Renal Replacement Therapy

CASE REPORT

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A maintenance hemodialysis patient complicated with hypogammaglobulinemia presenting typical COVID-19 pneumonia CT findings: a case report

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Abstract

Background With the widespread use of the vaccine and the predominance of the Omicron strain, the number of patients presenting with typical coronavirus-infection disease 2019 (COVID-19) pneumonia on computed tomography (CT) has decreased dramatically. This has also been true for hemodialysis patients.

Case report A 72-year-old female maintenance hemodialysis patient with hypogammaglobulinemia was diagnosed with COVID-19 based on a nasopharyngeal swab severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) polymerase chain reaction (PCR) test. She had previously received five doses of COVID-19 BNT162b2 vaccine. Initially, the patient had only a slight fever, mild sore throat and sputum, and molnupiravir 1600 mg/day was administered for 5 days. No high fever was observed during that period. On day 11 after diagnosis, bloody sputum was observed, and by day 13 the cough had worsened and her CRP level had increased to 13.10 mg/dL. Chest CT performed on the same day showed multiple subpleural ground-glass-like shadows typical of COVID-19 pneumonia predominantly in the right lung. She was immediately admitted to the hospital, where her temperature rose to 38.4 °C. Intravenous remdesivir 100 mg/day was administered for 5 days. This resolved her fever and the bloody sputum disappeared. She was discharged from the hospital without sequelae on the 21st day after diagnosis.

Conclusion We experienced a case of typical COVID-19 pneumonia in a patient on maintenance hemodialysis who had received five doses of COVID-19 BNT162b2 vaccine. There was a flare-up of symptoms after administration of molnupiravir, suggesting that a hypogammaglobulinemia complication was involved. This highlights the need for attention to its potential transition to severe disease when patients with hypogammaglobulinemia or other highly immunocompromised conditions are affected by COVID-19.

Keywords Hypogammaglobulinemia, Hemodialysis patient, COVID-19 pneumonia

Background

Until the Omicron strain became prevalent, the incidence of severe pneumonia among COVID-19 patients was high. This was especially true for hemodialysis patients, who experienced more severe illness and much higher mortality due to COVID-19 than the general population [1, 2]. The reason for this is that humoral and cellular immunity is impaired in hemodialysis patients [3]. However, with the advent of COVID-19 vaccine and

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the increased prevalence of the Omicron strain [4], the rate of severe cases and the number of cases decreased [5–7]. And typical COVID-19 pneumonia on CT has also decreased markedly, even among hemodialysis patients [8]. In this report, we describe the case of a patient on maintenance hemodialysis with hypogammaglobulinemia who showed typical pneumonia on CT, despite five COVID-19 vaccinations.

Case report

On May, 2023, a 72-year-old woman with a slight fever (37.0 °C; her usual temperature was 36.2–36.5 °C) and sputum came to our hospital. A nasopharyngeal swab SARS-CoV-2 PCR test was positive with a cycle threshold (Ct) value of 39/45, and COVID-19 was diagnosed. Her eldest son, who lived with her, had been diagnosed with COVID-19 the day before. She was administered molnupiravir 1,600 mg/day orally for 5 days and eprazinone hydrochloride 90 mg/day and ambroxol hydrochloride 45 mg/day orally for 13 days. In 1995, this patient was diagnosed with IgA nephropathy based on the results of a renal biopsy at another hospital following detection of proteinuria and microscopic hematuria. In 2002, she began continuous ambulatory peritoneal dialysis (CAPD) at our hospital. However, due to a refractory exit infection she was shifted to hemodialysis in 2005 and has recently been stabilized on intermittent infusion hemodiafiltration (I-HDF) three times a week. Although she had received five doses of BNT162b2 vaccine, her anti-spike antibody levels 2 weeks after vaccination were very low: 0 AU/mL, 0 AU/mL, 0 AU/mL, 302 AU/mL and 516 AU/mL after the 2nd, 3rd, 4th and 5th vaccinations, respectively (Fig. 1). Her last the fifth vaccinations were administered on December, 2022. A search for the cause of these low anti-spike antibody levels revealed hypogammaglobulinemia (IgG 539 mg/dL, IgM mg/dL14, IgA 42 mg/dL). The patient had no previous history of hospitalization for infectious diseases; moreover, none of her usual medications, which included fonoprazan fumarate 10 mg/day, montelukast sodium 10 mg/day, amiodarone hydrochloride 100 mg/day, ferrous sodium citrate 50 mg/day, mosapride citrate hydrate 15 mg/day, BIO-THREE 6 tabs/day, acetaminophen 600 mg/day and droxidopa 400 mg/before every hemodialysis, were thought to cause hypogammaglobulinemia. After contracting COVID-19, the patient's predialysis temperature was initially not elevated (35.7–36.6 °C), though she had a cough and sputum. However, by the 10th day after diagnosis of COVID-19, bloody sputum was observed. On the 13th day after diagnosis, CRP was elevated at 10.92 mg/dL at the start of dialysis, and the patient was hospitalized following her dialysis. Physical examination on admission revealed a body temperature of 38.4 °C, blood pressure of 149/92 mmHg, pulse of 86 beats/minute, respiratory rate of 23 breaths/minute and an oxygen saturation of 96% while the patient was breathing ambient air. Upon lung auscultation, a pronounced coarse crackle was heard in the right lower lung field. Subsequent chest CT revealed

