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ORIGINAL ARTICLE

COVID-19-associated pulmonary aspergillosis in hemodialysis patients

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ABSTRACT

Background. Coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis (CAPA) is a fatal complication in the general population. However, there are few reports on CAPA in patients undergoing hemodialysis (HD).
Methods. This retrospective observational cohort study was conducted at a single center between December 2020 and June 2021. We enrolled 21 HD patients with COVID-19 undergoing treatment and divided them into two groups, CAPA and non-CAPA (COVID-19 with and without pulmonary aspergillosis), and evaluated their characteristics, clinical outcomes and comorbidities.
Results. The log-rank test revealed that the 90-day survival rate after the initiation of treatment for COVID-19 was significantly lower in the CAPA ($n = 6$) than in the non-CAPA group ($n = 15$) ($P = 0.0002$), and the 90-day mortality rates were 66.6% and 0% in the CAPA and non-CAPA groups, respectively. In the CAPA group, four patients died due to respiratory failure (on Days 6 and 20), gastrointestinal bleeding (Day 8) and sepsis (Day 33); the reverse transcription-polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remained positive when they died. The remaining two patients survived and the negative conversion of RT-PCR for SARS-CoV-2 was confirmed on Days 10 and 15. The negative conversion of serum (1, 3)-β-D-glucan (BDG) was confirmed on Day 15 in one patient; the BDG remained positive on Day 64 in the other.
Conclusions. CAPA is a fatal complication in HD patients and the general population. Therefore, clinicians should consider the possibility of testing for CAPA in patients undergoing HD. Mycological workups may be helpful for the early detection of CAPA.

Keywords: COVID-19, end-stage kidney disease, hemodialysis, pulmonary aspergillosis, SARS-CoV-2

INTRODUCTION

The coronavirus disease that appeared in 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China and rapidly spread throughout the world [1]. Chronic kidney disease (CKD) is reported to be an independent factor affecting mortality and is associated with poor outcomes in patients diagnosed

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with COVID-19 [2]. Moreover, mortality due to COVID-19 is higher in dialysis than in non-dialysis patients [3]. Recently, reports of COVID-19 associated with pulmonary aspergillosis (CAPA) have been increasing in the general population [4, 5]. Therefore, it is possible that the number of dialysis patients with CAPA has also increased. However, few studies have reported on CAPA in patients undergoing hemodialysis (HD) [6–8].

Although the mechanism underlying the development of CAPA remains controversial, COVID-19 is suspected to cause lymphopenia, inflammatory cytokine responses and extensive damage to the respiratory epithelium, making affected patients prone to secondary infections [6, 9]. In addition, immunosuppressive therapies are considered one of the causes of secondary fungal infections [10]. Several studies have reported on CAPA in the general population; however, the factors adversely affecting outcomes and mortality have not been fully clarified [11–13]. We conducted a retrospective observational cohort study to compare patient characteristics, clinical outcomes and differences in complications between HD patients with and without CAPA (COVID-19 with and without pulmonary aspergillosis).

MATERIALS AND METHODS

Study population

The present study was a retrospective observational cohort study conducted at Tsuchiya General Hospital between 1 December 2020 and 30 June 2021. We enrolled 21 HD patients who were diagnosed with COVID-19 in the study and treated them in a dialysis intensive care unit (ICU), which was treated as a quarantine ward where depressurized rooms with high-efficiency particulate air filters were included. Of the 21 patients, three (14.3%) were transferred from other hospitals due to exacerbation of their symptoms and nine (42.9%) were treated in an inpatient setting. The present study was performed in accordance with the principles of the declaration of Helsinki and approved by the Tsuchiya General Hospital Institutional Review Board for Human Investigation (approval number: E210719-6). The requirement for written informed consent was waived because of the retrospective observational nature of the study and the strict maintenance of patient anonymity.

Measurements and definitions of the severity of COVID-19

The following clinical baseline [admission or transfer to the ICU due to positive reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2] data were recorded: age, sex, dialysis vintage, primary cause of end-stage kidney disease (ESKD), history of smoking, previous history, body mass index (BMI), comorbidities, immunosuppressive conditions, history of cancer, Charlson Comorbidity Index (CCI) and laboratory parameters. Chest computed tomography (CT) was performed to evaluate the severity of COVID-19 and the extent of pneumonia. The severity of COVID-19 symptoms at diagnosis was defined as follows: mild [non-pneumonia or mild pneumonia: the presence of clinical or radiographic evidence of lower respiratory tract disease, oxygen saturation (SpO_2) $\geq$96% (breathing ambient air)]; moderate (93% $<$ SpO_2 $<$ 96%); severe [marked tachypnea (respiratory rate, $\geq$30 breaths per minute), hypoxemia (SpO_2 $\leq$ 93%)]; and critical (respiratory failure, need for invasive mechanical ventilation) [14].

