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Effects of COVID-19 infection in patients with autoimmune pulmonary alveolar proteinosis: a single-center study

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Abstract

Background Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare interstitial lung disease. COVID-19 is associated with worse prognosis in previous lung diseases patients. But the prognosis of aPAP patients after infection with COVID-19 is unclear. In December 2022, China experienced a large-scale outbreak of Omicron variant of the SARS-CoV-2. In this study, we aim to explore the clinical outcomes of aPAP patients infected with COVID-19.

Results A total of 39 aPAP patients were included in this study. 30.77% patients had a decrease in oxygen saturation after COVID-19 infection. We compared the two groups of patients with or without decreased oxygen saturation after COVID-19 infection and found that patients who had previous oxygen therapy (decreased oxygen saturation vs. non decreased oxygen saturation: 6/12 vs. 4/27, $P=0.043$), with lower baseline arterial oxygen partial pressure (74.50 ± 13.61 mmHg vs. 86.49 ± 11.92 mmHg, $P=0.009$), lower baseline DLCO/VA% [77.0 (74.3, 93.6) % vs. 89.5 (78.2, 97.4) %, $P=0.036$], shorter baseline 6MWD [464 (406, 538) m vs. 532 (470, 575) m, $P=0.028$], higher disease severity score ($P=0.017$), were more likely to have decreased oxygen saturation after COVID-19 infection.

Conclusion aPAP patients with poor baseline respiration have a higher probability of hypoxia after COVID-19 infection, but fatal events were rare.

Keywords Autoimmune pulmonary alveolar proteinosis, COVID-19, Oxygen saturation

Background

Pulmonary alveolar proteinosis (PAP) is a rare interstitial lung disease, with a prevalence of at least 7 per million people in large population studies. There are three types of PAP, namely primary, congenital and secondary PAP. Primary PAP can be divided into autoimmune PAP and hereditary PAP [1]. Autoimmune pulmonary alveolar proteinosis (aPAP) is the most common type of PAP, originally known as idiopathic PAP or acquired PAP, and more than 90% of patients with PAP are of this type [2]. The anti granulocyte-macrophage colony-stimulating factor (GM-CSF) antibody in the blood of patients with aPAP blocked the signaling of GM-CSF, resulting in the

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dysfunction of alveolar macrophages in scavenging surfactant. aPAP can be diagnosed by detecting the presence of anti GM-CSF antibody in serum. For aPAP patients with treatment indications, inhalation of GM-CSF or whole lung lavage (WLL) can be used for treatment [3].

SARS-CoV-2, a new infection that causes COVID-19, is associated with worse prognosis in individuals with previous lung diseases [4]. Therefore, it is not difficult to speculate that patients with aPAP may have more serious complications and worse prognosis after infection with SARS-CoV-2. A European retrospective cohort study reported that the prevalence of COVID-19 was similar in the PAP population compared with the general population, but both the rates of hospitalizations and mortality were higher [5]. Meanwhile, some case reports have found that inhaling GM-CSF is feasible for PAP patients with COVID-19, while WLL therapy is controversial [6–8]. In December 2022, China experienced a large-scale outbreak of Omicron variant of the SARS-CoV-2. In this context, our research aims to explore the clinical outcomes of aPAP patients infected with SARS-CoV-2.

Methods

Study population

The patients included in the study were all from the Chinese PAP registry study follow-up cohort, while all were patients with aPAP diagnosed at Peking Union Medical College Hospital (PUMCH). The inclusion criteria included: (1) patients with a clinical diagnosis of PAP by high-resolution computed tomography (HRCT) and further pathologically reported to have positive staining for proteinaceous material periodic Acid-Schiff (PAS) and diastase periodic Acid-Schiff (D-PAS); (2) a positive serum GM-CSF antibody test which indicated an elevated serum GM-CSF antibody level [9]. All patients signed an informed consent form. Proteinaceous material positive for PAS staining and D-PAS staining was obtained from broncho-alveolar lavage fluid (BALF) or transbronchial lung biopsy (TBLB) or surgical lung biopsy (e.g. Video-assisted Thoracoscopic Surgery). The GM-CSF antibody test was performed according to the method established by Uchida et al. [10]. The cut-off point set by our center is 4 µg/ml, and measurements above this value are considered positive for the serum GM-CSF antibody test [11].

