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Case Series
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Clinical Features of Adult, Hospitalized, Non-Vaccinated COVID-19 Patients during the Omicron Variant Surge

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Abstract

Background: The mortality of SARS-CoV-2 infection in non-vaccinated patients is still thought to be high despite the appearance of the omicron subvariant. A total of 36 adult, non-vaccinated patients who were hospitalized with SARS-CoV-2 infection during the omicron variant surge were included in this study.

Case Series: Severity of illness at admission was mild, moderate, and severe in 0 (0%), 29 (80.6%), and 7 (19.4%) patients, respectively, and three (3/36=9.1%) patients died. The patients who died were as follows. (Case 1) A 64-year-old man on hemodialysis developed severe pneumonia caused by SARS-CoV-2 infection. His pneumonia did not worsen, but he developed septic shock on day 5 with a catheter-related blood stream infection due to Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Extended Spectrum Beta-Lactamase (ESBL)-producing *Escherichia coli*. (Case 2) An 87-year-old man with a history of esophageal cancer had moderate pneumonia at admission, but suddenly developed massive brain hemorrhage on day 6. (Case 3) A 94-year-old man with a history of brain infarction and atrial fibrillation had moderate pneumonia on admission. His pneumonia was improving, but he died on day 7 of acute renal failure and suspected recurrent brain infarction.

Conclusion: These data and cases suggest that non-vaccinated patients showed high mortality, especially elderly male patients with underlying diseases. They died due to reasons other than respiratory failure and/or pneumonia, and impairment of blood vessels, especially in the brain, heart, and kidneys, by SARS-CoV-2 infection was thought to have occurred, though the omicron variant has generally low pathogenicity.

Keywords: SARS-CoV-2; Catheter-related blood stream infection; Hemodialysis; Brain hemorrhage; Acute renal failure; Vaccine

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Background

Coronavirus Disease 2019 (COVID-19) has been a significant issue, but omicron (B.1.1.529) became the dominant variant of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in 2022, and the initial omicron variants, BA.1 and BA.2 (BA.1/2), were being progressively displaced by BA.5 in many countries, including Japan [1,2]. BA.5 showed greater transmissibility and a higher level of immunological evasion than BA.1/2, but it appeared to have less pathogenicity [2]. In addition, the treatment of SARS-CoV-2 infection has been improving and has progressed, especially for moderate to severe immunosuppressed patients [3,4]. In the guideline for the management of COVID-19, simultaneous use of antiviral agents, such as remdesivir, and corticosteroids is recommended for moderate to severe hospitalized patients who require conventional oxygen and/or a High-Flow Nasal Cannula (HFNC) [5].

Therefore, mortality was significantly lower in the BA.5 period than in the BA.1/2 period, as in previous reports from other countries [6,7], and we found similar results in our hospitalized patients, with mortality of 7.9% (10/135) in the BA1/2 period and 1.7% (2/160) in the BA.5 period [8]. The total mortality was 4.1% (12/295) during the omicron era in these patients who had already mostly been vaccinated by prime and booster vaccinations.

However, not a small number of people remain non-vaccinated in Japan, and it was found that non-vaccinated patients developed severe disease and were transferred to the emergency department in the same omicron period. The prognosis of these non-vaccinated patients might be poor, although most of them received the appropriate treatments in Intensive Care Units (ICUs).

Table 1: Clinical characteristics of 36 hospitalized COVID-19 patients who had not been vaccinated.

	Patients (n=36)
Age	62.4 (38-94)
Male/Female	22/14
Death (Mortality)	3 (9.1%)
Severity	
Mild	0 (0%)
Moderate	29 (80.6%)
Severe	7 (19.4%)

In this report, the clinical features and prognosis of non-vaccinated COVID-19 patients who were admitted to our hospital during the omicron period were investigated. A total of 36 adult, hospitalized, non-vaccinated patients were identified (Table 1). They were slightly older and predominantly male. Their conditions were mild (0, 0%), moderate (29, 80.6%), and severe (7, 19.4%), and three (3/36=9.1%) of them died. The three patients who died were elderly men with underlying diseases, but they died due to reasons other than pneumonia and/or respiratory failure.

These cases and the related study were approved as #2022-032 by the Institutional Review Board of Saitama Medical University International Medical Center on July 06th, 2022 and registered as UMIN000047691, and the patients whose specimens were used provided written, informed consent to have their case details and any accompanying images published.

