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Risk Factors for Secondary Organizing Pneumonia and Acute Fibrinous and Organizing Pneumonia in Patients with COVID-19 Pneumonia

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Purpose: Secondary organizing pneumonia (OP) and acute fibrinous and organizing pneumonia (AFOP) are frequently observed in cases of COVID-19 pneumonia. Nevertheless, the identification of risk factors related to OP/AFOP and their impact on patient outcomes remain inadequately elucidated.

Patients and Methods: This retrospective study aimed to identify risk factors associated with OP/AFOP in patients with COVID-19 pneumonia and to compare clinical outcomes between patients with and without OP/AFOP. The study included hospitalized patients with COVID-19 pneumonia admitted between July 1 and September 30, 2021. Factors associated with OP/AFOP were identified using multivariable regression analysis. Additionally, a multivariable Cox proportional hazard model was used to evaluate the association of OP/AFOP with 90-day mortality.

Results: Among the 666 hospitalized patients with COVID-19 pneumonia, 53 (8%) developed OP/AFOP during their admission. When compared to patients younger than 50 years old, those aged 50–70 and over 70 years old exhibited an increased risk of developing OP/AFOP, with adjusted odds ratios (aOR) of 3.87 (95% CI, 1.24–12.11; P=0.02) and 5.74 (95% CI, 1.80–18.27; P=0.003), respectively. Other factors associated with OP/AFOP included a history of diabetes mellitus (aOR 2.37; 95% CI, 1.27–4.44; P=0.01) and patients with oxygen saturation at admission below 88% (aOR 4.52; 95% CI, 1.22–16.67; P=0.02). Furthermore, the presence of OP/AFOP was correlated with an increased risk of various complications, such as respiratory failure, acute kidney injury, secondary infections, pneumothorax, pneumomediastinum, and pulmonary embolism. Lastly, patients with OP/AFOP exhibited significantly higher 90-day mortality (adjusted hazard ratio 3.40; 95% CI, 1.68–6.92; P=0.001) compared to those without OP/AFOP.

Conclusion: We identified factors associated with an increased risk of OP/AFOP in patients with COVID-19 pneumonia, which included age ≥50 years, a history of DM, and hypoxemia on admission (SpO2 <88%). Furthermore, our study revealed that OP/AFOP was significantly linked to higher 90-day mortality.

Keywords: COVID-19, pneumonia, organizing pneumonia, acute fibrinous and organizing pneumonia, risk factor, mortality, complication

Introduction

The novel Coronavirus Disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a significant global public health and economic burden.[1] Amid the delta variant pandemic, pneumonia developed in 50–90% of COVID-19 patients.[2] During the late phase of COVID-19 pneumonia, typically occurring after 2 weeks of infection, secondary organizing pneumonia (OP) and acute fibrinous and organizing pneumonia (AFOP) may emerge and significantly contribute to the majority of COVID-19 respiratory complications.

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The pathogenesis of OP originates with alveolar injury leading to an accumulation of fibrin and fibroblast, then followed by the formation of intra-alveolar buds of granulation tissue. On the other hand, AFOP is a more severe pattern of lung injury with hallmark histological findings include intra-alveolar "fibrin balls" accumulation within the alveolar spaces.[3] Organizing pneumonia and AFOP can be idiopathic or secondary to infections, connective tissue diseases, drug toxicity, or occupational exposures.[4] Post-mortem studies of patients with COVID-19 pneumonia have demonstrated a histological pattern of OP/AFOP in individuals who experienced symptoms lasting for more than 20 days. In contrast, in patients in the early phase of the disease, characterized by symptoms lasting ≤10 days, a predominantly diffuse alveolar damage (DAD) pattern was evident.[5,6] In addition, evidence of the histopathological transition of lung parenchyma from DAD to AFOP during the later stage of COVID-19 pneumonia has been documented.[7]

Nowadays, systemic corticosteroids remain the mainstay of treatment for secondary OP/AFOP in COVID-19 pneumonia. While the majority of patients with secondary OP/AFOP can resolve spontaneously or exhibit an excellent response to systemic corticosteroid therapy, approximately 5–8% of COVID-19 patients with OP/AFOP experience rapid progression to fulminant respiratory failure, extensive pulmonary fibrosis, and death.[3] Knowing the risk factors associated with OP/AFOP allows clinicians to focus on high-risk patients and diagnose this condition in a timely manner. To date, the knowledge of risk factors for secondary OP/AFOP in COVID-19 patients remains limited. Therefore, we conducted this study to identify the risk factors associated with developing secondary OP/AFOP and assess the outcome of OP/AFOP in patients with COVID-19 pneumonia.