Clinical data collection

All aPAP patients were patients in the China PAP registry study, who had a PAP-related condition assessment between November 15, 2021 and November 15, 2022, and were recorded into the China PAP registry study database. Patients were evaluated for demographics (including age, gender, smoking history, chronic medical history, previous treatment history, vaccination status),

arterial blood gas (ABG) analysis, serology (including lactate dehydrogenase, carcinoembryonic antigen levels, cytokeratin 19 fragment antigen21-1 levels), pulmonary function test results, chest CT score, six-minute walk test (6MWD), St. George's Respiratory Questionnaire (SGRQ), and disease severity score (DSS). The DSS categories were defined by Inoue et al. as follows: Grade 1: No symptoms and an arterial oxygen partial pressure (PaO_2) ≥ 70 mmHg; Grade 2: $\text{PaO}_2 \geq 70$ mmHg with symptoms; Grade 3: PaO_2 between 60 and 70 mmHg; Grade 4: PaO_2 between 50 and 60 mmHg; and Grade 5: PaO_2 below 50 mmHg [12].

A post-COVID-19 infection health status questionnaire and telephone follow-up had been administered to all registered patients included in our center through the Xingshulin MedClip app. Both the questionnaire distribution and telephone follow-up had been completed between January 1, 2023 and February 15, 2023. The questionnaire had been presented as attachments (Additional file 1). Patients were only diagnosed with COVID-19 infection if they tested positive for SARS-CoV-2 nucleic acid or antigen test, and they were confirmed between November 15, 2022 and January 31, 2023. All studies and data collection were reviewed by the ethics committee of Peking Union Medical College Hospital (JS-2639). In this study, patients were considered to have decreased oxygen saturation only if the decrease in oxygen saturation at rest was greater than or equal to 3% from before [13].

Statistical analysis

Continuous variables were reported as mean \pm standard deviation or median (P25, P75), and categorical variables were reported as percentages N (%). We used the independent samples t-test or Mann–Whitney U test for continuous variables and the chi-square or Fisher exact probability test for categorical variables. Predictors of prognosis were evaluated using univariate analysis first to screen variables, then inconsistent variables were excluded according to collinearity, and finally multivariate logistic regression analysis was performed according to the representative variables selected in clinic. Two-sided test was performed, and P value < 0.05 was considered a statistically significant difference. All statistical analyses were completed using SPSS version 25.0 software and R version 4.2.0 software.

Results

Ultimately, 41 patients with aPAP who had a PAP-related condition assessment within the last 1 year completed the questionnaire and telephone follow-up. Two patients were not infected with COVID-19, and the remaining 39 aPAP patients were infected with COVID-19 (Fig. 1).

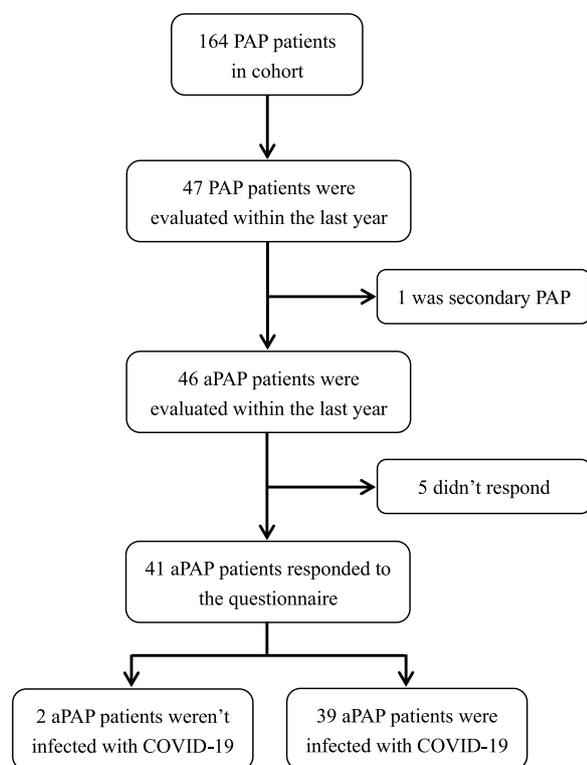


Fig. 1 Flow diagram of the study cohort. aPAP Autoimmune pulmonary alveolar proteinosis

A total of 39 aPAP patients were included in this study. Twelve of the 39 patients (30.77%) had a decrease in oxygen saturation after COVID-19 infection.

