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Association of Tocilizumab Treatment with Prolonged SARS-CoV-2 Shedding in Critically Ill COVID-19 Patients on Mechanical Ventilation with Nosocomial Pneumonia Across Alpha and Omicron Variants

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the global pandemic known as coronavirus disease 2019 (COVID-19). The detection of SARS-CoV-2 infection relies on real-time reverse transcriptase polymerase chain reaction (RT-PCR), where the cycle threshold (Ct) values indicate the number of cycles needed for detection. Previous studies explored that prolonged viral shedding is associated with advanced age, female gender, and co-infection with secondary pathogens. The aim of our study is to investigate the factors contributing to prolonged viral shedding and evaluate the clinical outcomes specifically related to the Alpha and Omicron variants of SARS-CoV-2 in critically ill patients receiving mechanical ventilation (MV) with nosocomial pneumonia.

Methods

This study was conducted at Taipei Veterans General Hospital in Taiwan from May 2021 to September 2021 and April 2022 to September 2022. The study focused on critically ill patients who were confirmed to have SARS-CoV-2 infection, required intubation with mechanical ventilation, and were diagnosed with bacterial pneumonia.

Results

This study enrolled 94 critically ill COVID-19 patients who developed secondary pneumonia and required intubation and intensive care unit (ICU) care. (Figure 1)

A total of 139 bacterial cultures were obtained from respiratory specimens, including sputum and endotracheal aspirate, in the Alpha variant group, with 59 being *Stenotrophomonas species* (42%), 21 being *Acinetobacter species* (15%), and 16 being *Pseudomonas species* (12%). In comparison, 239 positive cultures were collected in the Omicron group, with 50 being *Stenotrophomonas species* (21%), 50 being *Acinetobacter species* (21%), and 36 being *Klebsiella species* (15%) (Figure 2).

The Alpha group exhibited a longer duration of SARS-CoV-2 viral shedding (Figure 3), increased mechanical ventilation days, and extended ICU stay. Conversely, the Omicron group demonstrated older age, higher prevalence of comorbidities, elevated Acute Physiology and Chronic Health Evaluation II scores, and a higher rate of in-hospital mortality (47.0% vs. 25.0%, p = 0.047). (Table 2)

Figure 1. Study flow chart.

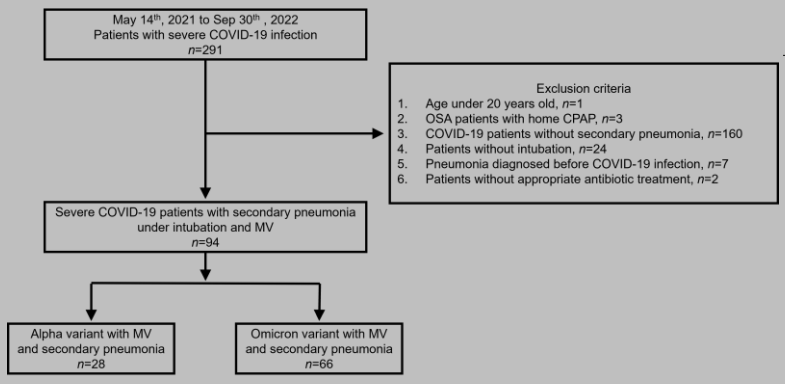

Figure 2. Microbiology distribution between different SARS-CoV-2 variants.

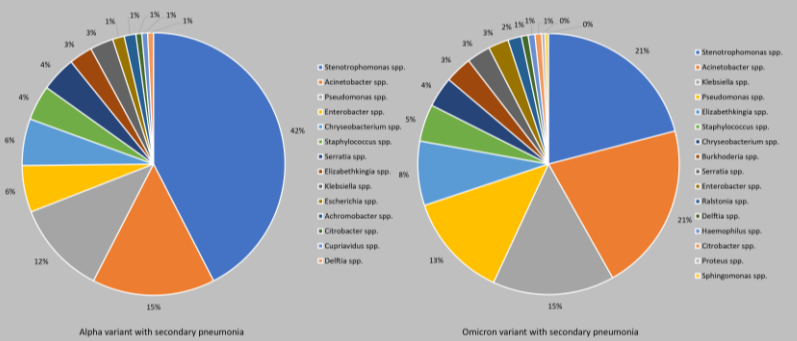

Table 1. Clinical characteristics of patients with different variant phenotypes.

