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Hypersensitivity pneumonitis in Covid-19: Mortality, risk factors, and clinical outcomes from a 30-case observational study

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To the editor,

Several clinical studies have been published that investigated risk factors and mortality of COVID-19 and preexisting lung diseases during the COVID-19 pandemic. There were some risk factors defined as associated with mortality of COVID-19, such as smoking, older age, male gender, diabetes, cardiovascular diseases, chronic obstructive lung disease, hypertension, thoracic malignancy and intersititial lung diseases (ILD) (1). However, there were a few studies on mortality in COVID-19 patients with hypersensitivity pneumonitis (HP). This paper aims to investigate the mortality and related risk factors in hospitalized patients with HP for COVID-19. Between March 11, 2020, and December 30, 2022, 30 patients with HP who were hospitalized for COVID-19 were retrospectively evaluated. The hospital database was queried for the demographic and clinical information of all patients. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) Version 25.0 (SPSS Inc.; Chicago, IL, USA). Absolute numbers and percentages were employed to represent categorical variables. As continuous variable numbers were presented them as the mean and standard deviation. The chi-square test/Fisher's exact test was used for categorical variables, and the Student's t-test was used for continuous variables. This study enrolled thirty patients (18 females, 12 males) diagnosed with HP and COVID-19 positive from throat swap by real-time PCR samples. All patients had dyspnea, cough, and fever at hospital admission. Blood C-reactive protein (CRP), sedimentation, Lactate dehydrogenase (LDH), d-dimer, procalcitonin, ferritin, and fibrinogen levels were higher than the normal range. Also, arterial blood gas analyses show hypoxemia at hospital admission. The demographic, clinical and functional characteristics of the patients are shown in Table. Thoracic computed tomography (CT) revealed that newly added ground-glass opacities (GGOs) (4, 13.3%), consolidation (10, 33.3%), both GGOs and consolidation (14, 46.7%), 2 (12.4%) of them had no newly added radiological (Figure 1).

Median hospital stay was 9 (IQR, 4-7; range 1-39) days, and the median hospital stay was longer in non-survival patients (8.2 (IQR 2.5) vs 21.5 (4.8) p=0.005). Twenty-three patients had used only methylprednisolone; the other four used methylprednisolone plus azathioprine before the COVID-19 diagnosis; the others had no treatment for HP in the previous six months. Non-specific antibiotics, low molecular weight heparin, proton pump inhibitor, and vitamin C were added to the treatment. Methylprednisolone treatment was added or increased to 80 mg/day in addition to routine COVID-19 treatment. Before COVID-19 infection, 5 (16.7%) patients had used LTOT at home,

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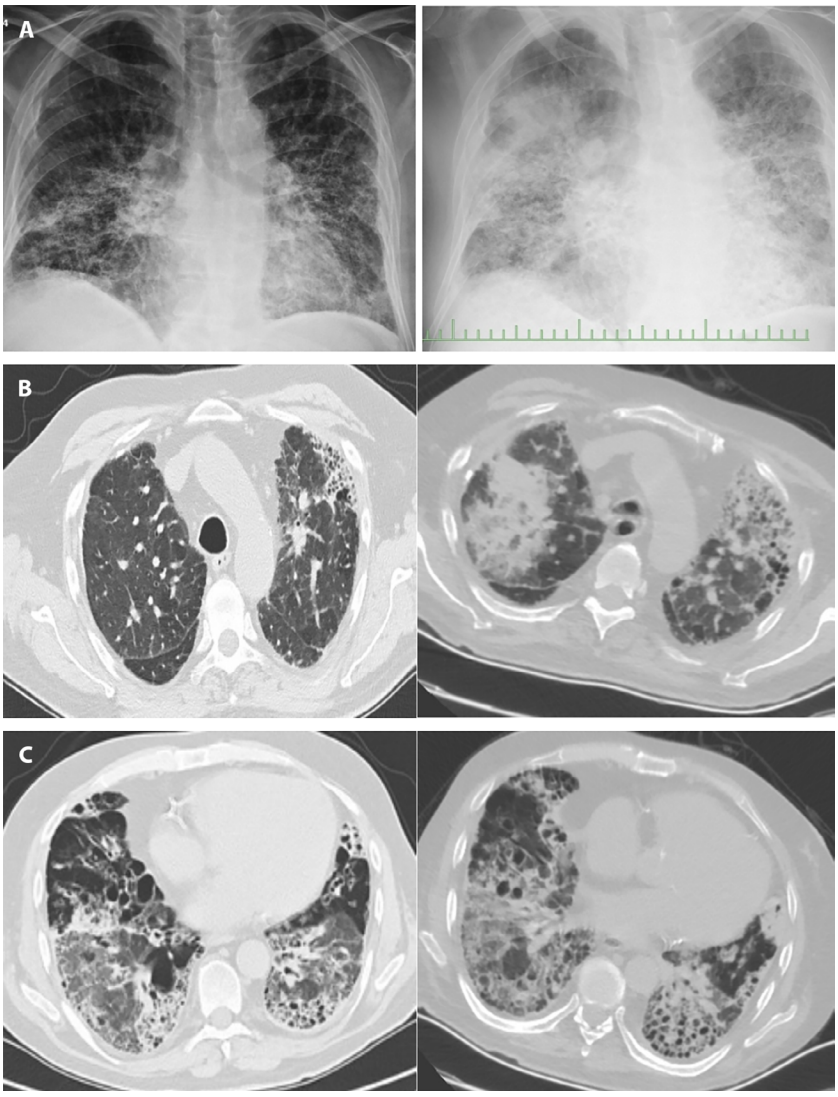

