



Hemodialysis patients with coronavirus disease 2019: reduced antibody response

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Abstract

Background Because patients on maintenance hemodialysis (HD) have an impaired immune response to pathogens, they are at higher risk of severe coronavirus disease 2019 (COVID-19). However, data on antibody production among HD patients with COVID-19 is scarce. Thus, we performed a retrospective cohort study evaluating severe acute respiratory syndrome coronavirus two antibody (SARS-CoV-2) production within 1 month after COVID-19 onset in hospitalized patients on HD.

Methods SARS-CoV-2-specific immunoglobulin (Ig) G levels were quantified using an iFlash 3000 Chemiluminescence Immunoassay analyzer (Shenzhen YHLO Biotech Co., Ltd.) to detect IgG antibodies specific for the S1 subunit of the spike protein (IgG-S1). Propensity score matching was used to balance covariate distribution in HD and non-HD patients. From April 2020 to February 2021, antibody testing was performed on 161 hospitalized patients with symptomatic COVID-19. Of them, 34 HD patients were matched to 68 non-HD patients.

Results After propensity score matching, the median levels of IgG-S1 in the HD patients at 7–13 days after symptom onset were significantly lower than in non-HD patients, especially in those with severe disease. Among all patients, those with severe disease produced lower levels of IgG-S1 at 7–13 days compared with non-severe patients.

Conclusion COVID-19 patients with severe disease, especially those undergoing HD, had lower IgG-S1 production in the second week of the disease. Thus, the increased risk of severe COVID-19 in HD patients may be, in part, due to a slow and reduced antibody response.

Keywords Hemodialysis · Immune response · COVID-19 · Antibody · Severe disease · SARS-CoV-2

Introduction

At the end of 2019, the coronavirus disease 2019 (COVID-19) which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread all over the world, and the World Health Organization declared this outbreak as a public health emergency of international concern [1]. Patients on maintenance hemodialysis (HD) are considered as a highly vulnerable population to COVID-19 infection due to the fact that they have a higher probability of having comorbidities such as diabetes and cardiovascular disease. Indeed, recent studies reported that patients on HD

are at high risk of adverse outcomes of COVID-19, and the mortality rates from COVID-19 can reach as high as 20% [2–5]. Patients on HD generally show an impaired immune response to pathogens [6], therefore, inadequate antibody production to SARS-CoV-2 may partially explain the association between HD and poor clinical outcome. However, data on antibody production among COVID-19 patients undergoing HD remain scarce. In this article, we retrospectively evaluated antibody responses to SARS-CoV-2 during the development of symptomatic COVID-19 in patients on HD and those not-on HD.

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Materials and methods

Study design and population

This retrospective cohort study evaluated SARS-CoV-2 antibody production within 1 month after symptom onset in adult patients with COVID-19 at Okubo Hospital, Tokyo, Japan. Okubo Hospital falls within the Tokyo Metropolitan public hospital network and is designated to provide inpatient care for COVID-19 patients who do not require high-flow oxygen or intensive care, particularly for patients on maintenance HD. Our study cohort included symptomatic patients with COVID-19 who were tested for anti-SARS-CoV-2 antibodies and compared antibody levels between HD and non-HD patients. Furthermore, we assessed differences in antibody levels according to the disease severity. Severe disease was defined as partial pressure of oxygen/fraction of inspired oxygen (P/F) ratio < 300 or oxygen saturation (SpO₂) < 94% during hospitalization, based, in part, on the definition according to the COVID-19 Treatment Guidelines Panel of the United States National Institutes of Health [7]. COVID-19 was diagnosed using a reverse transcription polymerase chain reaction.