Baseline demographic information

The mean age of the 39 aPAP patients infected with COVID-19 was 42.56 (± 12.28) years; 25 out of 39 (64.1%) of them were male. Only 2 patients (5.1%) were diagnosed with PAP by Video-assisted Thoracoscopic Surgery (VATS), 14 out of 39 (35.9%) by BALF only, 4 out of 39 (10.3%) by TBLB only, and 19 out of 39 (48.7%) by both BALF and TBLB. All patients were positive for serum GM-CSF antibody test (> 4 µg/ml) with a median of 31.68 (19.31, 70.34) µg/ml. Nine out of 39 patients (23.1%) were ex-smokers and 8 out of 39 patients (20.5%) were current smokers. Eight out of 39 patients (20.5%) had been treated with whole lung lavage, 17 out of 39 (43.6%) had been treated with GM-CSF inhalation that is Molgramostim, and 10 out of 39 (25.6%) had oxygen therapy. Regarding the status of vaccination against the COVID-19, 11 out of 39 patients (28.2%) had never received the vaccine, 5 out of 39 (12.8%) had received 2 doses of the vaccine, and 23 out of 39 (59.0%) had received 3 doses of the vaccine (Table 1).

We compared the 2 groups of patients with or without decreased oxygen saturation after COVID-19 infection and showed that patients who had previous oxygen therapy (decreased oxygen saturation vs. non decreased oxygen saturation: 6/12 vs. 4/27, *P* = 0.043) were more likely to have oxygen desaturation after COVID-19 infection. Patient age, gender, BMI, history of smoking, history of tuberculosis, comorbidities, history of whole lung lavage and GM-CSF inhalation therapy had no significant difference on whether patients had a decrease in oxygen saturation after COVID-19 infection. In addition, there was no significant difference in the number of doses of vaccination on whether oxygen saturation decreased after COVID-19 infection (*P* = 0.690) (Table 1).

Effect of baseline laboratory test information on whether oxygen saturation decreased after infection with COVID-19

For baseline ABG, patients with lower baseline PaO₂ were more likely to have decreased oxygen saturation after COVID-19 infection. PaO₂ (decreased oxygen saturation vs. non decreased oxygen saturation): 74.50 ± 13.61 mmHg versus 86.49 ± 11.92 mmHg, *P* = 0.009. For other blood parameters, we also found that patients with higher baseline LDH levels were more likely to have decreased oxygen saturation. LDH (decreased oxygen saturation vs. non decreased oxygen saturation): 298 (234, 377) U/L versus 218 (197, 309) U/L, *P* = 0.037 (Table 2).

For baseline pulmonary function, DLCO/VA% (decreased oxygen saturation vs. non decreased oxygen saturation): 77.0 (74.3, 93.6) % versus 89.5 (78.2, 97.4) %, *P* = 0.036. Patients with lower DLCO/VA% were more likely to have decreased oxygen saturation after infection with COVID-19. However, the remaining baseline pulmonary function measures were not statistically significantly different in predicting whether patients had a decrease in oxygen saturation after infection with COVID-19 (Table 2).

Results from the baseline 6MWD and SGRQ were also both correlated with whether patients had decreased oxygen saturation after infection with COVID-19. 6MWD (decreased oxygen saturation vs. non decreased oxygen saturation): 464 (406, 538) m versus 532 (470, 575) m, *P* = 0.028; total SGRQ score (decreased oxygen saturation vs. non decreased oxygen saturation): 46 (20, 64) versus 19 (8, 26), *P* = 0.009 (Table 2).

