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The Clinical Characteristics of Different SARS-COV-2 Variants in South Kalimantan

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Abstract: COVID-19 has numerous variations as a result of ongoing mutations. Presumably, each variant has its particular clinical characteristic. We present three cases of COVID-19 patients, each with a Non-VOC, delta variant, and probable omicron variant with equal severity and few comorbidities for uniform comparison. All three cases had common COVID-19 symptoms. However, anosmia or ageusia was not found in the probable Omicron case, and the onset was shorter. Infiltrates in chest X-rays were found in all three cases. Laboratory examination showed altered inflammatory markers, transaminitis, and electrolyte imbalance. The standard therapy was given to all patients. However, additional therapies, tocilizumab, IVIG, and plasma convalescent, were given only to Non-VOC and delta variants cases. Non-VOC and delta cases were discharged for self-isolation in 11 and 15 days of treatment. Meanwhile, in the probable Omicron variant, the patient was discharged by his will after being treated for eight days.

Keywords: COVID-19; delta; probable omicron; Non-VOC; clinical characteristics

INTRODUCTION

Corona Virus Disease 2019 (COVID-19) has infected over 400 million individuals and claimed at least five million lives across the globe since it originated in Wuhan, China, in late 2019.[1] As an RNA virus prone to mutations, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, has been reported to have a heterogeneous genetic composition in different geographical locations.[2] Several viral strains have emerged in various countries. The B.1.617.2 (Delta) and B.1.1.529 (Omicron) variations have been identified as variants of concern (VOC) by the World Health Organization (WHO).[3]

Alterations distinguish the Delta variation in the spike proteins, which are particularly prevalent in the B.1.617 lineage. This mutation has resulted in the virus becoming more transmissible, having a higher rate of reinfection, and being able to evade natural immunity.[4,5] Since its first appearance in April 2021, Indonesia's delta variant has become dominant.[6] The discovery of the first Omicron variant (B.1.1.529) of SARS-CoV-2 in Indonesia on December 15, 2021, raised interest.[7] The Omicron variant also has many notable traits, including the potential for enormous mutation and a higher risk of reinfection. According to available research, it may have a faster transmission rate than the prior delta version and the potential to bypass immune protection conferred by antibodies from the vaccine or previous SARS-CoV-2 infection.[8] Given the experience from other countries, delta will most certainly be superseded by Omicron as the dominant variant in Indonesia. New variants of coronavirus would cause differences in the clinical characteristic and outcomes of the affected patients.

We present three cases of COVID-19 patients, each with a Non-VOC, delta variant, and probable omicron variant with equal severity and few comorbidities for uniform comparison. We would like to evaluate the clinical presentation, radiographic changes, and clinical outcomes of three cases of confirmed COVID-19 with different variants through this case series.

CASES

Ulin General Hospital Banjarmasin is a COVID-19 referral Hospital in South Kalimantan and has treated several COVID-19 patients. Confirmed COVID-19 were patients with a positive result on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a specimen taken on a nasopharyngeal swab. We did a screening to differentiate the variant during the second and third waves in June 2021 and February 2022. The Delta variants and the non-VOCs were identified based on whole-genome sequencing (WGS) performed by the Indonesian Center for Biomedical Research and Development and Basic Health Technology. Probable Omicron infection was suggested by Spike-gene target failure (SGTF) on the COVID-19 RT-PCR test. We reported the clinical features in three patients, each with Non-VOC, delta, and probable Omicron COVID-19. Ulin General Hospital, as a referral hospital in South Kalimantan, had the most treated patients with severe diseases and comorbidities. We chose non-referral patients with equal severity and few comorbidities for uniform comparison.

Case 1

A 26-year-old female without significant past medical history was admitted with fever, anosmia, and fatigue four days before admission, followed by cough, shortness of breath, myalgia, and diarrhea. Patient after travel from Jakarta and contact with confirmed COVID-19 patient one week before. Based on the physical examination, her blood pressure was 120/70 mmHg, heart rate 119 bpm, respiratory rate reaching 35 times/minute, temperature 37.40C, and oxygen saturation was 81% on room air. She appeared comfortable on an oxygen 15 L/min non-rebreather mask (oxygen saturation increased to 97%). Her BMI was 24.3 kg/m2. There were rhonchi in the bilateral middle-lower lobes of the lungs during auscultation. The Chest X-Rays (CXR) showed bilaterally patchy infiltrates consistent with COVID-19 pneumonia (Figure 1A).