Materials and Methods

Study Population

A retrospective cohort study included patients admitted with COVID-19 pneumonia to Chakri Naruebodindra Medical Institute between July and September 2021. Confirmation of COVID-19 pneumonia was based on a positive polymerase chain reaction (PCR) test and radiological findings consistent with COVID-19 pneumonia on chest x-ray or computed tomography (CT). Patients with incomplete information on baseline characteristics and treatment, as well as those with a follow-up time of less than 14 days from the day of illness (DOI), were excluded from the study. Treatment of COVID-19 pneumonia, including the use of antivirals, steroids, and immunomodulators (tocilizumab, tofacitinib, and baricitinib), as well as the application of high-flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation, was based on local guidelines (Supplementary File) and the clinical judgment of the attending physicians. The study protocol was approved by the Ethics Committee on Human Experimentation of Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok (MURA2022/140). Informed consent was waived because of the retrospective nature of the study.

Data Collection

The electronic medical records of eligible patients were accessed on April 1, 2022. The authors had no access to information that could identify individual participants during or after data collection. The data was maintained with confidentiality. Baseline demographics, clinical manifestations, relevant laboratory tests at admission, treatment data, hospital length of stay, requirements for mechanical ventilation, acute kidney injury (AKI), secondary infections, pneumothorax, pneumomediastinum, pulmonary embolism, and death were collected.

Diagnosis of Secondary OP/AFOP

The diagnosis of OP/AFOP was based on clinical and radiological findings. Two physicians (T.P. and A.A.) reviewed all chest radiographs and chest CT scans to consider the diagnosis of OP/AFOP. Secondary OP/AFOP was defined as a worsening of respiratory symptoms and ongoing progression of pulmonary infiltration or new radiological changes compatible with OP/AFOP after 14 days from the day of illness (DOI). Additionally, these radiological changes were not attributable to other causes and showed a positive response to corticosteroid treatment.

Radiographic findings consistent with OP/AFOP included all of the following: 1) peripheral and/or peribronchovascular location; 2) consolidation with or without associated patchy ground-glass opacity; 3) lower lung predominance.[8–10] Representative chest X-ray and CT findings of the patient with OP/AFOP are provided in the Supplementary File.

Statistical Analysis

Continuous variables are summarized as mean and standard deviation or median with interquartile range, as appropriate. Categorical variables are presented as frequencies with percentages. Baseline characteristics and laboratory tests were compared between COVID-19 pneumonia patients with and those without OP/AFOP. Pearson's $\chi 2$ or Fisher's exact test was used to compare categorical variables. Continuous variables were compared using Student's *t*-test or Mann–Whitney *U*-test, as appropriate.

Multivariate logistic regression analysis was used to identify risk factors associated with the development of OP/AFOP. Survival curves were developed using the Kaplan-Meier. Cox proportional hazards model was used to assess the association of the development of OP/AFOP with the risk of mortality. The Cox proportional hazards model was adjusted for pre-specified risk factors for mortality in COVID-19 patients, including age, gender, body mass index (BMI), serum D-dimer levels, serum lactate dehydrogenase (LDH) levels, and serum creatinine levels.[11,12] *P*-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using Stata v. 17.0 software (Stata Corporation LLC, College Station, USA).

Results

Of 700 hospitalized patients with COVID-19 pneumonia, 34 patients were excluded due to missing data (2 patients) and having follow-up duration <14 days (32 patients). Remaining 666 patients were included in the final analysis.

