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COVID-19 outcomes in patients with pre-existing interstitial lung disease: A national multi-center registry-based study in China

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During the coronavirus disease 2019 (COVID-19) pandemic, the disease severity of COVID-19 varied widely depending on the underlying conditions of infected patients.[1] Interstitial lung disease (ILD) comprises a group of diffuse parenchymal lung disorders associated with substantial morbidity and mortality.[2] Currently, multi-center data evaluating outcomes in patients with pre-existing ILD and COVID-19 are limited in China. Our study was based on a national multi-center prospective ILD registry study conducted by our group in China from 2017. We followed up patients in this cohort for the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and described their characteristics, disease severity and outcomes. We also explored the risk factors for COVID-19 severity and outcomes.

Through rigorous screening criteria, 32 centers eventually participated in this study.[3] Patients with ILD were diagnosed by multidisciplinary discussion according to the guidelines.[3–6] Patients who died before SARS-CoV-2 infection or lacked data about COVID-19 were excluded [Figure 1A]. The Ethics Committee of China–Japan Friendship Hospital and other sites approved this study (No. 2022-KY-031), and all patients have signed informed consent forms. Baseline data of patients were collected when they were enrolled in the cohort, including demographic information, examination results and therapy. To compare the prognosis of different ILD subclasses, we divided patients into three groups: patients with idiopathic pulmonary fibrosis (IPF group); idiopathic interstitial pneumonia (IIP) other than IPF (non-IPF IIP group); and other than IIP (non-IIP group). Investigation for SARS-CoV-2 infection was conducted during the Omicron epidemic wave from December 2022 to March 2023 in this ILD cohort. If the patient was presented to a center in this cohort for COVID-19, the data were collected during hospitalization or outpatient visit. Otherwise, data were collected by telephone interviews. COVID-19 associated data included SARS-CoV-2 infection status, diagnostic method, COVID-19 outcomes, and treatment for COVID-19. COVID-19 outcomes included symptom after infection, blood oxygen without oxygen therapy, COVID-19 severity, oxygen therapy status, method of oxygen therapy, pneumonia, hospital admission, length of hospitalization, and death. Blood oxygen without oxygen therapy ≤93% was considered hypoxemia. Pneumonia was confirmed by computed tomography test.

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We first performed a descriptive analysis. Then we used univariable and multivariable logistic regression methods to analyze the association between factors and COVID-19 severity and other outcomes. SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to conduct all statistical analyses, and all statistical tests were two sided with *P* less than 0.05 being significant level.

A total of 1758 patients with ILD were included in this study. The proportions for patients in the IPF group, non-IPF IIP group and non-IIP group were 28.56% (502/1758), 22.75% (400/1758), and 48.69% (856/1758), respectively. Among them, 1245 (70.82%) patients were infected with SARS-CoV-2 by March 2023. Patients were mainly infected in December 2022 (949/1245, 76.22%) and January 2023 (142/1245, 11.41%) [Figure 1B]. Diagnostic methods for SARS-CoV-2 infection were mainly nasopharyngeal swab antigen test (478/1245, 38.39%) and polymerase chain reaction (PCR) test (206/1245, 16.55%), and the other patients were diagnosed clinically based on symptoms and contact history of infected person. Compared with patients without infection, those infected were significantly younger ([58.27 ± 12.19] years *vs*. [60.69 ± 11.20] years, *P* <0.001), and had a higher proportion of newly diagnosed ILD (69.24% [862/1245] *vs*. 59.65% [306/513], *P* <0.001) and receiving oxygen therapy at baseline (47.07% [586/1245] *vs*. 40.16% [206/513], *P* = 0.008) [Supplementary Table 1, http://links.lww.com/CM9/C409].