The baseline DSS of PAP patients better predicted the likelihood that PAP patients would have decreased oxygen saturation after COVID-19 infection. Patients with higher DSS, which means who suffered more severe disease with PAP, who were more likely to have decreased

Table 1 Baseline demographic characters

| Variables | All (n = 39) | Decreased oxygen saturation (n = 12) | Non decreased oxygen saturation (n = 27) | P value |
|--|----------------------|--------------------------------------|--|---------|
| Age (year) | 42.56 ± 12.28 | 44.92 ± 14.70 | 41.52 ± 11.19 | 0.485 |
| Male (%) | 25 (64.1%) | 6 (50.0%) | 19 (70.4%) | 0.287 |
| BMI (kg/m ²) | 24.61 (22.51, 26.78) | 23.42 (21.05, 26.67) | 24.61 (22.64, 26.78) | 0.480 |
| Main symptoms lead to medical advice | | | | 0.203 |
| Exertional dyspnea (%) | 12 (30.8%) | 5 (41.7%) | 7 (25.9%) | |
| Cough (%) | 16 (41.0%) | 6 (50.0%) | 10 (37.0%) | |
| Abnormal chest imaging found in physical examination (%) | 11 (28.2%) | 1 (8.3%) | 10 (37.0%) | |
| Smoking status | | | | 0.719 |
| Never (%) | 22 (56.4%) | 8 (66.7%) | 14 (51.9%) | |
| Ex-smoker (%) | 9 (23.1%) | 2 (16.7%) | 7 (25.9%) | |
| Current smoker (%) | 8 (20.5%) | 2 (16.7%) | 6 (22.2%) | |
| History of tuberculosis (%) | 5 (12.8%) | 1 (8.3%) | 4 (14.8%) | 1.000 |
| Hypertension (%) | 5 (12.8%) | 2 (16.7%) | 3 (11.1%) | 0.634 |
| Diabetes (%) | 3 (7.7%) | 2 (16.7%) | 1 (3.7%) | 0.219 |
| History of dust inhalation (%) | 14 (35.9%) | 4 (33.3%) | 10 (37.0%) | 1.000 |
| History of oxygen therapy (%) | 10 (25.6%) | 6 (50.0%) | 4 (14.8%) | 0.043 |
| History of systemic corticosteroids (%) | 12 (30.8%) | 3 (25.0%) | 9 (33.3%) | 0.719 |
| History of WLL (%) | 8 (20.5%) | 5 (41.7%) | 3 (11.1%) | 0.079 |
| History of GM-CSF inhalation (%) | 17 (43.6%) | 7 (58.3%) | 10 (37.0%) | 0.299 |
| Coronavirus vaccine (%) | | | | 0.690 |
| 0 | 11 (28.2%) | 4 (33.3%) | 7 (25.9%) | |
| 2 | 5 (12.8%) | 2 (16.7%) | 3 (11.1%) | |
| 3 | 23 (59.0%) | 6 (50.0%) | 17 (63.0%) | |

BMI Body mass index, CT Computer tomography, GM-CSF Granulocyte macrophage colony stimulating factor, WLL Whole lung lavage

oxygen saturation after COVID-19 infection ($P=0.017$) (Table 2).

In univariate analysis, DSS, LDH level and DLCO/VA% were all predictors of whether oxygen saturation decreased after infection with COVID-19. However, in multivariate analysis, only the DSS categories was independent predictor of whether oxygen saturation decreased in patients infected with COVID-19 in this cohort (≥ 3 ; OR 24.000; 95% CI 1.689–340.992; $P=0.019$).

Symptoms and interventions after infection with COVID-19

After COVID-19 infection, patients may develop a variety of clinically relevant symptoms, the most frequent of which is fever, with 33 out of 39 patients (84.6%) experiencing fever after COVID-19 infection, followed by asthenia in 24 out of 39 (61.5%), expectoration in 20 out of 39 (51.3%), headache in 19 out of 39 (48.7%), pharyngalgia or cough in 18 out of 39 (46.2%), and a number of other COVID-19 relevant symptoms, including nasal congestion, rhinorrhea, hyposmia, hypogeusia, myalgia, and diarrhea, none of which correlated significantly with whether patients had decreased oxygen saturation.