In the cohort of 666 patients, a subset of 53 individuals (8%) developed secondary OP/AFOP. The baseline characteristics of patients with and without OP/AFOP are shown in Table 1. The OP/AFOP group had a higher mean age compared to those without OP/AFOP. No significant gender difference was observed between the two groups (54.7% male in the OP/AFOP group; 46.3% male in the non-OP/AFOP group, P = 0.24). The majority of patients in this study did not receive the full course of COVID-19 vaccination (less than 2 doses). Only one (2.4%) patient in the OP/AFOP group and 82 patients

Table 1 Baseline Characteristics of Patients with COVID-19 Pneumonia with OP/AFOP and Without OP/AFOP

Baseline Characteristics	Patients With OP/AFOP, n (%) N = 53	Patients Without OP/AFOP, n (%) N = 613	*P*-value
Age	68.7 ± 14.7	56.2 ± 18.2	<0.001
Age group			<0.001
< 50 years	5 (9.4%)	224 (36.5%)	
50–70 years	23 (43.4%)	229 (37.4%)	
> 70 years	25 (47.2%)	160 (26.1%)	
Male sex	29 (54.7%)	284 (46.3%)	0.24
Smoking	7 (13.2%)	86 (14.0%)	0.87
BMI	25.8 ± 5.2	26.7 ± 6.3	0.32
History of COVID-19 vaccine			0.08
No vaccine	26 (61.9%)	338 (58.6%)	
1 dose	15 (35.7%)	157 (27.2%)	
Complete vaccination (at least 2 doses)	1 (2.4%)	82 (14.2%)	

(*Continued*)

Table 1 (Continued).

Baseline Characteristics	Patients With OP/AFOP, n (%) N = 53	Patients Without OP/AFOP, n (%) N = 613	*P*-value
Comorbid			
DM	30 (56.6%)	173 (28.2%)	<0.001
IHD	8 (15.1%)	41 (6.7%)	0.04
COPD	3 (5.7%)	13 (2.1%)	0.13
Asthma	4 (7.5%)	20 (3.3%)	0.12
CKD	11 (20.8%)	60 (9.8%)	0.01
Malignancy	5 (9.4%)	35 (5.7%)	0.24
Immunocompromised	4 (7.5%)	27 (4.4%)	0.30
Stroke	4 (7.5%)	36 (5.9%)	0.55
Initial symptoms			
Fever	39 (73.6%)	353 (57.6%)	0.02
Dyspnea	24 (45.3%)	118 (19.2%)	<0.001
Cough	39 (73.6%)	465 (75.9%)	0.71
Sputum	15 (28.3%)	206 (33.6%)	0.43
Sore throat	13 (24.5%)	176 (28.7%)	0.52
Rhinorrhea	17 (32.1%)	191 (31.2%)	0.89
Myalgia	13 (24.5%)	168 (27.4%)	0.65
Headache	9 (17.0%)	98 (16.0%)	0.85
Gastrointestinal symptoms	5 (9.4%)	124 (20.2%)	0.06
RT-PCR Ct value on admission	20.7 ± 6.0	20.3 ± 6.2	0.69
DOI on admission	4 (3–6)	6 (3–8)	0.01
SpO_2 RA on admission			<0.001
< 88%	8 (15.4%)	14 (2.3%)	
88–95%	21 (40.4%)	154 (25.3%)	
>95%	23 (44.2%)	440 (72.4%)	
Treatment in hospital			
Average accumulated steroid dose (dexamethasone equivalence dose)	36.1 ± 20.2	11.9 ± 14.9	<0.001
Steroids	52 (98.1%)	377 (61.5%)	<0.001
Immunomodulators	30 (56.6%)	72 (11.7%)	<0.001
Remdesivir	29 (55.8%)	83 (13.5%)	<0.001
Favipiravir	50 (94.3%)	575 (93.8%)	1.00

Notes: Data present as mean ± SD or median (interquartile range). Immunomodulators included tocilizumab, tofacitinib, and baricitinib.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; SpO2 RA, oximetry-measured oxygen saturation at room air; RT-PCR Ct value, real-time polymerase chain reaction cycle threshold.

(14.2%) in the non-OP/AFOP group had completed vaccination. Patients with OP/AFOP had a higher proportion of comorbidities, including diabetes mellitus (DM), ischemic heart disease, and chronic kidney disease (CKD).