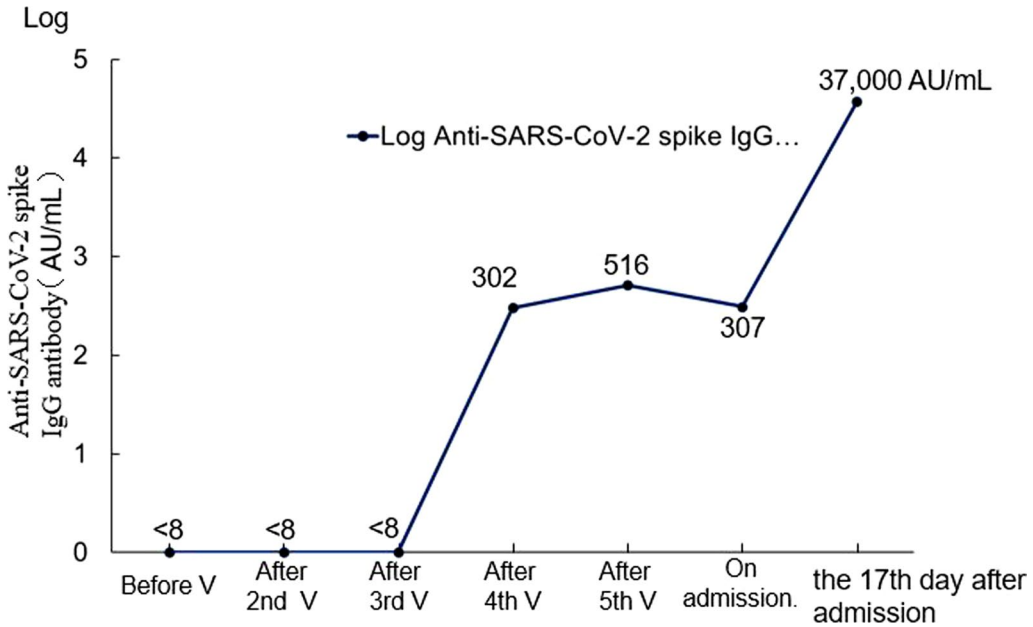

Fig. 1 Changes in anti-SARS-CoV-2 spike IgG antibody titer. Anti-spike antibody titers were measured 2 weeks after vaccination. The numbers in the figure indicate the real anti-SARS-CoV-2 spike IgG antibody titer. Abbreviation: V, vaccination

extensive ground-glass opacification consistent with right-dominant, COVID-19-related pneumonia (Fig. 2). At the time of admission, a nasopharyngeal swab SARS-CoV-2 PCR test was positive with a Ct of 27/45, which was considered to indicate a higher viral load than when first diagnosed 13 days prior. At the same time, laboratory results showed a white blood cell count of 4,600/mm^3 but a low lymphocyte count of 697 mm^3. CRP was elevated at 13.1 mg/dL but LDH was not elevated. Without oxygenation, PO2 was as low as 76.6 mmHg, but there was no complaint of breathlessness. BNP was historically high (516–967 pg/mL) due to the patient's cardiac hypertrophy but was even higher (1,299 pg/mL) at the time of admission. D-dimer was also high at 2,040 ng/mL.