Mycological workups and definitions of CAPA

The serum (1, 3)-β-D-glucan (BDG) concentration was measured at the initiation of treatment for COVID-19 patients. The BDG was detected using the β-glucan test (Wako Pure Chemical Industries, Osaka, Japan) according to the manufacturer's instructions. We considered the results of the BDG test positive when the serum BDG was 11.1 pg/mL or higher. Thereafter, the BDG was monitored based on the discretion of the attending physicians. If the BDG result was positive, we retrospectively performed a serum galactomannan (GM) test with stored serum using an enzyme-linked immunosorbent assay (GM-ELISA) (BioRad, Hemel Hempstead, UK) according to the manufacturer's instructions. In our hospital, a bronchoscopy was not performed because of the restricted uses and aerosol-generating nature of the procedure. We used the following criteria to define probable invasive pulmonary aspergillosis (IPA) in HD patients with COVID-19: (i) entry criteria, positive RT-PCR for SARS-CoV-2; (ii) clinical and radiological criteria, pulmonary infiltrates; and (iii) mycological criteria, serum GM index $>$0.5; we then performed diagnosis of CAPA in the enrolled patients according to the above-mentioned criteria [15].

Pharmacological treatment and renal replacement therapy for COVID-19 and/or pulmonary aspergillosis

Pharmacological treatment for COVID-19 was performed according to the severity of symptoms as follows. (i) Antiviral agents (mild: favipiravir; moderate, severe and critical: remdesivir). The indication for remdesivir was expanded to include moderate patients on 18 January 2021, in Japan. Therefore, only two mild and one moderate patient received favipiravir before 18 January 2021. (ii) Dexamethasone [mild, oral (Days 1–5: 6 mg; Days 6–7: 4 mg; Days 8–9: 2 mg); moderate, severe and critical, intravenous (Days 1–7: 6.6 mg; Days 8–9: 4.95 mg; Days 10–11: 3.3 mg; Days 12–15: 1.65 mg)]. (iii) Antibiotics: mild, oral azithromycin (AZM) or oral garenoxacin (GRNX); moderate, oral AZM or oral levofloxacin (LVFX) and tazobactam-piperacillin (TAZ-PIPC), meropenem (MEPM) or vancomycin (VCM); severe and critical, intravenous AZM and TAZ-PIPC, MEPM or VCM. (iv) Antithrombotic agents. (v) Intravenous immunoglobulin (IVIG, moderate, severe and critical, Days 1–3: 5 g).

Antifungal agents were administered at the discretion of the attending physician as follows: micafungin (MCFG), voriconazole (VRCZ), amphotericin B (AMPH-B) or itraconazole (ITCZ), and they were continued until negative BDG results were confirmed.

Renal replacement therapy (RRT) for COVID-19 was performed according to the severity of pulmonary congestion as follows: HD (three times per week), frequent HD (six times per week), or continuous renal replacement therapy (CRRT) and polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) [16]. HD was performed for 4 h with a polymethyl methacrylate membrane, blood flow rate of 100–300 mL/min, nafamostat mesylate at 30 mg/h for anticoagulation and dialysate flow rate of 500 mL/min. CRRT was performed for 72–96 h with an acrylonitrile-co-methallyl sulfonate surface-treated (AN69ST) membrane, blood flow rate of 100 mL/min, heparin sodium of 100 units/h, nafamostat mesylate at 30 mg/h for anticoagulation and dialysate flow rate of 500–1000 mL/h. PMX-DHP was performed for 3–6 h with a blood flow rate of 100 mL/min and nafamostat mesylate at 40 mg/h for anticoagulation. During CRRT, nafamostat mesilate (250 mg/day) and heparin sodium (5000 units/day) were continued in addition to

administering heparin sodium (100 units/h) and nafamostat mesylate (30 mg/h) for anticoagulation.

Oxygen inhalation and respiratory treatment

Moderately and severely affected patients received oxygen inhalation, while percutaneous oxygen saturation was monitored in real-time. Critically affected patients received oxygen inhalation, orotracheal intubation with a virus removal filter and invasive mechanical ventilation with a pressure-regulated, volume-controlled mode under deep sedation [Richmond Agitation-Sedation Scale (RASS): score −4] [17] while undergoing real-time monitoring for percutaneous oxygen saturation and end-tidal carbon dioxide in the ICU. When a patient could not be withdrawn from mechanical ventilation 2 weeks after initiation, a tracheostomy was performed.