Patients with OP/AFOP exhibited higher percentages of fever (73.6% vs 57.6%, P = 0.02) and dyspnea (45.3% vs 19.2%, P < 0.001) compared to those without OP/AFOP. On admission, the OP/AFOP group had a higher proportion of patients with oxygen saturation at room air (SpO2 RA) <95% than the non-OP/AFOP group (55.8% vs 27.6%, P < 0.001). Furthermore, in comparison to patients without OP/AFOP, those who developed OP/AFOP were more likely to receive a higher steroid dose (average dexamethasone equivalent dose of 36.1 mg vs 11.9 mg, P < 0.001), immunomodulators (56.6% vs 11.7%, P < 0.001), and Remdesivir (55.8% vs 13.5%, P < 0.001).

Patients with OP/AFOP had significantly higher levels of WBC count, CRP, LDH, creatinine, D-dimer, HbA1C, and AST when compared to patients without OP/AFOP, as shown in Table 2. On the other hand, the OP/AFOP group had significantly lower lymphocyte counts, total protein levels, and albumin levels than the non-OP/AFOP group.

In the multivariate logistic regression analysis, risk factors associated with the development of OP/AFOP included age groups 50–70 and >70 years (adjusted odds ratio [aOR]=3.87; 95% CI 1.24–12.11 and 5.74; 95% CI 1.80–18.27, respectively), diabetes mellitus (DM) (aOR=2.37; 95% CI 1.27–4.44), and SpO2 RA on admission <88% (aOR=4.52; 95% CI 1.22–16.67) (Table 3).

Cox proportional hazard models revealed a significantly higher 90-day mortality in patients with OP/AFOP, as compared to patients without OP/AFOP (adjusted HR=3.40; 95% CI 1.68–6.92) (Figure 1). Furthermore, patients with OP/AFOP experienced a longer hospital length of stay and were more likely to develop respiratory failure requiring intubation (50.9% vs 5.6%, P < 0.001), AKI (49.1% vs 13.7%, P < 0.001), various infections (fungal infection [18.9% vs

Table 2 Initial Laboratory Indices of Patients with COVID-19 Pneumonia with OP/AFOP and Without OP/AFOP

Baseline Characteristics	Patients With OP/AFOP, n (%) N = 53	Patients Without OP/AFOP, n (%) N = 613	*P*-value
Hemoglobin (g/dL)	12.6 ± 2.1	13.0 ± 2.0	0.18
WBC count (cells/mm3)	6977.4 ± 3530.3	5813.6 ± 2751.1	0.02
Lymphocyte count (cells/mm3)	988 (665–1353)	1395 (954–1993)	<0.001
Lymphopenia (%)	27 (50.9%)	167 (27.2%)	<0.001
Platelet count (cells/mm3)	215,018 ± 68,192	244,024 ± 109,288	0.06
Creatinine (mg/dL)	1.11 (0.89–1.37)	0.87 (0.72–1.08)	<0.001
CRP (mg/dL)	47.7 (21.3–122.5)	18.85 (6.25–47.7)	<0.001
D-dimer (ng/mL)	987 (415–1519)	540 (359–876)	<0.001
LDH (U/L)	317 ± 166.9	247.0 ± 100.0	0.004
HbA1C (%)	7.2 ± 2.8	6.2 ± 1.5	0.01
Total protein (g/L)	71.9 ± 7.6	74.8 ± 6.4	0.002
Albumin (g/L)	38.3 ± 5.2	41.4 ± 4.3	<0.001
Total bilirubin (mg/dL)	0.4 (0.4–0.7)	0.4 (0.3–0.6)	0.30
AST (U/L)	56 (29–72)	35 (25–51)	<0.001
ALT (U/L)	36 (23–50)	29 (19–47)	0.16

Notes: Data present as mean ± SD or median (interquartile range). [†]Definition: lymphopenia, lymphocyte counts < 1000 cells/mm3.

Abbreviations: WBC, white blood counts; CRP, C-reactive protein; LDH, lactate dehydrogenase; HbA1C, hemoglobin A1C; AST, aspartate aminotransferase; ALT, alanine transaminase.