However, dyspnea symptoms were significantly correlated with decreased oxygen saturation ($P<0.001$), with 7 out of 39 patients (17.9%) had new-onset dyspnea, 6 out of 39 patients (15.4%) had worsening dyspnea, and the remaining patients did not have dyspnea symptoms (Table 3).

Thirteen out of 39 patients (33.3%) had outpatient or emergency department visits after COVID-19 infection; 4 out of 39 (10.3%) were hospitalized, all of whom had decreased oxygen saturation, but none were admitted to the ICU. Six out of 39 patients (15.4%) required additional oxygen therapy or had increased oxygen conditions than before, all of whom were treated with nasal catheter oxygen therapy. Thirty-six out of 39 patients (92.3%) were taking NSAIDs or analgesics, including but not limited to acetaminophen, ibuprofen, and loxoprofen sodium; 9 out of 39 (23.1%) were taking antibiotics; 3 out of 39 (7.7%) were on systemic corticosteroids. Moreover, only 2 patients took antivirals for COVID-19, one for Azvudine and another for Nirmatrelvir/ritonavir. Patients with decreased oxygen saturation after COVID-19 infection were more

Table 2 Baseline laboratory test information

| Variables | All (n = 39) | Decreased oxygen saturation (n = 12) | Non decreased oxygen saturation (n = 27) | P value |
|--|--------------------|--------------------------------------|--|---------|
| Arterial blood gas | | | | |
| pH | 7.41 ± 0.02 | 7.41 ± 0.03 | 7.41 ± 0.02 | 0.351 |
| PaCO ₂ (mmHg) | 37.56 ± 3.11 | 37.92 ± 2.35 | 37.40 ± 3.42 | 0.639 |
| PaO ₂ (mmHg) | 82.80 ± 13.50 | 74.50 ± 13.61 | 86.49 ± 11.92 | 0.009 |
| SaO ₂ (%) | 96.5 (95.3, 97.7) | 95.4 (93.4, 97.7) | 96.5 (95.7, 97.7) | 0.245 |
| A-aDO ₂ (mmHg) | 21.8 (9.6, 31.2) | 26.8 (16.0, 42.9) | 21.8 (8.9, 27.7) | 0.159 |
| HCO ₃ ⁻ (mmol/L) | 23.04 ± 1.85 | 23.48 ± 1.62 | 22.85 ± 1.94 | 0.339 |
| Serology | | | | |
| HGB (g/L) | 158.36 ± 17.77 | 155.25 ± 21.39 | 159.74 ± 16.18 | 0.474 |
| RBC# (× 10 ¹² /L) | 5.21 ± 0.61 | 5.10 ± 0.82 | 5.26 ± 0.51 | 0.456 |
| HCT (%) | 45.65 ± 4.76 | 44.78 ± 6.00 | 46.04 ± 4.17 | 0.454 |
| CEA (ng/ml) | 4.00 (2.43, 7.60) | 4.00 (2.29, 20.40) | 3.90 (2.43, 7.30) | 0.298 |
| Cyfra21-1 (ng/ml) | 4.60 (2.60, 9.50) | 7.05 (4.00, 11.70) | 3.60 (2.30, 7.52) | 0.072 |
| LDH (U/L) | 243 (204, 350) | 298 (234, 377) | 218 (197, 309) | 0.037 |
| Pulmonary function | | | | |
| FEV ₁ pred (%) | 88.0 (75.5, 99.2) | 90.0 (67.0, 104.7) | 88.0 (77.0, 98.0) | 0.799 |
| FVC pred (%) | 91.0 (77.0, 101.0) | 86.0 (68.3, 105.5) | 95.0 (78.0, 101.0) | 0.753 |
| FEV ₁ /FVC (%) | 81.5 (77.9, 87.0) | 83.6 (81.1, 87.8) | 80.3 (76.8, 86.8) | 0.221 |
| TLC pred (%) | 85.0 (73.0, 94.0) | 83.9 (65.7, 103.7) | 85.0 (77.0, 94.0) | 0.799 |
| RV pred (%) | 86.0 (71.0, 99.0) | 91.0 (73.6, 105.8) | 85.0 (68.5, 99.0) | 0.822 |
| DLCO pred (%) | 68.3 (52.1, 81.8) | 63.3 (44.9, 83.8) | 69.6 (63.2, 80.5) | 0.284 |
| DLCO/VA pred (%) | 83.8 (75.4, 97.4) | 77.0 (74.3, 93.6) | 89.5 (78.2, 97.4) | 0.036 |
| 6MWD (m) | 512 (463, 570) | 464 (406, 538) | 532 (470, 575) | 0.028 |
| Borg at the end of 6MWD | 1 (0, 2) | 1 (0, 3) | 0 (0, 2) | 0.538 |
| SGRQ | | | | |
| Symptom | 28 (12, 47) | 43 (27, 69) | 24 (9, 36) | 0.010 |
| Activity | 29 (17, 47) | 56 (23, 82) | 23 (6, 36) | 0.005 |
| Impact | 14 (1, 43) | 40 (13, 56) | 9 (0, 23) | 0.022 |
| Total | 21 (9, 51) | 46 (20, 64) | 19 (8, 26) | 0.009 |
| DSS | | | | |
| 1 | 13 (33.3%) | 1 (8.3%) | 12 (44.4%) | |
| 2 | 20 (51.3%) | 7 (58.3%) | 13 (48.1%) | |
| ≥ 3 | 6 (15.4%) | 4 (33.3%) | 2 (7.4%) | |