Figure 1. Posteroanterior chest radiography (A) of Chest-X ray and axial-thin section thorax CT images (B, C) were shown for Case 3 with HP. On the left side, radiological images show before the Covid-19 pandemic, and on the right-side radiological images show during Covid-19 pneumonia. Reticulation, ground-glass opacities, and honeycombing were seen on the left side before Covid-19 pneumonia. Increased ground-glass opacities on the left upper lobe, new consolidation on the right upper lobe, and air trapping in the bilateral lower lobes were shown in Covid-19 pneumonia.

but during COVID-19 infection, all patients had needed supplemental oxygen therapy via nasal cannula (15, 50%) or high flow nasal oxygen (4, 13.3%). Others required non-invasive mechanical ventilation (NIMV) (2, 6.7%) or invasive mechanical ventilation (IMV) (9, 30%). During hospitalization for COVID-19 in preexisting HP, there were nine deaths, and overall mortality was 30%. No statistical significance was observed between survival and non-survival groups regarding gender, age, smoking history, and comorbidities. The mean FEV1% predicted, FVC% predicted, DLCO and 6MWT were lower in non-survivors than survivor patients. The mean neutrophil count, neutrophils- lymphocyte ratio, and CRP were higher in the non-survivor group (Table 1). The multivariate model was performed including age, gender, FVC% predicted, FEV1% predicted, DLCO%, 6MWT; and none of the factors related to mortality in HP patients with COVID-19.

Table 1. Demographic and clinical characteristics of survival and non-survival groups of HP Patients with COVID-19.

Variables	Survivors (n=21)	Non-survivors (n=9)	P value
Age, years old, Mean (SD)(Range)	58.1 (11.6)	60.9 (12.1)	0.548
Sex, Female/Male, n (%)	14 (66.7)/7 (33.3)	4 (44.5)/5 (55.5)	0.418
Smoking history, n (%)			
Non-smoker	15 (71.4)	3 (33.3)	0.102
Current smoker	6 (28.5)	6 (66.6)	
Comorbidities, n (%)			
Any comorbidities	12 (57.1)	7 (77.8)	0.419
Hypertension	6 (28.5)	5 (55.5)	0.227
CAD	7 (33.3)	4 (44.4)	0.687
Diabetes	5 (23.8)	4 (44.4)	0.389
FEV1, %predicted, Mean±SD (range)	86.6±23.8	54.9±19.1	**0.005**
FVC, % predicted, Mean±SD (range)	85.7±23.8	49.7±17.3	**0.001**
FEV1/FVC, Mean±SD (range)	88.2±10.8	90.4±11.4	0.661
DLCO, % predicted, Mean±SD (range)	60.5±11.6	44.3±17.9	**0.012**
6MWT, m, Mean±SD (range)	445±77	292±40	**0.002**
Lymphocyte count, 10^{-3}/uL	1890±855	1605±952	0.455
Neutrophils count, 10^{-3}/uL	6155±2107	9813±3200	**0.003**
N/L ratio	3.7±1.7	10.2±2.1	**0.035**
Platelet count, 10^{-3}/uL	263±82	285±51	0.484
Hemoglobin, g/dL	12.5±2.6	12.7±2.0	0.837
Creatinin, mg/dL	0.81±0.24	0.85±0.33	0.754
BUN, mg/dL	18.6±5.7	32.2±25.1	0.079
CRP, mg/L	31.9±8.2	102.7±9.8	**0.018**
Sedimentation, mm/h	47.7±20.2	42±19.6	0.700
Fibrinogen, mg/dL	484±91	558±99	0.172