Table 3 Multivariate Logistic Regression Analysis of Factors Associated with OP/AFOP Development

Patient Characteristic and Findings	OP/AFOP aOR (95% CI)	*P*-value
Age group		
< 50 years	References	
50–70 years	3.87 (1.24–12.11)	0.02
> 70 years	5.74 (1.80–18.27)	0.003
Diabetes mellitus	2.37 (1.27–4.44)	0.01
Lymphopenia	1.20 (0.60–2.39)	0.61
Creatinine	1.01 (0.90–1.13)	0.88
CRP	1.00 (0.99–1.01)	0.25
D-dimer	1.00 (1.00–1.00)	0.81
LDH	1.00 (0.99–1.01)	0.22
AST	1.00 (0.99–1.01)	0.95
SpO_2 RA on admission		
> 95%	References	
88–95%	1.27 (0.62–2.61)	0.52
< 88%	4.52 (1.22–16.67)	0.02

Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; SpO2 RA, oximetry-measured oxygen saturation at room air.

0.7%, $P < 0.001$], viral infection [24.5% vs 1.1%, P < 0.001], bacterial infection [69.8% vs 11.4%, P < 0.001]), pneumothorax (11.3% vs 0.3%, P < 0.001), pneumomediastinum (17% vs 0.7%, P < 0.001), and pulmonary embolism (13.2% vs 1.3%, P < 0.001) (Table 4).

Discussion

The incidence of patients developing secondary OP/AFOP after COVID-19 pneumonia in this study was found to be consistent with the findings of a previous study. In our study, 8% of patients with COVID-19 pneumonia developed OP/AFOP, while a previous study reported a 12.5% prevalence of COVID-19-related OP.[13] We identified older age, comorbid diabetes, and hypoxemia on admission (SpO2 RA < 88%) as potential predictors for the development of OP/AFOP in patients with COVID-19 pneumonia.

Data from the US Centers for Disease Control and Prevention shows that older adults have significantly higher rates of ICU admissions and deaths due to COVID-19 than younger age groups.[14] Currently, older age is considered the primary risk factor for COVID-19 complications, likely attributed to immune system dysregulation. Subsequent to the initial infection, secondary OP/AFOP from SARS-CoV-2 can occur as a consequence of immunological processes. However, the precise impact of immune system dysregulation on pathogenicity during COVID-19 in older adults remains unclear.[15] Hence, further research on the pathogenesis of secondary OP/AFOP in elderly patients is warranted.

Previous studies have consistently identified advanced age (>65 years) and comorbidities such as hypertension, diabetes, cardiovascular disease, or respiratory diseases as significant risk factors for critical COVID-19 infection.[9,16,17] To date, the pathogenesis of COVID-19 infection is not clearly understood. It is currently hypothesized that the respiratory system serves as the primary target for the virus, mainly due to the presence of the ACE-II protein acting as the binding receptor for the viral spike protein. While the ACE-II protein has been detected in various human organ