In the hospital, the patient was treated with remdesivir 100 mg IV for 5 days without a loading dose. In addition, 5 g of gammaglobulin preparation was administered for 3 days and 1 g of ceftriaxone was administered for 5 days as secondary infection prophylaxis (Fig. 3). The anticoagulant during hemodialysis was changed three times from the previously used parnaparin to nafamostat. On hospital day 8 (day 20 after diagnosis), a second CT showed a mixed picture of pneumonia with both mild and worsening lesions and a mixture of old and new lesions (Fig. 4). The patient was discharged on day 21 after diagnosis, although she continued to have a mild cough. At discharge, PO2 had normalized to 82.5 mmHg and BNP had decreased to 700 pg/mL. Although some myocardial damage due to COVID-19 was observed in this patient,

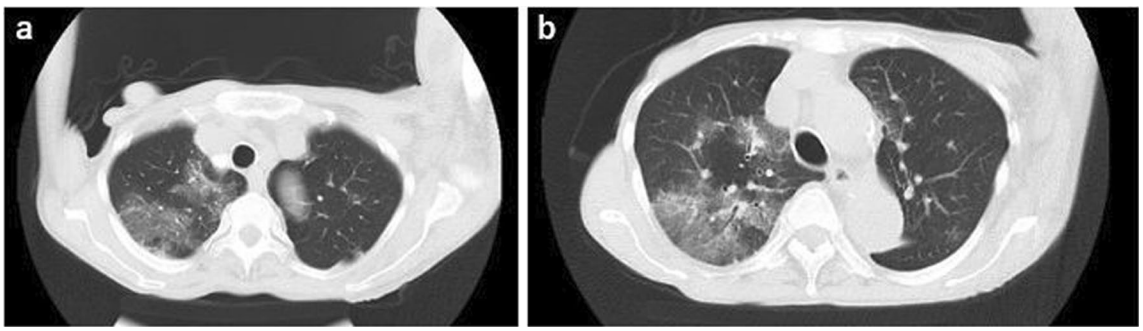

Fig. 2 CT image at admission. **a** Subpleural ground-glass shadow is seen in the right upper lung field. **b** More extensive ground-glass shadows are seen in the right middle lung field

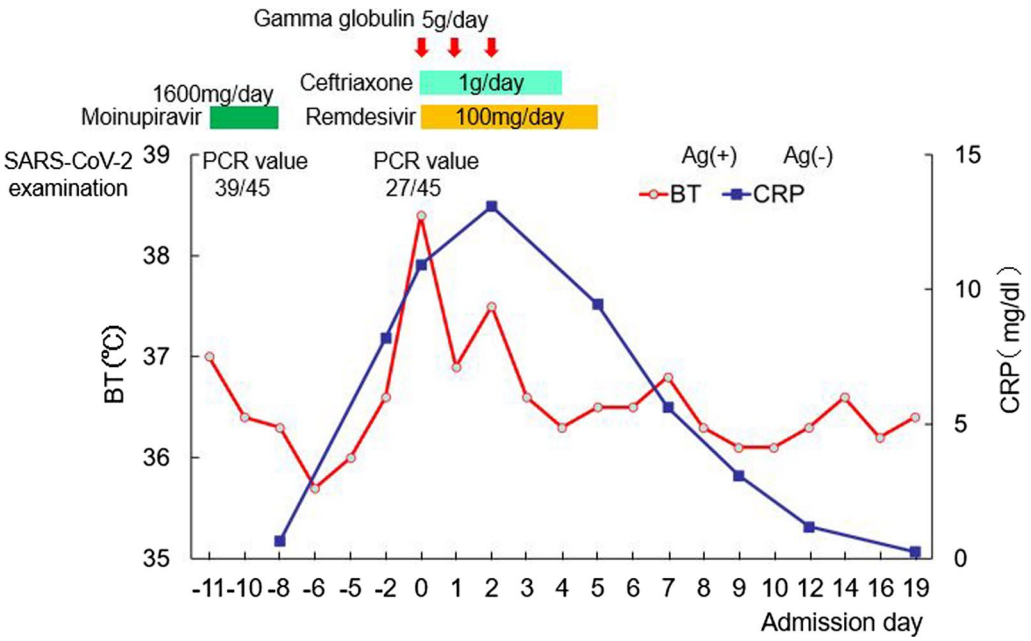

Fig. 3 Clinical course. Red line indicated BT changes. Blue line indicated CRP changes. Abbreviation: BT, bodily temperature; CRP, C-reactive protein