Abbreviations: SD: Standard deviation, CAD: Coronary artery disease, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, DLCO: Diffusion capacity of the lung for carbon monoxide, 6MWT: Six-minute walk test (m), N/L: Neutrophil to lymphocyte ratio, BUN: Blood urea nitrogen, CRP: C-reactive protein.

As a result, our analysis shows that functional parameters like lower FEV1% predicted, FVC% predicted, DLCO%, and 6MWT were related to a high risk of death in hospitalized HP patients with COVID-19 infection. Also, the mean neutrophil count, N/L ratio, and CRP level were higher in the non-survivor group than in the survivor group. In Drake and colleagues' study, in-hospital mortality of 161 patients with interstitial lung disease that included IPF (42.2%), HP (8.7%), connective tissue disease-related ILD (8.1%), rheumatoid-related ILD (6.2%), sarcoidosis (5.6%), and other types of ILD compare with a control group of patients with COVID-19 without underlying lung disease (2). They reported that patients with ILD have higher in-hospital mortality than the control group (49% vs. 35%); male sex and older age have increased mortality risk (2). Another study investigated 46 ILD patients with COVID-19 compared with a control group. The mortality rate was 33% for patients with ILD and 13% for the control group. They also compared survivor and non-survivor groups of ILD and age; serum ferritin and troponin levels were higher in the non-survivor group (3). In our study, the mechanical ventilation requirement rate and mortality rate in HP patients with COVID-19 were both 30%, respectively, and this mortality rate was lower than in Drake's study. This difference might be due to the study population; in Drake's study population was not only HP patients but also other ILDs like idiopathic pulmonary fibrosis, connective tissue disease-related ILD, and sarcoidosis. Our study showed no statistical difference between survival and non-survival groups in age, gender, and comorbidities. However, functional parameters like FEV1%, FVC%, DLCO%, and 6MWT, which had been used to determine the outcome for ILD patients, had related to mortality. Research on COVID-19 patients who need intubation for acute respiratory failure rate is changing between 42% to 88% in-hospital stay (4). In our cases, nine of them were intubated for acute respiratory failure, and died in ICU. However, increasing knowledge of the pathophysiology and treatment of COVID-19 over time, like using a high-flow nasal cannula, proning position, and the application of lung-protective mechanical ventilation strategy, might be increase the survival of HP patients with COVID-19. During the COVID-19 pandemic, treatment strategies have been changing, and steroids have been used more in COVID-19 patients with respiratory failure. Tomazini et al. reported that dexamethasone plus standard care for moderate or severe ARDS due to COVID-19 increased the number of days alive free of MV during the first 28 days (5). Although chronic steroid usage is one cause of immunosuppression, The Randomized Evaluation of

COVID-19 Therapy (RECOVERY) study showed that early use of dexamethasone reduced 28-day mortality in patients receiving invasive mechanical ventilation and oxygen alone (6). Recent guidelines for COVID-19 treatment have suggested using CS for respiratory failure in adult COVID-19 patients. In our study, some patients used CS alone or with azathioprine before COVID-19, CS dosage over 40mg per day was not given to HP patients with respiratory failure related to COVID-19. Neither national nor international guidelines recommended high-dose CS to treat COVID-19 in the first wave of the pandemic. We thought treatment strategies were changing during the pandemic period. Nowadays, healthcare professionals who care for COVID-19 tend to provide pulse or high dose CS for hospitalized patients with respiratory failure to increase survival and decrease pulmonary sequela. There are some limitations to this study. The number of patients was low, making it difficult to generalize the knowledge. Although our hospital is a reference center for chest disease, the study was performed single center, limiting the generalizability of the results. In conclusion, a limited number of studies investigate the impact of COVID-19 on patients with preexisting interstitial lung disease, especially in HP cases. In our observational study, we have noticed that functional parameters like lower FEV1% predicted, FVC% predicted, DLCO%, and 6MWT were related to a high risk of death in hospitalized HP patients. However, the impact of COVID-19 on patients with preexisting HP remains unknown, and it will be essential to plan new research by increasing the number of cases.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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