Among all infected patients, 78.71% (980/1245) were mild, 11.08% (138/1245) were moderate, and 10.20% (127/1245) were severe/critical. The overall percentage of hospitalization was 16.87% (210/1245). Among severe/critical patients, 76.38% (97/127) were hospitalized, and 45.65% (63/138) of moderate patients were hospitalized, while the proportion of hospitalization in mild patients was 5.10% (50/980). The overall proportion of patients with blood oxygen confirmed hypoxemia was 47.02% (323/687), that of patients receiving oxygen therapy was 27.71% (345/1245), and that of patients with pneumonia was 52.98% (258/487). In patients with hypoxemia, 56.04% (181/323) of patients received oxygen therapy, and 32.82% (106/323) of patients were hospitalized [Figure 1C]. Among patients with pneumonia, 59.30% (153/258) were hospitalized. A total of 22 deaths occurred. Among them, 16 died because of COVID-19, and 6 died of other reasons. Compared with non-IIP group, the IPF group had higher percentage of patients with severe/critical disease, hypoxemia, hospitalization, pneumonia, and oxygen therapy (*P* <0.05) [Supplementary Table 2, http://links.lww.com/CM9/C409].

The five most common symptoms in patients with COVID-19 were fever (945/1245, 75.90%), cough (710/1245, 57.03%), weakness (455/1245, 36.55%), sputum (364/1245, 29.24%), and muscular soreness (340/1245, 27.31%) [Figure 1D]. Among patients with infection, 20.64% (257/1245) and 16.39% (204/1245) experienced aggravation of cough and dyspnea, respectively. A total of 6.18% (77/1245) patients took antiviral drugs, such as nematavir/ritonavir and azvudine. The proportions of taking Chinese traditional medicine (CTM), CTM soup, steroids, antibiotic drugs, and antifebrile drugs were 27.39% (341/1245), 4.58% (57/1245), 7.23% (90/1245), 19.76% (246/1245) and 32.05% (399/1245), respectively.

We first analyzed the parameters associated with COVID-19 severity. Univariable analysis revealed that age, gender, smoking, ILD type, having fibrosis, comorbid with cardiovascular disease, diffusing capacity of the lung for carbon monoxide (DL_{CO}, % pred), gender–age–physiology (GAP) stage, and vaccine were associated with COVID-19 severity. After multivariable analysis, patients with IPF (odds ratio [OR]: 2.25; 95% confidence interval [CI]: 1.44–3.51) or non-IPF IIP (OR: 1.68; 95% CI: 1.09–2.58), and GAP stage III (OR: 3.50; 95% CI: 1.49–8.21) showed higher risk of being moderately and severely ill, while patients

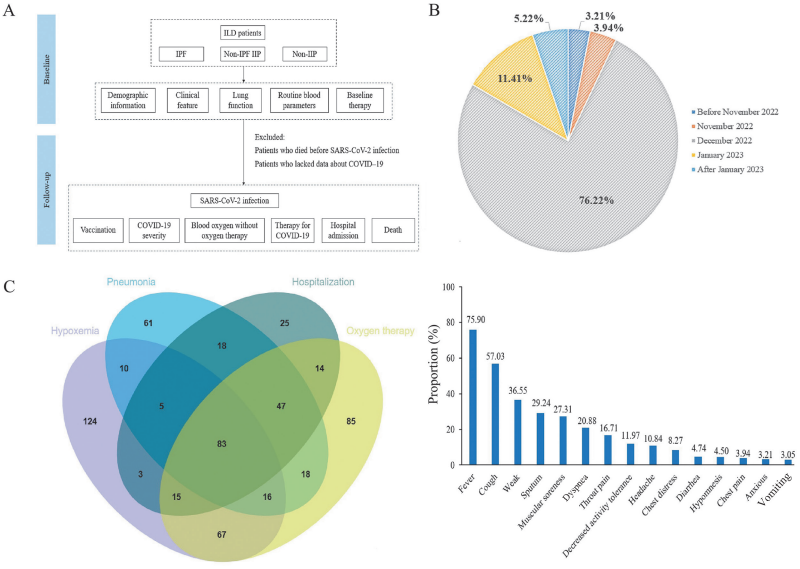

Figure 1: (A) Flow chart of this study on COVID-19 outcomes in patients with pre-existing interstitial lung disease. (B) The time distribution of SARS-CoV-2 infection. (C) Venn diagram about hypoxemia, oxygen therapy, pneumonia, and hospitalization. (D) Proportion of different symptoms in ILD patients with COVID-19. COVID-19: Coronavirus disease 2019; IIP: Idiopathic interstitial pneumonia; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

receiving two (OR: 0.48; 95% CI: 0.26–0.87) or three (OR: 0.48; 95% CI: 0.31–0.73) doses of COVID-19 vaccine showed lower risk of being moderately and severely ill [Supplementary Table 3, http://links.lww.com/CM9/C409].