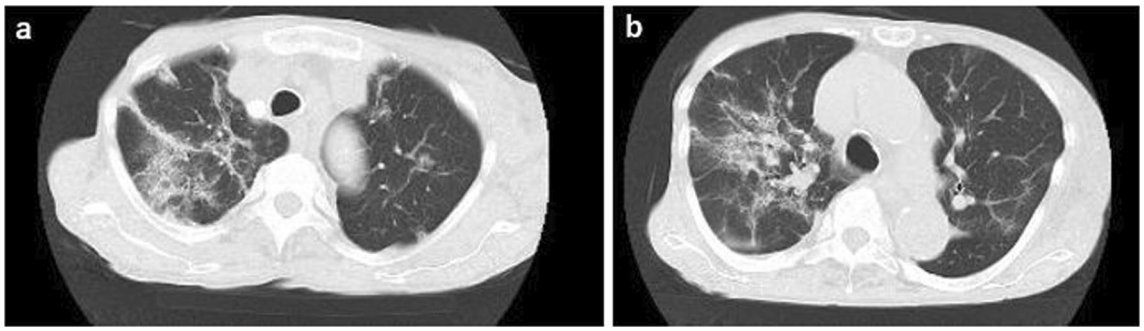

Fig. 4 Admission 8 day chest CT. **a** The lesions in the upper lung field showed a mixture of improving and worsening lesions compared to the onset of disease. **b** The lesion was in the middle lung field, similar to the lesion in the upper lung field

the rapid recovery suggested that the myocardial damage was mild. Klebsiella oxytoca was detected in her sputum at 1(+), with good sensitivity to ceftriaxone. However, based on chest CT images and the clinical course of the patient, Klebsiella oxytoca was considered unlikely to be the causative agent of the pneumonia. A pulmonary blood flow scan on the 15th day of discharge was normal with no evidence of a pulmonary embolism (Fig. 5), and venous ultrasound of the lower extremities showed no evidence of deep vein thrombosis in the lower extremities. Immunoglobulins were all low (IgG, 567 mg/dL; IgM, 15 mg/dL; and IgA, 39 mg/dL). CD4 and CD8 were normal, but CD19 and CD20 were very low (Table 1). The patient was then seen by a hematologist at a public hospital. Based on the absence of abnormalities detected in a bone marrow puncture and chromosome examination, the patient's hypogammaglobulinemia was diagnosed as common variable immunodeficiency (CVID). Figure 1 shows the changes in the patient's anti-SARS-CoV-2 spike IgG antibody titer. Anti-SARS-CoV-2 spike IgG antibody was undetectable after the first three doses of the original COVID-19 BNT162b2 vaccine. With two additional doses of COVID-19 BNT162b2 bivalent vaccine, the antibody titers were detectable but low. The antibody titer on admission was only 307 AU/mL. However, by the 17th day after admission, the antibody titer had marked increased to 37,000 AU/mL. Table 2 presents 43 similar COVID-19 breakthrough infection cases after mRNA vaccination among our hemodialysis patients. The median age of the patients was 70 years, 43 males and 11 females, the median dialysis history was 68 months, and the primary disease was DM in 14 cases. The median number of vaccinations before the onset of COVID-19 was 3.8, the median number of days after vaccination was 160 days, and the median antibody titer was 14,500 AU/mL just before the onset of the disease. The spread of disease despite high antibody titers suggests that days had passed since vaccination or that the vaccine