Case Series

Case 1

A 64-year-old man with chronic renal failure was on hemodialysis. He had received no vaccinations for SARS-CoV-2, but he had a past history of brain hemorrhage 10 years earlier. He developed a cough and fever on day -6. The Polymerase Chain Reaction (PCR: Cobas SARS-CoV-2, Roche, Basel, Switzerland) test for SARS-CoV-2 was positive on day -5. Five days later (day 0), his cough became much worse, and he was admitted to the tertiary hospital near our hospital. Interstitial shadows and Ground Glass Opacities (GGOs) with infiltration shadows were found on chest Computed Tomography (CT) on day 0 in the tertiary hospital (Figure 1A, 1B), and arterial Oxygen Saturation (SpO_2) was 95% (O_2 10-L mask). He was diagnosed with severe COVID-19 with pneumonia and transferred to our hospital.

Laboratory data on admission at our university hospital were as follows: White Blood Cell (WBC) count, 9.64 × 10^3/μL, with 96.4% neutrophils, 1.5% lymphocytes, 1.8% monocytes, 0.2% eosinophils, and 0.1% basophils; platelet count, 26.3 × 10^4/μL; hemoglobin, 10.2 g/dL; blood urea nitrogen, 74.0 g/L; serum creatinine, 9.45 mg/dL; Aspartate Aminotransferase (AST), 43 U/L; Alanine Aminotransferase (ALT), 51 U/L; and C-Reactive Protein (CRP), 4.409 mg/dL.

Although the SARS-CoV-2 Antigen (Ag) in the nasal swab showed a mild titer, 144 IU (Cobas SARS-CoV-2 Ag, Roche), respirator management and antiviral therapy with remdesivir (Gilead, Foster City, CA, USA) drip infusion 200 mg, followed by 100 mg per day for 5 days and dexamethasone 6 mg intravenously, were started. In addition, gamma globulin 5 g per day and tocilizumab 400 mg intravenously were started on day 1.

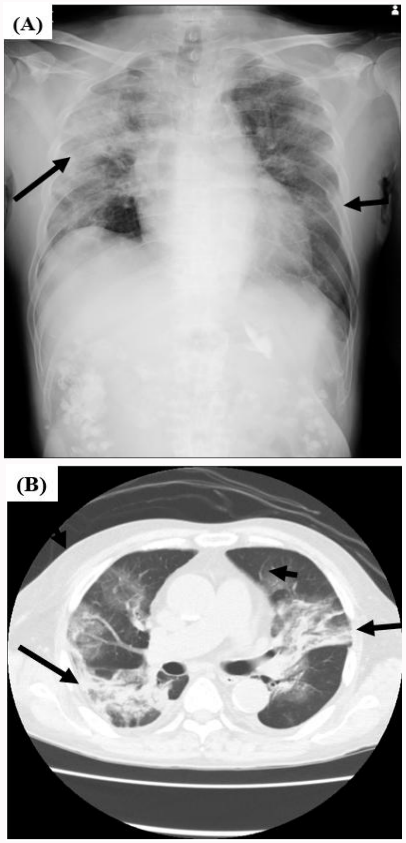

Figure 1: Chest X ray (A) and CT (B) of the case 1 patient on admission. Infiltration shadow is seen in his right upper lung field, and interstitial shadows on chest X-ray and Ground-Glass Opacities (GGOs) are found in both lung fields. Arrows indicate the abnormal shadows on chest X-ray and CT, such as infiltration, interstitial shadows, and GGOs.

His pneumonia remained stable, but he developed shock on Day 5 and Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Extended Spectrum Beta-Lactamase (ESBL)-producing *Escherichia coli* were isolated on blood culture. Catheter-related blood stream infection was suspected, and the central venous catheters were removed immediately. Antibiotic therapy (meropenem 1 g three times/day) and noradrenaline were also started. However, the hemodialysis could not be continued, and he finally died on day 7.

Case 2

An 87-year-old man with a history of esophageal cancer developed a fever and general malaise on day -2, and the antigen test for SARS-CoV-2 was positive: 90 IU (Cobas SARS-CoV-2 Ag). He had received no vaccinations for SARS-CoV-2.

He stayed at home, but two days later (day 0), his condition did not improve, and cough and dyspnea appeared. He was admitted to our hospital. Laboratory data on admission at our hospital were as follows: WBC count, 10.23 × 10^3/μL, with 84.0% neutrophils, 10.5% lymphocytes, 10.5% monocytes, 0.0% eosinophils, and 0.0% basophils; platelet count, 95 × 10^3/μL; hemoglobin, 11.9 g/dL; blood urea nitrogen, 52.8 g/L; serum creatinine, 2.55 mg/dL; AST, 31 U/L; ALT, 18 U/L; and CRP, 10.482 mg/dL. In addition, coagulation-related data were almost normal: D-dimer 2.30 μ g/ml, PT-INR 0.94, and APTT 27.3 sec. Chest X-ray/CT showed infiltration in the right upper lung field (Figure 2A, 2B), and SpO_2 was 94% by nasal canula at 3 L.