Antibody measurement

Frozen and stored serum samples left over after clinical testing were used to measure the concentration of anti-SARS-CoV-2 antibodies using iFlash 3000 chemiluminescence immunoassay analyzer (Shenzhen YHLO Biotech, China). We purchased two kits; the iFlash–SARS-CoV-2 IgG-S1 kit and the iFlash SARS-CoV-2 IgG kit. The iFlash–SARS-CoV-2 IgG-S1 kit detected immunoglobulin (Ig) G specific to the S1 subunit of the spike protein (IgG-S1). The iFlash–SARS-CoV-2 IgG kit detected IgG to the nucleocapsid (N) and spike (S) proteins (IgG). According to the manufacturer's instructions, results with values ≥ 10 arbitrary units (AU)/mL were considered positive.

Clinical data collection

We obtained data on comorbidities [diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and cancer history], demographics (age, sex, body mass index, and smoking status), information related to disease severity (SpO₂, P/F ratio, and type of oxygen therapy), laboratory test results, and medication (renin–angiotensin–aldosterone system inhibitors, immunosuppressive agents and iron supplementation) from the electronic medical records of each patient. Baseline clinical data were collected on the first day of admission. In patients

on HD, laboratory parameters at baseline were determined using the results of blood samples taken before dialysis. Hypertension was diagnosed based on the history in the medical record or current use of antihypertensive medications. Diabetes mellitus was diagnosed based on the history in the medical record, current use of antidiabetic medications, or glycated hemoglobin $\geq 6.5\%$ on admission. COPD was diagnosed based on the history in the medical record or the presence of typical COPD changes on high-resolution computed tomography scans. Cardiovascular disease was diagnosed based on the history of stroke, unstable angina, myocardial infarction, percutaneous coronary intervention, coronary bypass grafting, angioplasty, or major amputation as a result of peripheral arterial disease in the medical record. For the accuracy of clinical outcome data, patients with COVID-19 who developed severe disease necessitating transfer to another hospital for intensive care were tracked to ensure accuracy of the clinical outcome data and to record the mortality rate.

Statistical analysis

Data were presented as mean \pm standard deviation, median with interquartile range, or percentage according to data distribution. Categorical variables were compared using the chi-squared test. Differences were analyzed using the *t* test or Mann–Whitney *U* test, as appropriate for the data distribution. The propensity score for HD in each patient was calculated using a logistic regression model incorporating covariates (age, sex, body mass index, diabetes mellitus, hypertension, cardiovascular disease, and COPD) to balance covariate distribution between the HD and non-HD patients. Then, we used the propensity scores to perform 1:2 matching between HD and non-HD patients with the nearest neighbor algorithm. *p* values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS v21.0 (IBM Corp., Armonk, NY, USA).

Results

Figure 1 shows the study flow chart. Antibody testing was performed on 172 of 225 COVID-19 patients admitted between April 2020 and February 2021. After excluding 11 asymptomatic patients, the final study cohort comprised 161 symptomatic patients (34 on maintenance HD). The causes of end-stage renal disease among the HD patients were diabetes mellitus ($n = 11$), hypertension ($n = 7$), glomerular disease ($n = 7$), autosomal dominant polycystic kidney disease ($n = 1$), and others or unknown ($n = 8$). We used propensity score matching to match 34 HD patients to 68 non-HD patients; baseline clinical characteristics, except the prevalence of current smoking, comorbidities,