6MWD 6 min walking distance (test), A-aDO₂ Alveolar arterial oxygen gradient, CEA Carcinoembryonic antigen, Cyfra21-1 Cytokeratin 19 fragment antigen21-1, DLCO Diffusing capacity for carbon monoxide, DLCO/VA Diffusing capacity for carbon monoxide corrected for alveolar volume, DSS Disease severity score, FEV₁ Forced expiratory volume in the first second, FVC Forced vital capacity, HCO₃⁻ Carbonic acid hydrogen radical, HCT Hematocrit, HGB Hemoglobin, pH Pondus hydrogenii, LDH Lactate dehydrogenase, PaCO₂ Partial pressure of carbon dioxide, PaO₂ Partial pressure of oxygen, RBC Red blood cell, RV Residual volume, SaO₂ Oxygen saturation of blood, SGRQ St George Respiratory Questionnaire, TLC Total lung capacity

likely to require oxygen therapy ($P < 0.001$) and to be taking systemic corticosteroids ($P = 0.024$) and antibiotic ($P = 0.014$) medications. For aPAP patients on GM-CSF inhalation therapy, 8 out of 13 (61.5%) of such patients continuously GM-CSF inhalation therapy after COVID-19 infection compared with 5 out of 13 (38.5%) who discontinued it. There was no significant difference in whether aPAP patients continuously used or discontinued GM-CSF inhalation therapy after COVID-19 infection on whether patients had a decrease in oxygen saturation (Table 3).

Discussion

In this study, we reported the clinical manifestations of patients with aPAP after infection with Omicron variants of SARS-CoV-2 for the first time. We found that aPAP patients with worse baseline respiratory status were more likely to have oxygen desaturation after COVID-19 infection, which means that such patients are more likely to have relatively serious symptoms such as dyspnea or worse prognosis after COVID-19 infection. In addition, we first reported the hospitalization rate of patients with aPAP after infection with Omicron strain, which was

Table 3 Symptoms and interventions after infection with COVID-19

| Variables | All (n = 39) | Decreased oxygen saturation (n = 12) | Non decreased oxygen saturation (n = 27) | P value |
|--------------------------|--------------|--------------------------------------|--|---------|
| Dyspnea | | | | < 0.001 |
| Never | 26 (66.7%) | 3 (25.0%) | 23 (85.2%) | |
| New-onset | 7 (17.9%) | 5 (41.7%) | 2 (7.4%) | |
| Worsen | 6 (15.4%) | 4 (33.3%) | 2 (7.4%) | |
| Interventions | | | | |
| Outpatient or emergency | 13 (33.3%) | 6 (50.0%) | 7 (25.9%) | 0.163 |
| NSAIDs or analgesics | 36 (92.3%) | 11 (91.7%) | 25 (92.6%) | 1.000 |
| Systemic corticosteroids | 3 (7.7%) | 3 (25.0%) | 0 (0.0%) | 0.024 |
| Antibiotics | 9 (23.1%) | 6 (50.0%) | 3 (11.1%) | 0.014 |
| Hospitalized | 4 (10.3%) | 4 (33.3%) | 0 (0.0%) | 0.006 |
| GM-CSF inhalation | | | | 0.222 |
| Never | 26 (66.7%) | 6 (50.0%) | 20 (74.1%) | |
| Continuously used | 8 (20.5%) | 3 (25.0%) | 5 (18.5%) | |
| Discontinue | 5 (12.8%) | 3 (25.0%) | 2 (7.4%) | |