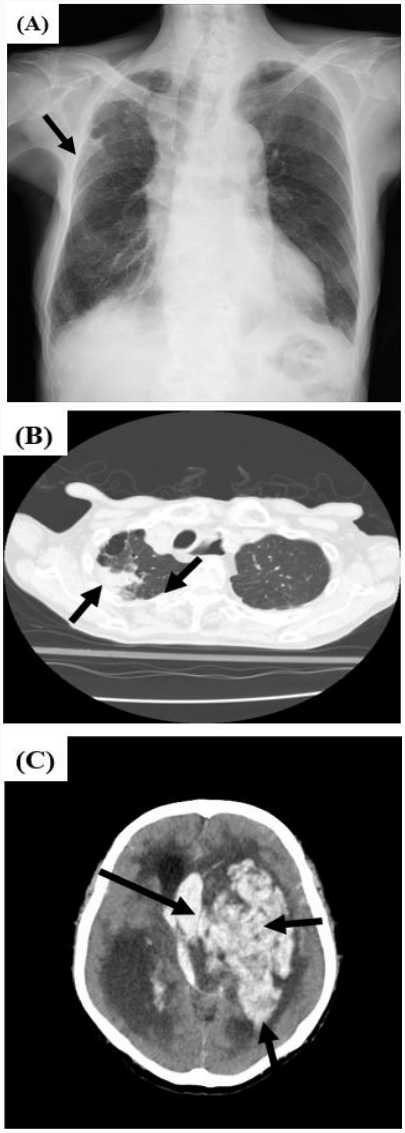

Figure 2: Chest X-ray (A), CT (B), and brain CT (C) of the case 2 patient on admission. Infiltration shadow is found in his right upper lung field (A and B). On day 6, massive brain hemorrhage has suddenly developed (C). Arrows indicate the abnormal shadows on chest X-ray, CT, and brain CT, such as infiltration shadows in the lungs and hemorrhage in the brain.

Remdesivir 200 mg was started on day 0, followed by 100 mg per day for 5 days with sulbactam/ampicillin 3 g twice per day intravenously because bacterial pneumonia and aspiration pneumonia were also suspected based on the chest X-ray/CT findings. Appropriate drip infusions were also performed to improve his dehydration.

His fever decreased (<37°C), and SpO_2 also improved to 95% by nasal canula at 1 L, but at midnight of day 6, he suddenly lost consciousness and went into shock, and massive brain hemorrhage was found on brain CT (Figure 2C). Emergency measures including cardiopulmonary resuscitation were performed, but the patient could not be rescued.

Case 3

A 94-year-old man with a history of brain infarction with atrial fibrillation and spinal tumor had been admitted to our hospital, and he developed a fever and general malaise on day 0. The antigen test

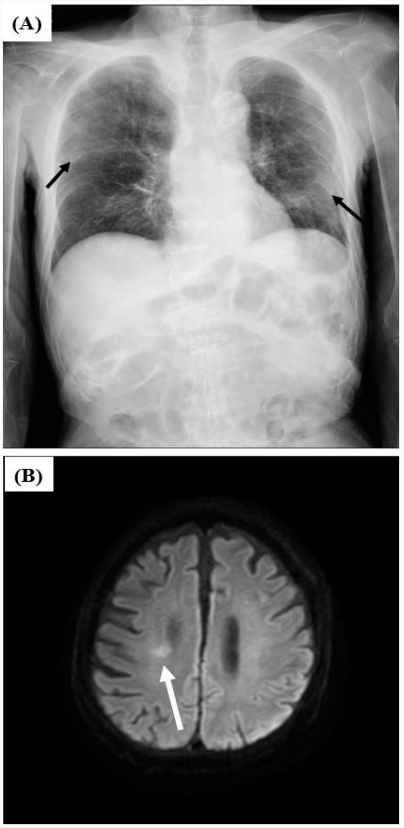

Figure 3: Chest X-ray (A) and brain MRI (B) of the case 3 patient on admission. Interstitial shadows are seen in both lung fields (A), and infarction is found in his right brain (B). Arrows indicate the abnormal shadows on chest X-ray and brain CT, such as interstitial shadows in the lungs and the infarction site in the brain.

for SARS-CoV-2 (Cobas SARS-CoV-2 Ag) was positive (3695 IU). He had received no vaccinations for SARS-CoV-2.

It appeared that he had been nosocomially infected by a nurse who had COVID-19, and he was transferred to the infectious diseases ward.

