 control subjects (mean age, 5.8 yr [4 mo to 12.6 yr]; 21 males, 17 females) included small shunt lesions (21), repaired forms of congenital heart disease with two-ventricle physiology (11), vascular stenosis (5), valvar obstructive lesions (2), and hypertrophic cardiomyopathy (1). Primary cardiac diagnoses in nine Glenn cases (mean age, 2.9 yr [range, 22 mo to 5.1 yr]; 7 males, 2 females) included variants of hypoplastic left heart syndrome (5), pulmonary atresia with intact ventricular septum (2), double outlet right ventricle with pulmonary atresia (1), and heterotaxy with right atrial isomerism (1).

BMPs are generated as proprotein dimers that are cleaved between the N-terminal prodomains and C-terminal growth factor domains, releasing the disulfide-bonded GFD (growth factor dimer). In control plasma, we detected BMP9 GFD, BMP10 proprotein, and BMP9/10 GFD (Figure 1) but not BMP10 GFD (DY2926; R&D Systems; data not shown). However, we found no differences in plasma concentrations of any ALK1 ligand when comparing within-subject values across the right atrium, pulmonary artery, aorta, SVC, and IVC (Figure 1). This result suggests that these ligands are neither particularly labile nor actively removed on first pass through the systemic or pulmonary circulation, failing to support the hypothesis that they represent the hepatic factor required to prevent PAVMs.

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