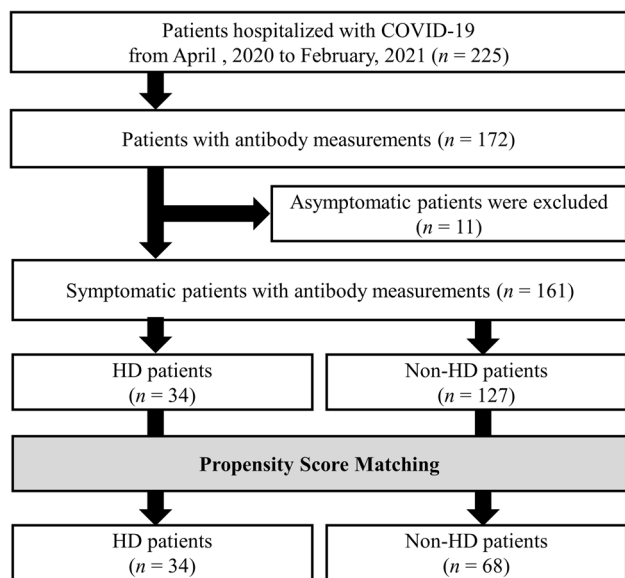


Fig. 1 Study flow chart

and specific medications, were comparable between the two groups. Lymphocyte counts (HD: 0.6×10^9 vs. non-HD $1.0 \times 10^9/l$, $p < 0.001$) and albumin levels (HD 31 vs. non-HD 36 g/l, $p = 0.001$) were significantly lower in HD patients than non-HD patients. C-reactive protein (HD 2.71 vs. non-HD 3.56 mg/dl) and ferritin (HD 279 vs. non-HD 347 ng/ml) levels were not significant. As for baseline medication, the number of patients receiving iron supplementation was significantly higher in the HD patients than non-HD patients (15 vs. 0%, respectively, $p = 0.003$). The proportion of HD patients who received remdesivir was significantly lower than non-HD patients (0 vs. 19%, respectively, $p = 0.004$), but there was no significant difference in steroid use (64 vs. 50%, respectively, $p = 0.261$) or favipiravir (85 vs. 75%, respectively, $p = 0.233$). The proportion of HD versus non-HD patients who developed the severe disease (13 of 34, 38% vs. 16 of 68, 24%, respectively, $p = 0.187$) and the mortality rate between the two groups (HD 6 of 34, 18% vs. non-HD 7 of 68, 10%, $p = 0.350$) were similar (Table 1).

We used 596 samples obtained from 102 propensity score-matched patients up to 27 days after symptom onset to measure IgG-S1 and IgG concentrations. The median number of antibody measurements during hospitalization was not significantly different between the two groups (HD 5 times vs. non-HD 4 times, $p = 0.108$).

As shown in Fig. 2, in HD patients, the median (interquartile range [IQR]) levels of IgG-S1 at 7–13 days were significantly lower than those in non-HD patients [Fig. 2a, 5.4 (0.7–42.1) vs. 11.7 (1.9–107.4) AU/ml, $p = 0.032$]. In patients with severe COVID-19, the IgG-S1 levels at 7–13 days in HD patients were significantly lower than in non-HD patients [1.5 (0.5–5.2) vs. 5.7 (0.7–38.3) AU/

ml, $p = 0.018$]. There was no difference in IgG-S1 levels at 7–13 days between the HD and non-HD patients with non-severe disease [11.7 (1.5–127.0) vs. 18.4 (2.8–117.6) AU/ml, $p = 0.368$]. Regardless of disease severity, strong and similar IgG-S1 antibody responses were observed 14 days after symptom onset in both cohorts. Similar to the kinetics of IgG-S1, the levels of IgG in 7–13 days in the HD patients were significantly lower than those in the non-HD patients [Fig. 2b, 8.8 (1.0–41.7) AU/mL vs. 20.5 (1.4–56.5) AU/mL, $p = 0.042$]. In patients with severe disease, HD patients had a tendency to show lower IgG response than non-HD patients at 7–13 days [1.5 (0.5–8.7) AU/mL vs. 6.9 (0.8–43.1) AU/mL, $p = 0.101$].

Figure 3 illustrates the difference in antibody responses between severe patients and non-severe patients. In both HD and non-HD patients, those with severe disease showed a significantly lower IgG-S1 antibody response at 7–13 days (Fig. 3a). The median (IQR) level of IgG-S1 at 7–13 days for all patients was 3.7 (0.6–34.0) AU/ml in severe patients and 11.7 (1.9–107.4) AU/ml in non-severe patients ($p = 0.042$). IgG levels were consistently lower in severe patients compared with that in non-severe patients throughout the 28 days after symptom onset (Fig. 3b).