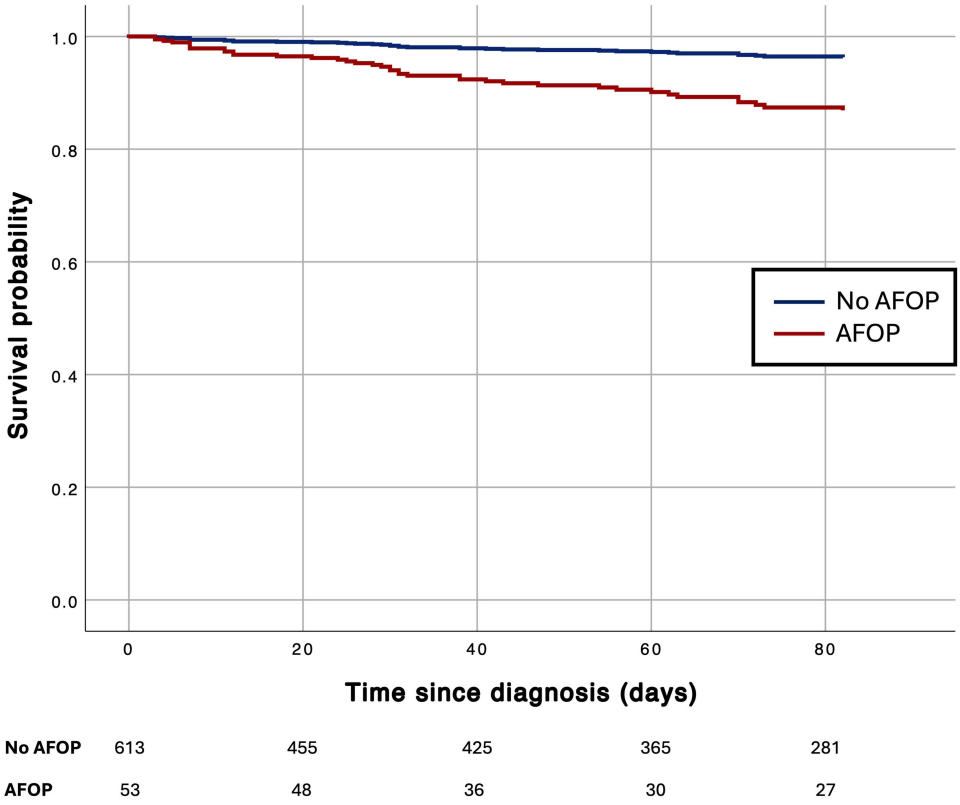

Figure 1 Kaplan-Meier Survival Analysis for Mortality.

systems, it is particularly abundant in type II alveolar epithelial cells (pneumocytes).[18] In a previous study, it was revealed that diabetic patients exhibit an increased expression of ACE-II, which corresponds to higher viral load, viral entrance, and replication of SARS-CoV-2.[19] Moreover, diabetic patients are more susceptible to compromised immune responses, potentially leading to the development of severe COVID-19 complications.

Our findings indicated that severe hypoxemia on admission (SpO_2 RA < 88%) was associated with the development of secondary OP/AFOP. Severe hypoxemia in early COVID-19 acute respiratory distress syndrome is a consequence of

Table 4 Clinical Outcomes in Patients with COVID-19 Pneumonia with OP/AFOP and Without OP/AFOP

Clinical Outcomes	Patients With OP/AFOP, n (%) N = 53	Patients Without OP/AFOP, n (%) N = 613	*P*-value
90-day mortality	15 (28.3%)	24 (3.9%)	<0.001
Hospital Length of Stay	34 (22–44)	8 (6–12)	<0.001
Intubation	27 (50.9%)	34 (5.6%)	<0.001
Complications			
AKI	26 (49.1%)	84 (13.7%)	<0.001
Required acute RRT	2 (3.8%)	5 (0.8%)	0.10
Fungal infection	10 (18.9%)	4 (0.7%)	<0.001

(*Continued*)

Table 4 (Continued).

Clinical Outcomes	Patients With OP/AFOP, n (%) N = 53	Patients Without OP/AFOP, n (%) N = 613	*P*-value
Viral infection	13 (24.5%)	7 (1.1%)	<0.001
Bacterial infection	37 (69.8%)	70 (11.4%)	<0.001
Pneumothorax	6 (11.3%)	2 (0.3%)	<0.001
Pneumomediastinum	9 (17.0%)	4 (0.7%)	<0.001
Pulmonary embolism	7 (13.2%)	8 (1.3%)	<0.001

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.

diminished oxygen diffusion and impaired hypoxic vasoconstriction.[3,20] The pathogenesis of OP/AFOP is characterized by alveolar epithelial injury, resulting in coagulative protein leakage and fibrin accumulation due to reduced fibrinolytic activity.[3] The observed severe inflammatory response in severe COVID-19 pneumonia may trigger alveolar epithelial injury, thus contributing to the development of OP/AFOP.[21] Further research is required to comprehensively understand the intricate mechanisms driving this association and its potential implications for patient management. In addition, further studies to identify risk factors for the development of OP/AFOP in patients with severe COVID-19 pneumonia could provide valuable clinical insights.