On admission, a complete blood count showed normal white blood cells of 4.100/ul (normal reference: 4.000-10.500/ul) with a decreased lymphocyte count of 16.7% (normal reference: 20-40%), and NLR and ALC were 4.7 and 684, respectively. The metabolic blood panel was normal except for AST 35 U/L (normal reference: 5-34 U/L), hyponatremia 129 Meq/L (normal reference: 136-145 Meq/L), increased LDH 756 U/L (normal reference: <480 U/L), and D-dimer 0.37 (normal reference: <0.22). Arterial blood gas was taken with oxygen supplement 15 L/m with pH 7.46, PaCO2 38.8, PaO2 86 mmHg, HCO3 27.4, BE 4, SaO2 97%, and ratio PaO2/FiO2 106. She tested positive for SARS-CoV-2 via nasopharyngeal RT-PCR, and non-VOC was identified based on whole-genome sequencing. Her oxygenation status progressively worsened during hospitalization and required a high-flow nasal cannula (HFNC) with a flow of 40 L/min and FiO2 90%, which helped maintain an O2 saturation of more than 95%. The patient had standard treatments like remdesivir, hydrocortisone, heparin as anticoagulant therapy, and meropenem. On day two, she was also administered additional therapy, tocilizumab, and intravenous immunoglobulin (IVIG). After five days, the flow and FiO2 HFNC were de-escalated through her hospital stay and finally reached 96% saturation in room air on the eleventh day. The patient had lymphocyte 37.1%, NLR 1, ALC 1892, decreased LDH to 333 U/L, and CRP to 6.1 mg/dL after one week. She was discharged for self-isolation with clinical improvement after 11 days of treatment.

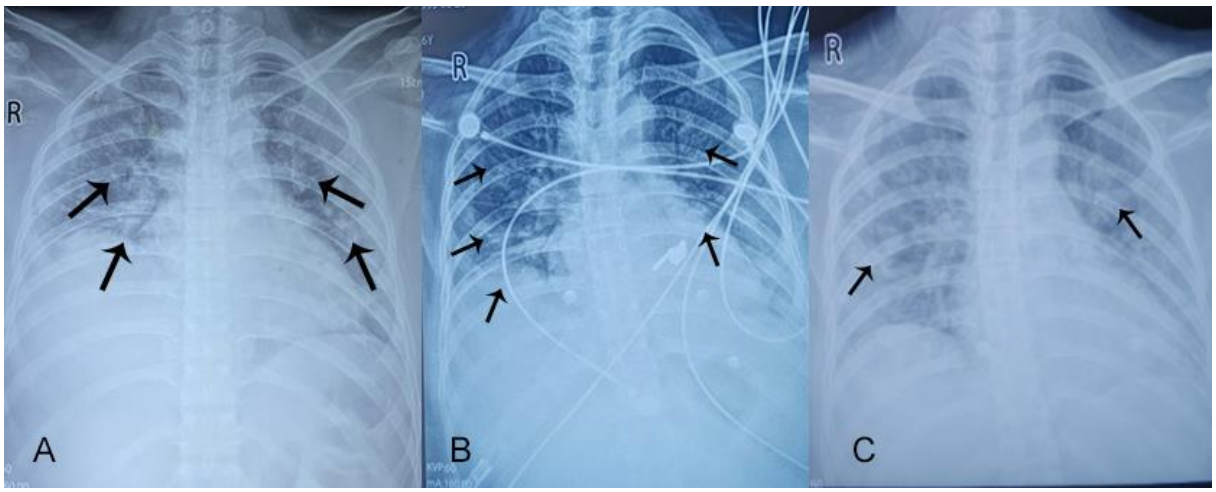

Figure 1. CXR of Case 1 (A) at admission, infiltrates bilateral; (B) day 3rd of hospitalization, infiltrates bilateral; (C) day 8th of hospitalization, infiltrates diminished (indicated by arrows)

Case 2

A 51-year-old male with a past medical history of type 2 diabetes came to the hospital with fever, cough, and myalgia for four days before admission, followed by shortness of breath, anosmia, ageusia, nausea, and vomiting. The patient, after traveling from Jakarta one week before and self –quarantining for two days after a positive antigen COVID-19 test. On examination, the patient looked compos mentis. Blood pressure was 118/71 mmHg, heart rate 81 bpm, respiratory rate 28 times per minute, temperature 37oC, oxygen saturation was 89% on room air, and 97% on 10 liters per minute oxygenation via a simple mask. His BMI was 27.7 kg/m2. There were rhonchi in the bilateral middle-lower lobes of the lungs during auscultation. Chest X-Rays showed bilateral patchy infiltrates in all lung lobes consistent with COVID-19 pneumonia (Figure 2A).