Discussion

COVID-19 patients who developed severe illness, especially those receiving maintenance HD, had lower IgG-S1 production than non-severe patients during the second week of the disease after symptom onset. The increased risk of severe COVID-19 could be attributed to a slow antibody response to SARS-CoV-2 spike protein. Anti-spike IgG antibodies are significantly correlated with virus-neutralizing antibody titers [8], suggesting a critical role in protection against SARS-CoV-2 infection. Lucas et al. recently reported that deceased COVID-19 patients showed delayed anti-spike IgG production and neutralizing antibody response before the second week after symptom onset compared with discharged patients [9]. This may support our findings that slow IgG-S seroconversion was significantly more frequently observed in patients who developed a severe illness.

To the best of our knowledge, this is the first study showing different IgG-S1 antibody responses between HD and non-HD patients who developed severe illness in the early stage of SARS-CoV-2 infection. The majority of HD patients with COVID-19 have been reported to develop specific antibodies, including IgG, within 1 month after symptom onset [10, 11], which is consistent with our study finding that most patients produced IgG antibodies within 3 weeks after onset, plateauing in the third week after onset. However, we found that IgG-S1 responses were significantly much lower in the second week in the HD patients compared with the non-HD

Table 1 Baseline clinical characteristics, comorbidities, medication, and the clinical outcomes in patients on HD and those not on HD

	Unmatched patients <i>n</i> = 59	Propensity score matched patients		<i>p</i> value ^a
		HD-group <i>n</i> = 34	Non-HD group <i>n</i> = 68	
Clinical characteristics at baseline				
Age, yr	52.8 ± 21.3	66.3 ± 17.2	59.7 ± 22.3	0.110
Female sex	18 (31)	10 (29)	25 (37)	0.606
Body mass index, kg/m ²	24.0 ± 3.7 (<i>N</i> = 56)	22.6 ± 4.3	23.7 ± 3.7	0.143
Current smoker	16 (27)	9 (26)	34 (50)	0.004
Comorbidities				
Diabetes mellitus	10 (17)	15 (44)	25 (37)	0.616
Hypertension	1 (0)	31 (91)	64 (94)	0.890
COPD	4 (7)	1 (3)	3 (4)	1.000
Cardiovascular disease	0 (0)	15 (47)	16 (24)	0.057
Cancer history	6 (10)	7 (21)	6 (9)	0.172
Symptom onset to admission, d	6.5 ± 3.1	5.6 ± 6.8	5.9 ± 4.1	0.785
Baseline medications				
RAS inhibitors	2 (3)	15 (44)	23 (34)	0.452
Immunosuppressive agent	0 (0)	3 (9)	2 (3)	0.205
Iron supplementation	0 (0)	5 (15)	0 (0)	0.003
Laboratory parameters at admission				
White blood cells, 10 ⁹ /l	5.0 (4.0–5.9)	4.6 (3.5–5.8)	5.3 (4.1–7.2)	0.088
Neutrophils, 10 ⁹ /l	2.9 (2.4–3.7)	3.0 (2.2–4.2)	3.3 (2.4–4.9)	0.348
Lymphocyte, 10 ⁹ /l	1.1 (0.8–1.6)	0.6 (0.3–1.0)	1.0 (7.2–1.3)	<0.001
Albumin, g/l	39 (37–43)	31 (28–34)	36 (32–41)	0.001
BUN, mg/dl	11.5 (9.1–13.8)	51.3 (39.9–67.4)	15.1 (11.7–25.0)	<0.001
Serum creatinine, mg/dl	0.80 (0.65–0.95)	9.90 (7.45–13.01)	0.84 (0.70–1.09)	<0.001
eGFR, ml/min per 1.73 m ²	80.0 (66.5–88.5)	N/A	63.8 (48.6–85.0)	N/A
C-reactive protein, mg/l	2.58 (0.59–5.01)	2.71 (1.10–5.28)	3.56 (0.96–7.30)	0.943
Ferritin, µg/l	296 (210–586)	279 (164–564) (<i>N</i> = 33)	347 (216–665)	0.074
D-dimer, mg/l	0.87 (0.65–1.14)	1.31 (0.90–2.35) (<i>N</i> = 33)	0.94 (0.75–1.98)	0.302
Adjuvant COVID-19 therapy				
Remdesivir	7 (12)	0 (0)	13 (19)	0.004
Steroid	18 (31)	21 (64)	34 (50)	0.261
Favipiravir	37 (63)	29 (85)	51 (75)	0.233
Clinical outcomes				
Severe disease	9 (15)	13 (38)	16 (24)	0.187
Death	0 (0)	6 (18)	7 (10)	0.350