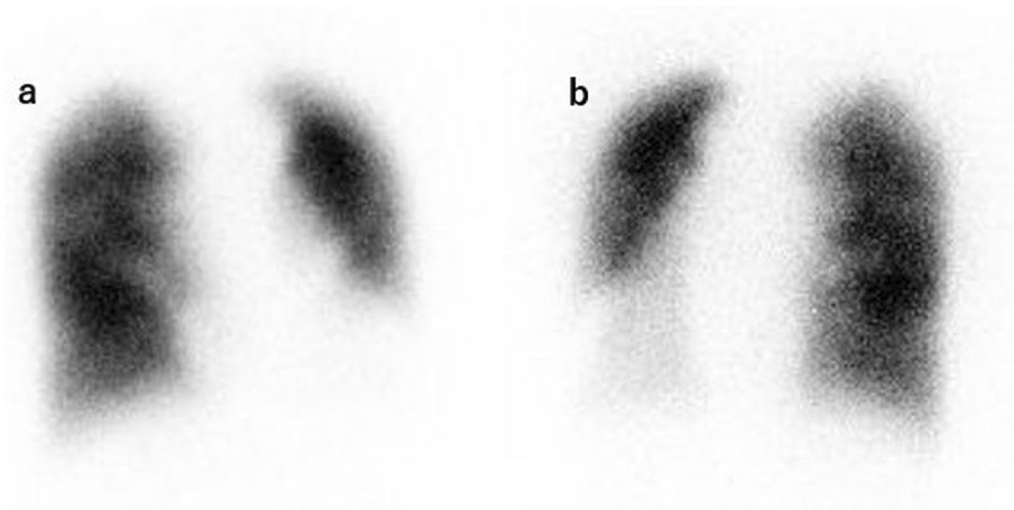

Fig. 5 Pulmonary blood flow scan on admission day 24. **a** Scanning frontal image. **b** Scanning of the rear image

Table 1 Results of blood panel on admission

WBC	4600/μL
Lymphocytes	697/μL
RBC	4,250,000/μL
Hb	12.3 g/dL
Ht	38.5%
PLT	156,000/μL
CRP	13.10 md/dL
BUN	80.45 mg/dL
Cr	7.37 mg/dL
AST	15 U/L
ALT	8 U/L
LDH	197 IU/L
ALP	69 IU/L
γGTP	12 IU/L
CPK	97 IU/L
Na	132 mEq/L
Cl	96 mEq/L
K	5.0 mEq/L
PO2 (at room air.)	76.6 mEq/L
PCO2 (at room air.)	38.4 mEq/L
$HCO3^-$	19.1 mEq/L
BNP	2,040 pg/mL
KL-6	376 U/mL
IgG	567 mg/dL
IgM	15 mg/dL
IgA	39 mg/dL
CD4	66.6%
CD8	21.3%
CD19	0.4%
CD20	0.5%

Table 2 COVID-19 breakthrough infection after mRNA CVID-19 vaccination in hemodialysis patients ($n=42$)

Age	69.0 [54.3–74.0]
Male/female	31:11
Hemodialysis vintage (month)	68 [23–119]
DM: non-DM	14:28
Number of vaccinations	3.8 [3–5]
Days after last vaccination	160 [97–206]
Ant-SARS-Cov2 IgG antibody	14,500 [5126–29,250]IU/mL
Typical COVID-19 pneumonia findings + :-	1*:41

Results are shown as the median [interquartile range] for continuous variables

* Present case

Abbreviation: DM, diabetes mellitus

type had not kept pace with the mutation of the SARS-CoV-2 virus. The occurrence of COVID-19 breakthrough infection despite high antibody titers suggests that either days had passed after vaccination or the vaccine type had not caught up with the mutation of the SARS-CoV-2 virus.

Discussion

The Omicron variant of SARS-CoV-2 has a higher rate of transmission than the earlier variants, which has led to its reported predominance in at least one study in every country where it was tested [4]. Fortunately, the risk of serious outcomes after SARS-CoV-2 infection is substantially lower for Omicron than for Delta and other variants [5–7]. The reason for the lower virulence of the Omicron strain is reportedly related to the finding that this virus multiplies primarily in the upper airway mucosa rather than in the lungs, possibly because interferon production in the airway mucosa inhibits replication of this strain in the lungs [9, 10]. Consequently, Omicron efficiently infects human airways but not the alveolar epithelium. Even with Omicron, however, there are reports of severe COVID-19 cases among hemodialysis patients [11, 12].

Following infection by the earlier SARS-CoV2 variants, chest CT is abnormal, even in asymptomatic patients, and localized unilateral subpleural ground-glass opacities became more diffuse and bilateral within 1–3 weeks [13, 14]. However, Tsakok MT et al. and Han et al. found that the Omicron variant showed less lung injury on CT than the original or Delta variant [8, 15]. In addition, Crombé et al. reported that both the Omicron variant and vaccination were associated with fewer typical chest CT manifestations of COVID-19 and lesser disease severity [16]. By contrast, our patient showed typical COVID-19 pneumonia on CT, even after five doses of BNT162b2 vaccine during the Omicron epidemic. However, this case was complicated by hypogammaglobulinemia, which led to a very low anti-SARS-CoV-2 spike antibody titer, even after five vaccinations (Fig. 1). We think that this hypogammaglobulinemia accounts for the COVID-19 pneumonia detected on this patient's CT. The cause of hypogammaglobulinemia was clinically diagnosed as CVID based on of the very mild elevation of anti-SARS-CoV-2 spike antibody after BNT162b2 vaccination. Consistent with that diagnosis, bone marrow puncture and genetic testing were normal, and drug involvement was unlikely [17].