Complete blood count showed a normal white blood count of 5.600/uL with decreased lymphocytes by 15.9% and thrombocytopenia (145,000/ul; normal reference: 150.000-450.000/ul). The metabolic blood panel revealed hyperglycemia (blood glucose 400 mg/dL; normal reference: <200 mg/dL) with HbA1C 8.4 (normal reference: 4-5.6). Increase AST 99 U/L (normal reference: 5-34 U/L), hyponatremia (130 Meq/L), and hypokalemia (3.4 Meq/L; normal reference: 3.5-5.1 Meq/L). The inflammatory marker profile was NLR 4.8, ALC 890, CRP 99.4 mg/L, LDH 840 U/L, D-dimer 0.41, and ferritin 732.88 mcg/L. Arterial blood gas with oxygen supplement 10 L/m was taken with pH 7.377, PaCO2 35.1, PaO2 of 114 mmHg, HCO3 20.7, BE -5, SaO2 98%, and PaO2/FiO2 ratio of 187. RT-PCR-positive COVID-19 with whole-genome sequencing revealed infection of the delta variant. The patient's oxygen deteriorated, and need 15 liters per minute via a non-rebreathing mask (NRM) to help maintain an O2 saturation of more than 95%. On day 10th, the patient can be tapering off and finally reached 97% saturation in room air on the twelve-day. The patient had standard treatments like remdesivir, hydrocortisone, heparin as anticoagulant therapy, and levofloxacin. The patient was also regulated blood glucose using insulin injection. On the second day of hospitalization, they were administered tocilizumab and plasma convalescent. After one week, the laboratory tests evaluation found blood glucose 149 mg/dL, NLR 6, ALC 998, AST 145 U/L, ALT 89 U/L, CRP 8.1 mg/L, LDH 602 U/L, D-dimer 4.46, Ferritin 1086 mcg/L. In two weeks of hospitalization, the laboratory result improved with NLR 3.1, ALC 1926, AST 40 U/L, ALT 51 U/L, CRP 1 mg/L, LDH 307 U/L, D-dimer 1.05, Ferritin 367.97 mcg/L. CXR on day 14 showed improvement in bilateral infiltrates (figure 2C). The patient was discharged for self-isolation with clinical improvement after 15 days of treatment.

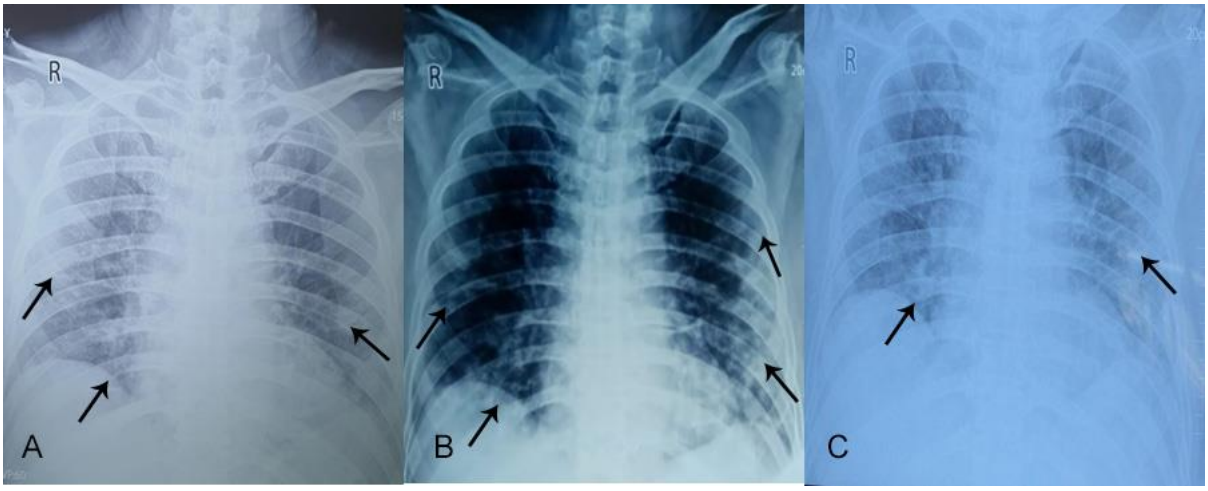

Figure 2. CXR of Case 2 (A) at admission, infiltrates; (B) day 6th of hospitalization, increase infiltrates (C) day 14th of hospitalization, infiltrates diminished (indicated by arrows)