Patients with COVID-19 pneumonia and OP/AFOP had a higher rate of 90-day mortality, consistent with previous study.[22] This finding may be attributed to the increased likelihood of developing complications such as respiratory failure, AKI, secondary infection, pneumothorax, pneumomediastinum, and pulmonary embolism, which are well-recognized complications of COVID-19 pneumonia, particularly in moderate to severe cases.[23] Our study, along with several case reports, indicates that patients with OP/AFOP were more prone to requiring higher doses and longer durations of corticosteroid therapy.[24,25] Such treatment may serve as an independent risk factor for community-acquired infections, sepsis, and opportunistic infections.[26,27]

The occurrence of spontaneous pneumothorax and pneumomediastinum is linked to a ruptured alveolar wall and air migration resulting from increased intra-alveolar pressure, which shears off the bronchovascular sheaths.[23] In patients with OP/AFOP, the peripheral peribronchovascular ground-glass opacity (GGO) or consolidation typically extends to the subpleural region, leading to the formation of pneumatocele and bullae.[28] As for pulmonary embolism, patients with COVID-19 infection already face a heightened thrombotic risk due to systemic inflammation, endothelial damage resulting from the virus's binding to ACE-II receptors, and prolonged bed rest.[23] In patients with OP/AFOP, ongoing inflammation may account for the increased incidence of pulmonary embolism within this group. The D-dimer serves as a cornerstone marker for predicting a worse prognosis and mortality in COVID-19 pneumonia patients with pulmonary embolism.[29,30] Our study found that patients with OP/AFOP had higher D-dimer levels, which correlated with a higher incidence of pulmonary embolism in this cohort.

The study possesses several strengths, including the accuracy and completeness of data resulting from the use of electronic medical records and the standardized protocol for laboratory testing and imaging in patients admitted to CNMI. Additionally, this study was conducted in a large tertiary center with a high prevalence of COVID-19 pneumonia. The criteria for diagnosing OP/AFOP were robustly defined, and the involvement of two reviewers further strengthened the diagnostic process.

There were several limitations in this study. Firstly, a definitive diagnosis of OP/AFOP requires histopathological examination, but in this study, the diagnosis primarily based on clinical and radiological findings. Due to the pandemic, performing bronchoscopy with transbronchial biopsy in COVID-19 patients was generally unsuitable due to the risk of virus transmission and complications like pneumothorax and pneumomediastinum. As a result, most studies, including ours, have relied on radiological findings to make a presumptive diagnosis of organizing pneumonia.[8,9,31,32] Secondly,

during the study period, there were no established treatment guidelines for severe COVID-19 pneumonia and OP/AFOP. Therefore, the use of antivirals, steroids, and immunomodulators was determined at the discretion of the attending physicians based on local guidelines, which may have resulted in variations in treatment approaches. Regarding mortality, there may be potential bias related to the treatments for COVID-19-related OP/AFOP, as these treatments are determined by the attending physicians. Thirdly, the data from this study were obtained during a time when access to COVID-19 vaccines was limited, and less than 20% of patients had received complete vaccination. Consequently, the results might not be fully applicable to the present situation where a larger proportion of the population has been immunized. Lastly, this study primarily focused on the Delta variant, the predominant COVID-19 strain at the time of data collection. However, it is important to note that the Omicron variant has since surpassed Delta as the leading cause of infections worldwide. There are key differences between these variants. The Omicron variant has a higher transmissibility rate compared to previous variants, such as Alpha, Beta, and Delta. Infections with Omicron tend to cause milder lung symptoms, resulting in shorter hospital stays, fewer ICU admissions, and lower mortality rates.[33,34] Additionally, Omicron replicates in the lungs at a rate 10 times lower than the Delta variant.[35]

Conclusion

Based on our findings, we observed that age ≥50 years, diabetes mellitus, and severe hypoxemia on admission (SpO2 <88%) were significantly associated with an increased risk of developing OP/AFOP in patients with COVID-19 pneumonia. Furthermore, we found that patients with COVID-19 pneumonia who developed OP/AFOP had a higher mortality rate at 90 days. Therefore, it is crucial to monitor COVID-19 pneumonia patients with these risk factors closely. Early detection of OP/AFOP can provide tangible benefits in terms of timely treatment and prevention of its complications.

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Disclosure

The authors report no conflicts of interest in this work.

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