Although there are few reports of CVID among COVID cases, it is known to be severe when it occurs [18, 19]. This patient showed markedly reduced CD19 and CD20 levels, which is similar to the status following rituximab administration. Patients on rituximab are known to be severely affected by COVID-19 and to show a poor antibody response after COVID-19 vaccination [20–23]. On admission of this patient, we also detected elevated blood levels of D-dimer, which is reportedly a marker of poor prognosis in COVID-19 patients not on hemodialysis [24]. However,

D-dimer is said to be elevated in hemodialysis patients even in the absence of thrombosis [25], and its elevated level should be interpreted with caution. In the present case, there was no obvious evidence of thrombosis, and D-dimer levels decreased over time to a normal value (data not shown).

As mentioned, this patient received 100 mg of remdesivir intravenously without a loading dose for 5 days. There is a paucity of randomized controlled trials on the safety and efficacy of remdesivir in patients with renal impairment having GFR < 30 mL/min due to devastating complications related to the prolonged half-life of the drug itself and its vehicle sulfobutylether-β-cyclodextrin (SBECD) [26]. That said, there have been reports of the use of remdesivir to treat COVID-19 in hemodialysis patients, though the doses varied [27–29].

Conclusion

We report the case of a maintenance hemodialysis patient complicated with hypogammaglobulinemia presenting with typical COVID-19 pneumonia CT findings. Even with the Omicron variant, COVID-19 can be severe in hemodialysis patients with complications such as hypogammaglobulinemia. It therefore requires careful attention.

Abbreviations

BT	Body temperature
CVID	Common variable immunodeficiency
CT	Computed tomography
CAPD	Continuous ambulatory peritoneal dialysis
COVID-19	Coronavirus-infection disease 2019
Ct	Cycle threshold
eGFR	Estimated glomerular filtration rate
I-HDF	Intermittent infusion hemodiafiltration
PCR	Polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus
SBECD	Sulfobutylether-β-cyclodextrin

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Author contributions

RM, KM and SH took care of patients and participated in the decisions about treatment. RM prepared the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

The study was conducted in compliance with the Declaration of Helsinki and approved by the ethics committee in the Fujita Memorial Hospital, Fukui, Japan (Approval number: 58).

Consent for publication

Written informed consent was obtained from the present patient.

Competing interests

No authors have conflicts to report.

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References

1. Kikuchi K, Nangaku M, Ryuzaki M, Yamakawa T, Yoshihiro O, Hanafusa N, et al. Survival and predictive factors in dialysis patients with COVID-19 in Japan: a nationwide cohort study. Renal Replacement Therapy. 2020;6:55.
2. Hsu CM, Weiner DE, Aweh G, Miskulin DC, Manley HJ, Stewart C, Ladik V, et al. COVID-19 Among US Dialysis Patients: risk factors and outcomes from a National Dialysis Provider. Am J Kidney Dis. 2021;77:748–56.
3. Espi M, Charmetant X, Barba T, Mathieu C, Pelletier C, Koppe L, et al. A prospective observational study for justification, safety, and efficacy of a third dose of mRNA vaccine in patients receiving maintenance hemodialysis. Kidney Int. 2022;101:390–402.
4. Sarkar A, Omar S, Alshareef A, Fanous K, Sarker S, Alroobi H, et al. The relative prevalence of the Omicron variant within SARS-CoV-2 infected cohorts in different countries: a systematic review. Hum Vaccin Immunother. 2023;19:2212568.
5. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. Lancet. 2022;399:437–46.
6. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet. 2022;399:1303–12.
7. Mohsin M, Mahmud S. Omicron SARS-CoV-2 variant of concern: a review on its transmissibility, immune evasion, reinfection, and severity. Medicine (Baltimore). 2022;101:e29165.
8. Tsakok MT, Watson RA, Saujani SJ, Kong M, Xie C, Peschl H, et al. Reduction in chest CT severity and improved hospital outcomes in SARS-CoV-2 omicron compared with delta variant infection. Radiology. 2023;306:261–9.
9. Chiu MC, Li C, Liu X, Yu Y, Huang J, Wan Z, et al. A bipotential organoid model of respiratory epithelium recapitulates high infectivity of SARS-CoV-2 omicron variant. Cell Discov. 2022;8:57.
10. Alfi O, Hamdan M, Wald O, Yakirevitch A, Wandel O, Oiknine-Djian E, et al. SARS-CoV-2 omicron induces enhanced mucosal interferon response compared to other variants of concern, associated with restricted replication in human lung tissues. Viruses. 2022;14:1583.
11. Haruta M, Otsubo S, Otsubo Y. Characteristics of the 6th Japanese wave of COVID-19 in hemodialysis patients. Ren Replace Ther. 2022;8:61.
12. Wen W, Cai S, Li Y, Wu X. Risk factors and prognosis for coronavirus disease 2019 among 131 hemodialysis patients during the Omicron variant epidemic. Ren Fail. 2023;45:2228924.
13. Shi H, Han X, Jiang N, Cao Y, Alwalid O, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20:425–34.
14. Zhou S, Wang Y, Zhu T, Xia L. CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan. China AJR Am J Roentgenol. 2020;214:1287–94.
15. Han X, Chen J, Chen L, Jia X, Fan Y, Zheng Y, et al. Comparative analysis of clinical and CT findings in patients with SARS-CoV-2 original strain, delta and omicron variants. Biomedicines. 2023;11:901.
16. Crombé A, Bensid L, Seux M, Fadli D, Arnaud F, Benhamed A, et al. Impact of vaccination and the omicron variant on COVID-19-related chest CT findings: a multicenter study. Radiology. 2023;307:e222730.
17. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. J Allergy Clin Immunol Pract. 2019;7:1763–70.