Case 3

A geriatric 73-year-old male diagnosed with a past medical history of arthritis complained of shortness of breath, cough, fever, and sore throat two days before admission. The patient did not mention anosmia or ageusia. He was conscious on arrival, with a blood pressure of 148/70 mmHg, heart rate of 92 bpm, respiratory rate of 26 times per minute, a temperature of 37.10C, and oxygen saturation of 89% on room air. This patient had 5 L/min supplemental oxygen via a nasal cannula, which helped maintain an O2 saturation of 96-97%. His BMI was 23.4 kg/m^2. Rhonchi in bilateral lower lobes of the lungs during auscultation. Chest radiograph showed infiltrates on lower lobes bilaterally consistent with COVID-19 pneumonia (Figure 3). Based on the

complete blood count, it was found normal white blood cells (7.700/L), decreased lymphocytes (18.4%), and thrombocytopenia (121,000/uL). The metabolic blood panel revealed transaminitis (AST 108 U/L and ALT 66 U/L) and hypokalemia (3.0 Meq/L). The inflammatory marker profile was NLR 4.09, ALC 1,400, and CRP 137.6 mg/L. Blood gas analysis was taken with supplemental oxygen 5L/min, pH 7.456, $PaCO_2$ 37.1, PaO_2 of 81 mmHg, HCO_3 26.2, BE 2.0, SaO_2 97%, and PaO_2/FiO_2 ratio of 219. Probable infection of omicron variant COVID-19 was revealed by Spike-gene target failure (SGTF) on the COVID-19 PCR test. The patient had standard treatments like remdesivir, dexamethasone, heparin as an anticoagulant therapy, and antibiotics ceftriaxone combined with azithromycin. The patient's oxygen deteriorated, and he needed 7-8 liters per minute via a simple mask to help maintain an O_2 saturation of more than 95%. However, he was discharged based on his will after eight days of hospitalization.

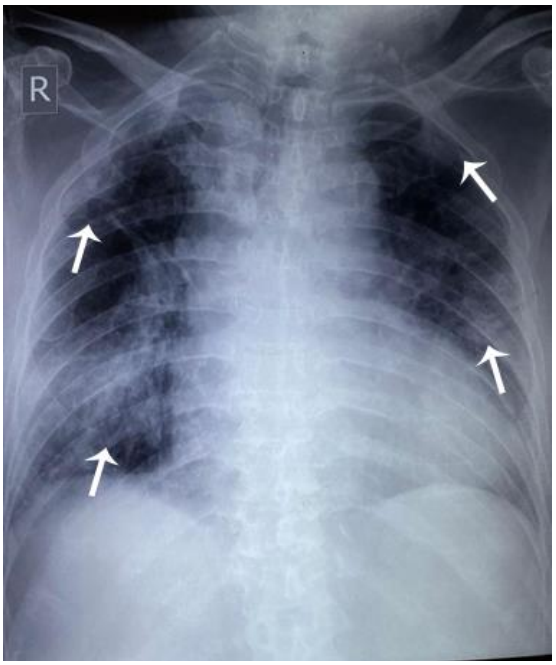

Figure 3. CXR of Case 3 at admission, infiltrate (arrows) bilateral

We discovered certain similarities and differences in each case in this study. A summary of patients' clinical courses is shown in Table 1.