Data are expressed as mean ± standard deviation (SD), median [interquartile range (IQR)], or as number [proportion (%)]

COPD chronic obstructive pulmonary disease, *RAS* renin–angiotensin–aldosterone system, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration ratio, *COVID-19* coronavirus disease 2019, *N/A* not applicable

^a*p* value for difference between non-HD and HD group in percent (Chi-square test), means (*t* test), or medians (Mann–Whitney *U* test)

patients, especially those with severe disease, suggesting that the delayed antibody response partly contributes to worse clinical outcomes in HD patients.

The percentage of patients who smoked in our study was significantly higher among the non-HD patients than among the HD patients. People who smoke have shown decreased production of IgG [12, 13], and therefore the antibody response to SARS-CoV-2 may be impaired in

smokers. In fact, a study in individuals who recovered from SARS-CoV-2 infection demonstrated that those who smoked had lower anti-SARS-CoV-2 IgG levels up to 4 months after diagnosis of COVID-19 [14]. However, it is currently unclear whether the antibody response within 1 month after COVID-19 onset is impaired in people who smoke. Therefore, we evaluated the differences in antibody responses between patients who smoked and those who did

Fig. 2 Kinetics of anti-SARS-CoV-2 antibodies in 34 HD patients and 68 non-HD patients. **a** Kinetics of anti-SARS-CoV-2 IgG-S1. **b** Kinetics of anti-SARS-CoV-2 IgG. Antibody levels were log₂-transformed. Blue lines represent the threshold value for positive. Comparisons of antibody titers in the same time period were performed using the Mann–Whitney *U* test. **p* < 0.05. Abbreviations: *HD* hemodialysis, *IgG-S* immunoglobulin G specific for the S1 subunit of the S protein, *IgG* immunoglobulin G that detected N and S proteins, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