In univariable analysis, patients with older age, IPF, and GAP stage II/III showed higher risk for hypoxemia, while patients who had higher DL_{CO} (% pred) showed lower risk [Supplementary Table 4, http://links.lww.com/CM9/C409]. Multivariable analysis revealed that GAP stage was the only independent risk factor of hypoxemia. The risk of hypoxemia in patients with GAP stage II (OR: 2.25; 95% CI: 1.41–3.58) was elevated [Supplementary Table 5, http://links.lww.com/CM9/C409].

Univariable analysis indicated that age, gender, smoking, ILD type, comorbid with cardiovascular disease, and GAP stage were significantly associated with pneumonia [Supplementary Table 4, http://links.lww.com/CM9/C409]. Multivariable analysis indicated that patients with IPF (OR: 2.39; 95% CI: 1.39–4.09) or non-IPF IIP (OR: 1.82; 95% CI: 1.07–3.09) showed increased risk for pneumonia [Supplementary Table 5, http://links.lww.com/CM9/C409].

Hospitalization included emergency, general, and ICU hospitalization. Age, gender, smoking, ILD type, fibrosis, forced expiratory volume in 1 second (FEV_1, % pred), DL_{CO} (% pred), GAP stage, vaccine, and hypoxemia were significantly associated with hospitalization [Supplementary Table 4, http://links.lww.com/CM9/C409]. Multivariable analysis showed that IPF (OR: 2.63; 95% CI: 1.46–4.73), baseline oxygen therapy (OR: 1.86; 95% CI: 1.12–3.10), and hypoxemia (OR: 2.65; 95% CI: 1.62–4.35) could elevate patients' risk for hospitalization, while more than one dose of vaccine (two doses, OR: 0.35; 95% CI: 0.16–0.79; three doses, OR: 0.39; 95% CI: 0.22–0.68; equal and more than four doses, OR: 0.26; 95% CI: 0.09–0.74) could decrease their risk [Supplementary Table 5, http://links.lww.com/CM9/C409].

In our current study, increased age resulted in severe disease and poorer outcomes, including pneumonia, and hospitalization. Among all age groups, the proportion of severe illness and death caused by COVID-19 was the highest among elderly patients. There are three main reasons for this. Firstly, the immunity of the elderly weakens with age; secondly, once infected with a virus or bacteria, elderly adults were more prone to immune paralysis in the later stage;[7] thirdly, most elderly people have underlying diseases, and infection with the virus will not only lead to more serious symptoms of the original disease, but also is more likely to induce complications.

Generally, vaccines are protective against SARS-CoV-2 infection. In our study, vaccination was a protective factor against disease severity and other outcomes in patients with COVID-19. Importantly, the global immunization strategy has prioritized the elderly and people with underlying medical conditions, such as chronic diseases, for vaccine.

The main strength of this study is that it was a multi-center prospective registry study across China. All patients had detailed baseline data and followed a rigorous follow–up regimen. However, potential limitations also exist. In this study, we only focus on the outcomes in patients with COVID-19, and the outcomes of patients without COVID-19 were not investigated. Whether COVID-19 increases the risk for poor outcomes in patients with ILD will be investigated in the future.

In conclusion, patients with IPF had the poorest COVID-19 outcomes, followed by those with non-IPF IIP. Baseline ILD severity was significantly associated with COVID-19 severity and hypoxemia, while vaccine showed a protective effect against severe COVID-19 and hospitalization. In addition, patients with baseline oxygen therapy for pre-existing ILD before SARS-CoV-2 infection and hypoxemia during SARS-CoV-2 infection were more likely to be hospitalized. More attention is needed for this vulnerable population.

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Conflicts of interest

None.

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