Table 1. Patients' Clinical Characteristics Based on COVID-19 Variants

Characteristics	Case 1 (Non-VOC)	Case 2 (Delta variant)	Case 3 (Probable Omicron)
Age in year	26	51	73
Gender	Female	Male	Male
BMI	24.3	27.7	23.4
Comorbidities	-	DM	Arthritis Genu
Days of onset	4	4	2
Symptom			
Cough	Yes	Yes	Yes
Fever	Yes	Yes	Yes
Shortness of breath	Yes	Yes	Yes
Anosmia and/or ageusia	Yes	Yes	No
Nausea or vomitus	No	Yes	No
Diarrhea	Yes	No	No
Fatigue	Yes	No	No
Myalgia	Yes	Yes	No
Sore throat	No	No	Yes
Headache	No	No	No
Runny nose	No	No	No
Clinical manifestation on arrival			
RR (per minute)	35	28	26
HR (per minute)	119	81	92
SpO2 room air (in %)	81	92	89
PaO2/FiO2 (after O_2 supplementation)	106	186	219
Chest X-ray	Bilateral infiltrates	Bilateral infiltrates	Bilateral infiltrates
Laboratory findings	Lymphocytopenia Transaminitis Hyponatremia Altered inflammatory marker	Lymphocytopenia Thrombocytopenia Hyperglycemia Transaminitis Hyponatremia Hypokalemia Altered inflammatory marker	Lymphocytopenia Thrombocytopenia Transaminitis Hypokalemia Altered inflammatory marker
Treatment			
Oxygenation	HFNC 40 L/min, FiO2 90%	10 – 15 L/min via NRM	5 L/min via NC
Antiviral	Remdesivir	Remdesivir	Remdesivir
Glucocorticoids	Hydrocortisone	Hydrocortisone	Dexamethasone
Anticoagulants	Heparin	Heparin	Heparin
Antibiotics	Meropenem IV	Levofloxacin IV	Ceftriaxone IV Azithromycin oral
Additional	Tocilizumab IVIG	Tocilizumab Plasma Convalescent	-
Days of hospitalization	11	15	8

DISCUSSION

Comorbidity and Symptom

COVID-19 has numerous variations as a result of ongoing mutations. Presumably, each variant has its particular clinical characteristic.[4,5] COVID-19 infection has a broad spectrum of severity ranging from an asymptomatic form to a severe acute respiratory syndrome. Prior studies on SARS-CoV-2 found that comorbidities were strongly related to COVID-19 hospitalization, and severity has a higher probability of poor clinical outcomes, [9,10] with cardiovascular illnesses and diabetes seem to be the most important components. [11] In our case series, case 1 had no comorbidities, but case 2 had diabetes mellitus, and case 3 was a geriatric patient with arthritis. Due to various immunological changes, geriatric patients are more susceptible to severe SARS-CoV-2 infection. This population is at the highest risk of fatal outcomes when accompanied by comorbidities.[12,13] Both patients in cases 1 and 2 came after four days of symptoms, while case 3 came to the hospital after only two days. These findings showed that the omicron variant had a slightly shorter interval between the onset of symptoms and hospital admission. In previous research on COVID-19, the interval between symptoms and hospital admission was 5-7 days.[14,15] The common symptoms of COVID-19 were fever, cough, shortness of breath, fatigue, muscle aches, headache, loss of taste or smell, sore throat, runny nose,

nausea or vomiting, and diarrhea.[16] In this study, we found common symptoms of COVID-19 in all three cases: cough, fever, shortness of breath, nausea, and vomiting. Ageusia was found in case 1 (Non-VOC), anosmia and ageusia were also found in case 2 (confirmed delta variant), but in case 3 (probable Omicron), neither anosmia nor ageusia was found. The results align with prior studies suggesting that anosmia is less common in Omicron infection than other strains and variants reported.[17] This finding means that omicron infection is not affecting the olfactory bulb and is supported by an experimental study by Armando et al. that showed omicron infection caused less damage to the olfactory mucosa in the golden hamsters and most likely lowered the risk of developing anosmia.[17,18]

Physical Findings and Imaging

On arrival, all three cases presented full consciousness and desaturation with peripheral oxygen saturation (SpO2) of 81%, 92%, and 89% on room air in case 1, case 2, and case 3, respectively. In a study by Sohrabi et al., SpO2 ≤ 93% on admission was related to COVID-19 mortality.[19] Another finding suggested that compared to those with SpO2 ≥90%, patients with SpO2 <90% had a 3.8-fold higher risk of one-month death.[20] Based on these data, it was safe to presume that all case arrived in a worse state and was more likely to develop more severe COVID-19 and have a bad prognosis. On physical examination of the lungs, we found rhonchi during auscultation in all three cases, suggesting pneumonia. In all patients in this study, infiltrates were found on CXR, consistent with COVID-19 pneumonia.