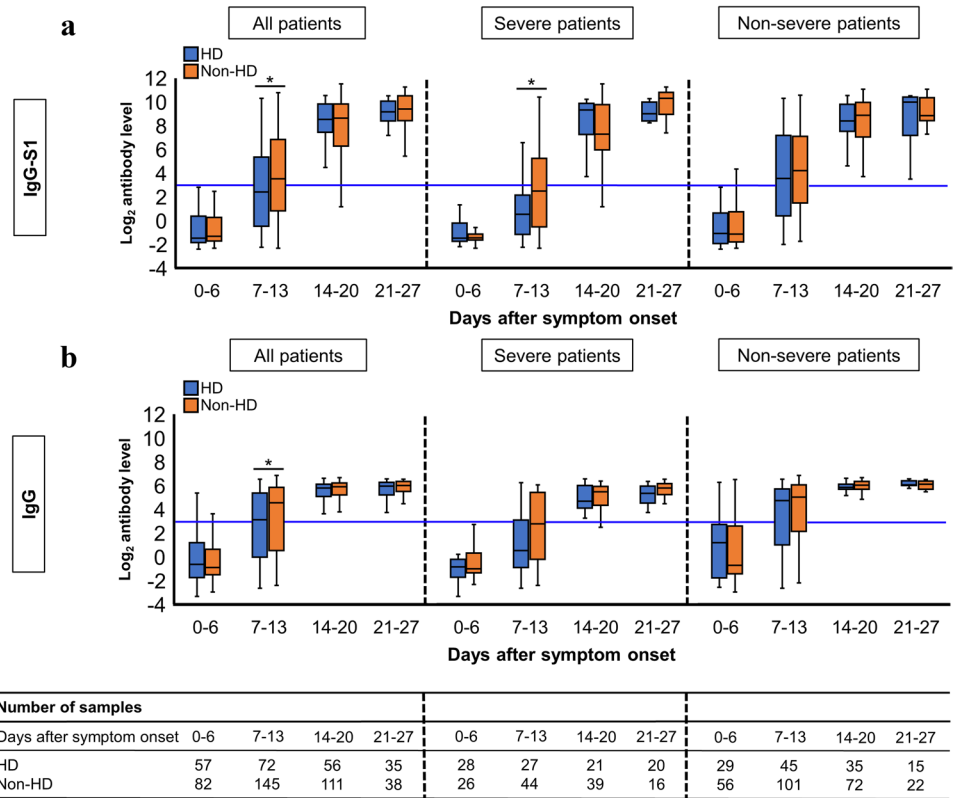
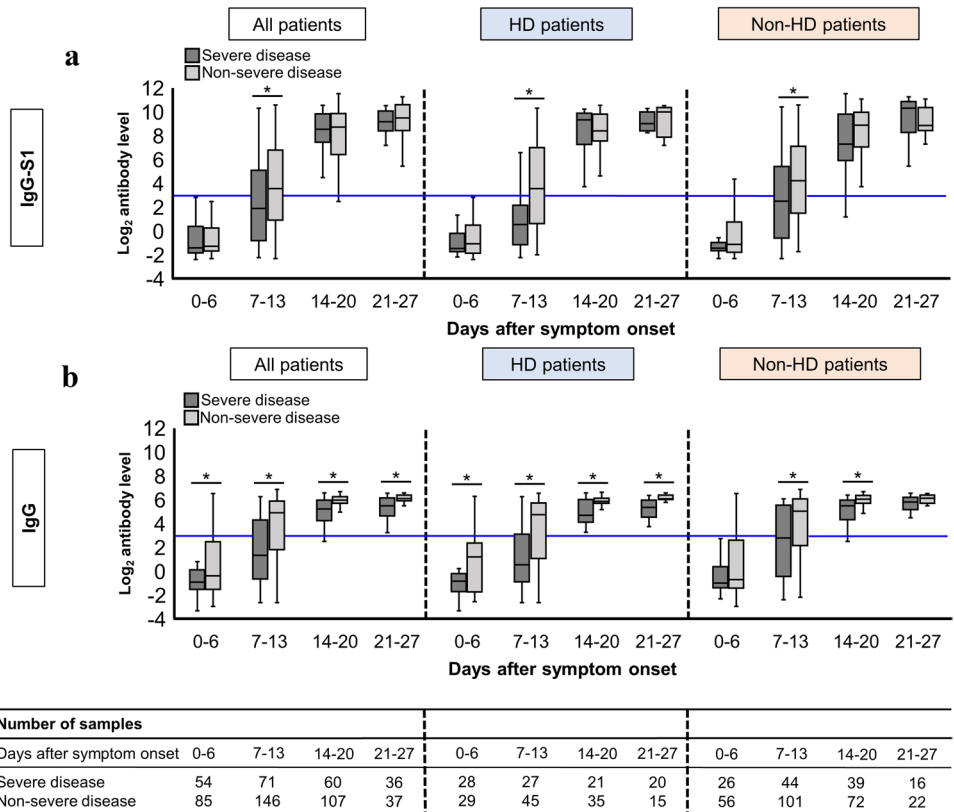