Laboratory data on admission to our ward were as follows: WBC count, 5.95 × 10^3/μL, with 64.2% neutrophils, 27.7% lymphocytes, 6.6% monocytes, 1.2% eosinophils, and 0.3% basophils; platelet count, 29.1 × 10^3/μL; hemoglobin, 11.0 g/dL; blood urea nitrogen, 8.2 g/L; serum creatinine, 0.42 mg/dL; estimated Glomerular Filtration Rate (eGFR) 161 mL/min/1.73 m^2; AST, 22 U/L; ALT, 11 U/L; and CRP, 0.379 mg/dL. Furthermore, coagulation-related data were almost normal: D-dimer 1.87 μ g/ml, PT-INR 0.98, and APTT 39.8 sec. Chest X-ray showed interstitial shadows in both lung fields (Figure 3A), and SpO_2 was 95% by nasal canula at 4 L. An old infarction was found in his right brain on brain Magnetic Resonance Imaging (MRI) (Figure 3B).

Remdesivir 200 mg was started on day 0, followed by 100 mg per day for 5 days with sulbactam/ampicillin 3 g twice per day intravenously due to suspected bacterial pneumonia and aspiration pneumonia based on the chest X-ray findings.

His fever decreased (<37°C), and SpO_2 also improved to 96% by nasal canula at 1 L, but his consciousness and renal function worsened despite appropriate drip infusions to improve his dehydration and

recurrent stroke. On day 7, his blood pressure decreased, and his renal function did not improve, with the following results: eGFR 161 to 57 mL/min/1.73 m^2 and BUN 8.2 g/L to 47.8 g/L. He and his family had requested do not attempt resuscitation, and he ultimately died on day 9 without ICU management.

Discussion

Patients who are not vaccinated for COVID-19 have a high risk of infection due to the lack of established immune protection against SARS-CoV2 infection. It has been reported that three-dose vaccination by mRNA-1,273 maintains high Vaccine Effectiveness (VE) against omicron infection, 71.6% (69.7-73.4%) at 14 to 60 days, but 47.4% (40.5-53.5%) at >60 days [9]. With BNT162b2 mRNA COVID-19 vaccine, relative protection against infection waned from 53.4% a month after vaccination to 16.5% three months after vaccination [10]. However, the bivalent omicron-containing vaccine booster vaccine showed double the VE compared to the previous BNT162b2 mRNA COVID-19 vaccine, and VE has been maintained in most people in the world who received recent mRNA vaccines [11].

The present case series included three COVID-19 patients who had not been vaccinated and presented during the omicron-dominant period. All cases became severe and died despite appropriate treatment and management. These worse outcomes matched the previous reports that also suggested that COVID-19 patients without vaccination had a poor prognosis, especially immune-compromised patients with underlying diseases, and the necessity of vaccination, though the omicron sub-strain showed lower pathogenicity than the previous sub-strains, including alpha and delta variants [11-13].

Surprisingly, the causes of death of these patients were not respiratory failure and/or pneumonia, but were related to brain, heart, and kidney diseases. These data suggest that the treatment and management of respiratory failure and/or pneumonia have been established in the last few years, but we should now take more care of the possibility that SARS-CoV-2 impairs endothelial cells of vessels in the organs, including the brain, heart, and kidneys. SARS-CoV-2 uses the angiotensin-converting enzyme 2 distributed in the human vascular endothelium as a receptor, and it thus has a strong affinity for vascular endothelial cells in particular, which facilitates vascular permeability and makes angiopathy and microthrombosis due to cytokine disease from viral infection and subsequent vascular destruction more likely, compared with other respiratory viruses, such as influenza [4,14]. Varga et al. reported endothelial cell involvement across vascular beds of different organs, including kidneys, small intestines, and lungs in a series of patients with COVID-19, and they suggested that the vascular complications were rapidly emerging as a key threat in COVID-19, in addition to respiratory disease [14]. Anticoagulant therapy has been recommended for COVID-19 patients, though Asian patients showed less coagulopathy than Caucasian patients [15,16].

Though we may be able to control the pulmonary edema and pneumonia due to cytokine storm and increased viral load by immunosuppressive agents and antiviral agents, such as steroids and remdesivir, we might not be able to prevent vessel impairment and related invasion of bacteria and decreased renal and/or brain blood flows, which induce bacteremia and septic shock, sudden-onset stroke, and decreased renal function. We should attempt to prevent SARS-CoV-2 infection by vaccination and infection control, especially in elderly persons with underlying diseases.

Conclusion

The cases of three COVID-19 patients who had not been vaccinated and who progressed to severe disease and finally died were described. The mortality of non-vaccinated patients who develop COVID-19 might be twice as high as that of vaccinated patients, and the causes of death of the non-vaccinated patients were other than respiratory failure and/or pneumonia, such as bacterial blood stream infection, sudden brain hemorrhage, and acute renal failure by dehydration. All three patients were elderly and had underlying diseases, including chronic renal failure with hemodialysis, esophageal cancer, and old brain infarction. These data suggest that SARS-CoV-2 infection impairs blood vessels and the necessity to prevent COVID-19 infection, especially by vaccination of such high-risk patients.

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