	Alpha (n=28)	Omicron (n=66)	*p*-value
Demographics			
Age, years	66.0 (59.5-73.0)	75.0 (67.8-84.0)	0.001
Male	22 (78.6)	43 (65.2)	0.198
BMI	24.6 (22.1-28.4)	21.5 (18.8-24.6)	0.001
Time from symptoms onset to secondary pneumonia diagnosis, days	20.0 (14.8-29.0)	10.5 (7.0-19.0)	<0.001
MDR proportion of first respiratory specimens	8 (28.6)	24 (36.4)	0.466
Bacteremia	10 (35.7)	29 (43.9)	0.459
Underlying disease			
Cardiovascular disease	1 (3.6)	13 (19.7)	0.045
Diabetes mellitus	12 (42.9)	28 (42.4)	0.969
Chronic kidney disease	2 (7.1)	8 (12.1)	0.474
COPD	3 (10.7)	4 (6.1)	0.432
Hemodialysis	1 (3.6)	7 (10.6)	0.264
Malignancy	4 (14.3)	26 (39.4)	0.017
Laboratory tests at ICU admission			
White blood cells, 10^9/L	6413.0 (4750.0-13125.0)	11045.0 (8255.0-16120.0)	0.002
Albumin, g/dL	3.3 (3.1-3.7)	2.9 (2.6-3.8)	0.068
C-reactive protein, mg/dL	8.0 (3.5-13.4)	6.0 (1.6-14.6)	0.520
Procalcitonin, ng/mL	0.2 (0.1-0.6)	0.9 (0.2-4.9)	0.002
LDH, U/L	531.5 (406.3-707.0)	370.0 (235.0-489.5)	0.001
Lactate, mg/dL	18.5 (14.9-29.6)	21.5 (14.3-44.1)	0.409
D-dimer, ug/mL	1.3 (0.6-5.8)	2.4 (1.4-4.8)	0.044
Ferritin, ng/mL	2529.0 (799.0-5028.0)	782.0 (454.0-3421.5)	0.069
Fibrinogen, mg/dL	410.1 (283.9-487.5)	394.2 (323.6-522.9)	0.675
Treatment			
Cumulative dose of dexamethasone	211.0 (149.5-280.8)	65.6 (52.9-143.2)	<0.001
Tocilizumab	18 (64.3)	22 (33.3)	0.006
Remdesivir	23 (82.1)	54 (81.8)	0.970
Enoxaparin	25 (89.3)	24 (36.4)	<0.001
Severity scores			
APACHE II score at admission	15.5 (9.5-25.75)	25.5 (21.8-31.3)	<0.001

Data are presented as the median (IQR) and number (%) unless otherwise indicated.
NA: not applicable; ICU: intensive care unit; LDH: lactate dehydrogenase; SOFA: sequential organ failure assessment.

Table 2. Clinical outcomes of patients according to different variant phenotypes.

	Alpha (n=28)	Omicron (n=66)	*p*-value
Clinical course and outcomes			
ECMO	5 (17.9)	4 (6.1)	0.075
GI bleeding events	13 (46.4)	33 (50.0)	0.751
SARS-CoV-2 shedding days	27.0 (17.3-35.5)	12.5 (7.0-20.0)	<0.001
ICU stay, days	46.0 (20.3-67.3)	27.5 (16.0-48.3)	0.032
Hospital stay, days	58.5 (28.8-91.0)	41.0 (29.0-72.5)	0.206
Mechanical ventilator days	27.0 (16.0-59.8)	18.5 (11.3-31.8)	0.025
In-hospital mortality	7 (25.0)	31 (47.0)	0.047

Data are presented as the median (IQR) and number (%) unless otherwise indicated. ECMO: extracorporeal membrane oxygenation; GI: gastrointestinal; ICU: intensive care unit.

Kaplan Meier survival analysis revealed that patients infected with Alpha variant or patients treated with tocilizumab had a longer duration of viral shedding and tocilizumab treatment was identified as a significant risk factor associated with prolonged viral shedding via multivariate regression (Odds ratio: 3.599, 95% CI: 1.252-10.345, p = 0.017). (Figure 3)

Figure 3. Kaplan Meier survival analysis of duration of viral shedding.

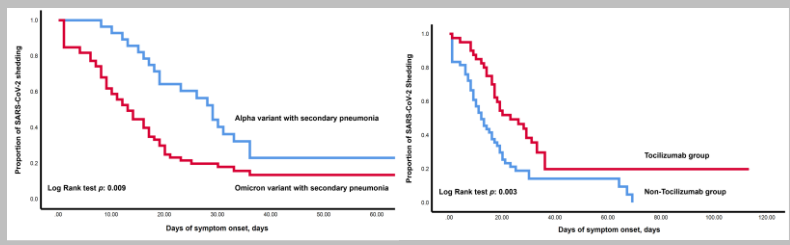

Figure 3A.
Kaplan Meier analysis of duration of viral shedding in different SARS-CoV-2 variants.

Figure 3B.
Kaplan Meier analysis of duration of viral shedding in treatment of tocilizumab.

Conclusion

Our study revealed a higher in-hospital mortality rate among severe COVID-19 patients who required MV and developed secondary pneumonia when infected with the Omicron variant, as compared to the Alpha variant. Furthermore, tocilizumab treatment was identified as a risk factor associated with prolonged viral shedding.

References

1. Sun CY, Feng JY, Huang JR, Shen HC, Chen YM, Chen WC, et al. Clinical Outcomes and Prolonged SARS-CoV-2 Viral Shedding in ICU Patients with Severe COVID-19 Infection and Nosocomial Bacterial Pneumonia: A Retrospective Cohort Study. J Clin Med. 2022;11(22).
2. Huang JR, Shen HC, Sun CY, Chen WC, Chen YM, Feng JY, et al. COVID-19-associated pulmonary aspergillosis is associated with increased in-hospital mortality and prolonged SARS-CoV-2 viral shedding. J Formos Med Assoc. 2022;121(12):2617-25.