18. Weifenbach N, Jung A, Lötters S. COVID-19 infection in CVID patients: What we know so far. Immun Inflamm Dis. 2021;9(3):632–4.
19. Ferenc T, Vilibić-Čavlek T. Common variable immunodeficiency: Predisposing or protective factor for severe complications of COVID-19? Acta Clin Croat. 2022;61:107–14.
20. Levavi H, Lancman G, Gabrilove J. Impact of rituximab on COVID-19 outcomes. Ann Hematol. 2021;100:2805–12.
21. Nelson MC, Manos CK, Flanagan E, Prahalad S. COVID-19 after rituximab therapy in cSLE patients. Ther Adv Vaccines Immunother. 2023;11:25151355231181240.
22. Ishio T, Tsukamoto S, Yokoyama E, Izumiyama K, Saito M, Muraki H, et al. Anti-CD20 antibodies and bendamustine attenuate humoral immunity to COVID-19 vaccination in patients with B-cell non-Hodgkin lymphoma. Ann Hematol. 2023;102:1421–31.
23. Zhang-Sun J, Kirou RA, Kirou KA. Low peripheral B-cell counts in patients with systemic rheumatic diseases due to treatment with Belimumab and/or Rituximab are associated with low antibody responses to primary COVID-19 vaccination. HSS J. 2023;19:180–6.
24. Zhan H, Chen H, Liu C, Cheng L, Yan S, Li H, et al. Diagnostic value of D-dimer in COVID-19: a meta-analysis and meta-regression. Clin Appl Thromb Hemost. 2021;27:10760296211010976.
25. Gubensek J, Lolic M, Ponikvar R, Buturovic-Ponikvar J. D-dimer levels in maintenance hemodialysis patients: High prevalence of positive values also in the group without predisposing diseases. Hemodial Int. 2016;20:198–203.
26. Butt B, Hussain T, Jarrar M, Khalid K, Albaker W, Ambreen A, et al. Efficacy and safety of remdesivir in COVID-19 Positive dialysis patients. Antibiotics (Basel). 2022;11:156.
27. Lim JH, Park SD, Jeon Y, Chung YK, Kwon JW, Jeon YH, et al. Clinical effectiveness and safety of remdesivir in hemodialysis patients with COVID-19. Kidney Int Rep. 2022;7:2522–5.
28. Butt B, Hussain T, Jarrar M, Khalid K, Albaker W, Ambreen A, et al. Efficacy and safety of remdesivir in COVID-19 Positive dialysis patients. Antibiotics (Basel). 2022;11(2):156.
29. Shah MK, Parikh M, Prajapati D, Kute VB, Bhende P, Prajapati A, et al. Safety and tolerability of remdesivir in patients with end-stage renal disease on maintenance hemodialysis. Indian J Crit Care Med. 2022;26(5):619–25.

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