GM-CSF Granulocyte macrophage colony stimulating factor

lower than the previously reported hospitalization rate of PAP patients infected with COVID-19 [5].

Our study found that the infection rate of COVID-19 in aPAP patients was a little bit higher than that estimated by the Chinese Center for Disease Control and Prevention (CDC) in the same period. The infection rate of COVID-19 in aPAP patients in this study was 95.12%, while the CDC estimated that the infection rate of COVID-19 in China was 82.4% as of February 7, 2023 [14]. We believe that this is likely due to the estimated results of the CDC through online survey. A considerable part of the population directly took non-steroidal anti-inflammatory drugs due to fever or other symptoms after COVID-19 infection, and did not report the infection, which may underestimate the infection rate of the COVID-19 pandemic in China. Meanwhile, a retrospective cohort study in Europe found that the infection rate of PAP patients was similar to that of the general population [5]. Therefore, we believe that aPAP does not increase the probability of COVID-19 infection in patients.

The main finding of this study was that patients with poor baseline respiration have a higher probability of hypoxia after COVID-19 infection. Previous research has not mentioned this point. Our study found that the indicators indicating the baseline respiratory status of patients with aPAP, previous oxygen therapy, PO₂, DLCO/VA%, 6MWD, SGRQ total score, DSS categories, all of which showed that patients with poor baseline respiratory status were more likely to have oxygen saturation decline after COVID-19 infection. This is of great significance for the treatment of PAP patients and even

patients with other interstitial lung diseases after infection with COVID-19. When patients with COVID-19 develop hypoxemia, it often means the progression of COVID-19, more serious symptoms, and worse prognosis. Therefore, for those PAP patients with poor baseline respiratory condition, when they are diagnosed with COVID-19 infection, doctors should pay more attention and take more active treatment strategies to avoid disease progression.

Another important finding was our study first reported the hospitalization rate of patients with aPAP infected with Omicron strain. Only 4 out of 39 patients were hospitalized, and the hospitalization rate was 10.3%, which is much lower than the previous reported in the European cohort with the rate of 35.5%. Meanwhile, all hospitalized patients in this study did not need ICU admission, and none of our patients including no responded patients died or need lung transplantation. However, almost 50% of hospitalized patients in the European cohort entered the ICU. Besides, there were also 2 out of 11 hospitalized patients died and 1 out of 11 hospitalized patients underwent lung transplantation [5]. This huge difference between the two studies may be caused by a variety of factors. Firstly, none of the patients in the European cohort study were vaccinated, while the vaccination rate of patients in our study was 71.8%. Although it was not found in our study that the dose of vaccination had a significant difference on whether patients would suffer from hypoxia after COVID-19 infection, a large number of previous studies have shown that vaccination can provide a very high level of protection and effectively reduce the rates of severity and mortality after COVID-19 infection

[15]. Secondly, the SARS-CoV-2 strains infected by the patients in this study were all Omicron strains, while the European cohort did not mention what their infected strains were. Based on the enrollment time, it is speculated that the European cohort may be infected with Alpha or Delta strains, and Omicron strains should not be included. Different strains of the SARS-CoV-2 can lead to different infection and severity rates. Although the 10.3% hospitalization rate is not as high as expected, it is still relatively high compared to the general population (less than 1%), highlighting the vulnerability of the PAP population and the need for more attention after infection [16].