Laboratory Finding

We found altered inflammatory markers NLR, ALC, LDH, CRP, and D-dimer in all three cases. Prior studies suggested elevated ANC, NLR, LDH, CRP, and D-dimer values on admission were associated with severity and increased mortality risk in COVID-19.[21,22] We also found thrombocytopenia in cases 2 and case 3. A meta-analysis by Pranata et al. demonstrated that thrombocytopenia was associated with mortality and severity.[23] The association between thrombocytopenia and poor outcome did not vary significantly with age, gender, lymphocyte, D-dimer, hypertension, CKD, and diabetes.[23] Transaminitis was found in all three cases. Liver function abnormalities are common in patients with COVID-19 due to immune dysfunction and cytokine storm-related multi-organ damage, hypoxia-reperfusion injury, and idiosyncratic drug-induced liver injury attributable to drugs used to treat COVID-19.[24] A study by Vadiraj et al. suggested that transaminitis was related to the disease severity of COVID-19, and SGOT levels could effectively predict disease severity and mortality.[25] We also found electrolyte disturbances, namely hyponatremia in cases 1 and 2 and hypokalemia in cases 3. Pourfridoni et al. stated that the most common electrolyte imbalances in COVID-19 were hyponatremia and hypokalemia. Hypokalemia can enhance acute respiratory distress syndrome (ARDS) and increase the risk of cardiac damage in hospitalized patients. Meanwhile, hyponatremia can heighten the risk of mortality in hospitalized patients.[26]

Treatment

All three patients were given standard therapy for critical COVID-19 based on Indonesian COVID-19 management guidelines. These include oxygenation, antiviral, glucocorticoid, anticoagulant therapy, and antibiotics if the bacterial infection is suspected.[27] All patients came with SpO2 < 93% on room air and were treated with oxygen therapy. Oxygen therapy will be initiated from the nasal cannula to NRM 15 L/min, then titrated according to the target SpO2 92-96%. If no clinical improvement within 1 hour or clinical deterioration occurs, oxygen therapy is increased using a High Flow Nasal Cannula (HFNC), starting with a flow of 30 L/min and 40% FiO2.[19,27]

According to guidelines, the antiviral used in this study was remdesivir 200 mg IV drip (day 1) followed by 100 mg IV drip (days 2-10). Glucocorticoid therapy was given short-term usage in individuals with severe or critical COVID-19 due to its anti-inflammatory properties. Dexamethasone, methylprednisolone, or hydrocortisone for ten days were the glucocorticoids of choice in Indonesia.[27,28] In this study, hydrocortisone was given to cases 1 and 2, and dexamethasone was given to case 3. COVID-19 infection is associated with an inflammatory and prothrombotic state characterized by increased fibrin, fibrin degradation products, fibrinogen, and D-dimer. Previous research suggested that coagulation might have a role in predicting the severity of COVID-19. Anticoagulants were recommended for severe-critical individuals.[27,29] The anticoagulant used in this study was heparin, with consideration of the bleeding risk of each patient. Antibiotic therapy is indicated if bacterial infection is suspected, especially in severe-critical cases. The selection of empirical antibiotics was adjusted to each hospital's microbiological and local resistance patterns.[27] Case 1 was with levofloxacin plus meropenem, case 2 was with meropenem, and case 3 was with ceftriaxone and oral azithromycin.

In addition to standard therapy, we also administered tocilizumab in cases 1 and 2. Tocilizumab is a monoclonal antibody targeting IL-6 pathways in pathogenic T cells and inflammatory monocytes. It may help calm the inflammatory storm, as demonstrated by clinical improvements, such as a return to average temperature and improved respiratory function, which can also be seen in these patients.[30] Another additional therapy, in this case, was intravenous immunoglobulin (IVIG) in case 1 and plasma convalescent in case 2. Although the clinical result of IVIG therapy for severe COVID-19 is unknown, it is widely utilized. Herth et al. conducted retrospective research and found that IVIG enhanced the clinical course, with rapid and significant changes in clinical symptomatology, chest imaging, and laboratory results.[31] Convalescent plasma is obtained from people who have recovered from COVID-19, providing passive short-term immunity to susceptible individuals. A retrospective study by Huang et al. revealed that convalescent plasma therapy could benefit patient outcomes.[32]

Patients in the first (non-VOC) and second (delta variant) cases were discharged for self-isolation after 11 and 15 days of treatment, respectively. Meanwhile, in the third case (omicron variant), the patient was treated for eight days, and unfortunately, the patient was discharged based on his will.

CONCLUSION

The clinical presentation was similar in all three variants, except that anosmia and ageusia and the duration days of onset were shorter in the omicron variant. Radiographic and laboratory changes did not differ in the three variants. Clinical outcomes in the three cases were similar and influenced by many factors, including the patient's underlying condition and treatment. SARS-CoV-2 variants have constantly been evolving and changing and could lead to changes in the characteristic of the virus. Information on infection characteristics with new variants is crucial for decision-making on control approaches and strategies.

CONFLICT OF INTEREST

There are no conflicts of interest declared by either of the contributors.

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