Fig. 3 Kinetics of anti-SARS-CoV-2 antibodies 29 severe patients and 73 non-severe patients. **a** Kinetics of anti-SARS-CoV-2 IgG-S1. **b** Kinetics of anti-SARS-CoV-2 IgG. Antibody levels were log₂-transformed. Blue lines represent the threshold value for positive. Comparisons of antibody titers in the same time period were performed using the Mann–Whitney *U* test. **p* < 0.05. Abbreviations: *HD* hemodialysis, *IgG-S* immunoglobulin G specific to the S1 subunit of the S protein, *IgG* immunoglobulin G that detected N and S proteins, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2



not smoke in both HD and non-HD patients, respectively. As expected, we noted that among the HD patients, IgG-S1 levels at 7–20 days were significantly lower in the smokers than in the nonsmokers (data not shown). However, we found no significant differences in either the IgG-N or IgG-S1 response among non-HD patients. Further studies are warranted to investigate whether smoking affects antibody responses to SARS-CoV-2.

Regarding laboratory parameters at admission, the lymphocyte counts in HD patients were significantly lower than that in non-HD patients on admission. A low lymphocyte count was reported as associated with severe COVID-19 [15]. Thus, reduced antibody production in the early stage of the illness in patients on HD could be associated with severe disease. A randomized clinical trial showed the efficacy of an anti-SARS-CoV-2 monoclonal antibody cocktail for reducing the viral load among outpatients with mild to moderate COVID-19 [16]. Therefore, timely antibody supplementation could decrease the risk of progression to severe disease in high-risk populations, such as HD patients.

Although iFlash–SARS-CoV-2 IgG kit used a combination of both N and S antigens, IgG levels measured by this kit were reported to be strongly correlated with the antibody levels against SARS-CoV-2 N protein [17]. The reason for this was speculated that the magnetic beads were predominantly coated with the N protein, with only a small proportion of S protein. Thus, we considered the iFlash–SARS-CoV-2 IgG kit to mainly detect anti-N IgG antibody and found that not only IgG-S1 but also anti-N IgG antibody might have been reduced in the second week in HD patients compared with non-HD patients. Although a correlation between anti-N IgG antibody levels and a poor clinical outcome has been reported [18], the clinical significance of IgG response to SARS-CoV-2 N protein, especially a delayed one, remains unelucidated.

Our study had several limitations. First, it was a single-centered design, and the sample size was small. Second, because of the wide variety of SARS-CoV-2 assays, our antibody tests for IgG-S1 might not have targeted the same spike protein domain as other studies. Third, we did not assess the neutralizing antibody response. Fourth, although we used propensity score matching, unmeasured confounding variables could have affected the differences in antibody response between HD and non-HD patients.

In conclusion, patients with severe COVID-19, especially those receiving maintenance HD, produced significantly lower IgG-S1 antibody levels than patients with the non-severe disease during the second week after symptom onset. A slow and partially reduced antibody response may explain the increased risk of severe COVID-19 among HD patients.

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Author contributions HB and TF researched data and wrote the manuscript. HB, TF, and HK performed the statistical analyses. FY and MK measured antibodies. HB, TF, TK, MT, FY, KO, SH, MK, and SW contributed to intellectual discussion and reviewed and edited the manuscript. YN, YN, KW, HO, AI, YK, TO, YA, ME, TH, RM, CS, and TY contributed to interpretation of the data. TF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and approved the final manuscript.

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Data availability and material All data were available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have declared that no conflict of interest exist.

Ethical approval This study was conducted in accordance with the principles of the Declaration of Helsinki and with the approval of the ethical committee of Okubo Hospital (No. 2020–11).

Informed consent Written informed consent was waived because of the retrospective design. We provided patients with the opportunity to opt out by displaying an outline of the analysis on the hospital Web site.


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