Our single-center study found that aPAP patients infected with COVID-19 in our cohort rarely used antiviral therapy. One out of 2 patients receiving antiviral therapy was hospitalized. Patients with high viral load of SARS-CoV-2 are more likely to develop severe disease, and early inhibition of viral replication can significantly improve the prognosis of patients with COVID-19 [17, 18]. PAP patients with worse baseline respiratory status are more prone to hypoxia after infection, so we'd like to suggest that PAP patients prescribe timely antiviral therapy.

GM-CSF plays a key role in host lung defense. The presence of anti GM-CSF antibodies in patients with aPAP leads to a reduction in the ability of alveolar macrophages to clear debris and pathogens, maintain surfactant homeostasis, and limit inflammation in the alveolar environment [19]. A study of inhaled GM-CSF in the treatment of COVID-19-related hypoxemia found that inhaled GM-CSF treatment could effectively improve A-aDO₂ in patients [7]. The European cohort study found that previous inhalation of GM-CSF treatment had no effect on the outcome or hospitalization of PAP patients infected with COVID-19, which is consistent with our findings [5]. There was no significant difference in the decrease of blood oxygen saturation no matter whether GM-CSF inhalation therapy was used in the past ($P=0.299$), or GM-CSF inhalation therapy was continuously used or discontinued after covid-19 infection ($P=0.222$). Therefore, whether inhaled GM-CSF treatment has benefits for PAP patients with COVID-19 still needs to be explored.

As an interstitial lung disease, doctors should take different treatments and monitoring strategies for PAP patients infected with COVID-19 according to different conditions. An international multicenter study showed that patients with interstitial lung disease had higher mortality after infection with COVID-19 compared with patients without interstitial lung disease or other chronic lung diseases [4]. However, data on COVID-19 in rare lung diseases are still scarce. Although a European cohort

study showed that PAP patients had higher hospitalization rate and mortality after infection [5], but there still lacks of guideline or standards for PAP patients to better cope with COVID-19 in the current medical system. Our research fills this gap well. PAP patients simultaneously infected with COVID-19 has the risk of aggravating COVID-19. For patients with mild PAP, the risk of progression of COVID-19 is not much. However, for patients with higher DSS and more severity of PAP, the probability of oxygen desaturation greatly increases. Vaccination, timely oxygen therapy, early use of antiviral medication, and timely vital signs monitoring may minimize the disease progression of patients. It's urgent to establish a treatment strategy for patients with PAP after infected with COVID-19 in the future (Additional file 1).

There are some limitations in this study. Due to the fact that PAP is a rare lung disease and this study is a single center study, the number of PAP patients eligible for inclusion in the study is relatively small. In addition, due to the COVID-19 pandemic, many PAP patients have not been followed up in the past year due to the lockdown policy. This may lead us to underestimate the probability of serious events occurring in PAP patients infected with COVID-19. Although multivariate analysis was carried out, due to the limited number of patients and oxygen saturation decrease events, we only found DSS as a predictor to predict the possibility of patients' oxygen saturation decline. Whether PAP itself will progress after infection with COVID-19 in PAP patients is also a point of great interest to us, which requires further follow-up research.

Conclusion

In conclusion, we found for the first time that the worse baseline respiratory status of patients with aPAP increased the probability of oxygen desaturation after infection with COVID-19. Meanwhile, we first reported the hospitalization rate of patients with aPAP caused by Omicron variant of SARS-CoV-2. All these will provide valuable data to make better medical strategies for PAP patients infected with COVID-19 in the future.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13023-023-02950-9>.

Additional file 1. Questionnaire of pulmonary alveolar proteinosis patients infected with COVID-19.

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Author contributions

XT proposed the idea and contributed a critical review of the manuscript. CD and WZ wrote the initial draft to which all authors contributed. CD, WZ, MZ, CC, WX, JD, SM, KC, YZ contributed to the collection of data. CD, WZ, SL, SW, YY, KX and XT contributed to data analysis, data interpretation, and approval of the final version. All authors read and approved the final manuscript.

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Availability of data and materials

Raw data for Tables 1, 2 and 3 are not publicly available due individual privacy but are available from the corresponding author on reasonable request.

Declarations**Ethics approval and consent to participate**

The protocol was approved by the ethical committee of the Peking Union Medical College Hospital (JS-2639). Informed consents were signed by all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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