Outcomes

The primary outcome was defined as 90-day survival after the initiation of treatment for COVID-19 in our hospital. The secondary outcome was the length of stay in the ICU. Moreover, among the patients with CAPA, the patient characteristics, antifungal agents used, complications, causes of death and period from the initiation of treatment for COVID-19 to the beginning of the administration of antifungal agents were examined. The enrolled patients were followed-up until the study's endpoint was reached, which could include death and the analysis period ended on 30 September 2021.

Statistical analysis

The data were analyzed using JMP® 14.2.0 (SAS Institute Inc., Cary, NC, USA) and were expressed as either the number of participants or the percentage of the study population. The remaining data are expressed as the mean ± standard deviation (SD) or median (range). The Student's *t*-test and Mann–Whitney U test were used for the continuous variables, and the Chi-squared test was used for the categorical variables. The Kaplan–Meier method and log-rank test were used to evaluate the survival curve after the initiation of treatment for COVID-19 in our hospital. In all analyses, *P*-values <0.05 were considered statistically significant.

RESULTS

Patient characteristics

Twenty-one HD patients with COVID-19 were treated in our hospital during the study period and all the participants were enrolled. We divided the HD patients with COVID-19 into two groups according to the above-mentioned definition: patients with probable IPA (CAPA group, $n = 6$) and patients without probable IPA (non-CAPA group, $n = 15$). The baseline characteristics of the patients in both groups are shown in Table 1. The BMI ($P = 0.03$) and serum albumin level ($P = 0.03$) were lower, whereas the proportion of ischemic heart disease (IHD) ($P = 0.01$) and mean baseline BDG level ($P < 0.001$) were higher in the CAPA than in the non-CAPA group. The proportion of patients with mild COVID-19 was lower in the CAPA group ($P = 0.03$).

Pharmacological treatment and RRT for COVID-19

All 21 patients received antiviral agents (18 patients received remdesivir in the CAPA and non-CAPA groups; three patients received favipiravir in the non-CAPA group), antibiotics and antithrombotic agents. Twenty patients received dexamethasone in the CAPA and non-CAPA groups, except for one mildly affected patient in the non-CAPA group. There were no significant differences in the dosage per day, total dosage or duration of dexamethasone between the two groups. IVIG was administered more frequently in the CAPA ($n = 6$, 100%) than in the non-CAPA group ($n = 6$, 40%; $P = 0.02$). Two critically ill patients

Table 1. Characteristics at the initiation of treatment in hemodialysis patients with COVID-19 CAPA versus non-CAPA groups

Variables	CAPA	Non-CAPA	P-value
Number	6	15	
Age, years	68 (61–89)	74 (47–91)	0.6
Male, *n* (%)	4 (67)	8 (53)	0.7
Dialysis vintage, years	11.7 (4.1–36.5)	3.8 (0.1–33.0)	0.1
Body mass index, kg/m^2	19.2 (16.2–22.6)	22.6 (18.3–27.2)	0.03
Primary cause of ESKD			
DKD, *n* (%)	3 (50)	9 (60)	0.7
CGN, *n* (%)	3 (50)	1 (7)	0.02
Hypertension, *n* (%)	0 (0)	4 (26)	0.2
NS, *n* (%)	0 (0)	1 (7)	0.5
Major comorbidity			
PVD, *n* (%)	5 (83)	8 (53)	0.3
CHF, *n* (%)	5 (83)	9 (60)	0.6
IHD, *n* (%)	5 (83)	3 (20)	0.01
CBVD, *n* (%)	3 (50)	4 (27)	0.4
COPD, *n* (%)	0 (0)	2 (13)	1.0
History of smoking, *n* (%)	3 (50)	5 (33)	0.6
History of cancer, *n* (%)	0 (0)	1 (7)	1.0
CCI	8 (5–10)	6 (4–9)	0.4
RT-PCR (Ct)[a]	24 (17–32)	22 (18–37)[b]	1.00
Severity of COVID-19, *n* (%)			
Mild	0 (0)	6 (40)	0.03
Moderate	4 (67)	4 (27)	0.09
Severe	2 (33)	3 (20)	0.5
Critical	0 (0)	2 (13)	0.2
Laboratory parameters			
WBC count/μL	5887 ± 2773	5845 ± 2879	0.98
Neutrophil count/μL	4888 ± 2481	4373 ± 2555	0.7
Lymphocyte count/μL	573 ± 114	831 ± 530	0.3
Platelet count, $\times 10^4$/μL	11.4 ± 7.5	13.8 ± 4.1	0.4
Hemoglobin, g/dL	10.9 ± 1.6	11.9 ± 2.4	0.4
Albumin, g/dL	2.3 ± 0.4	2.8 ± 0.5	0.03
CRP, mg/dL	8.9 (2.8–25.8)	4.6 (0.5–24.9)	0.2
Procalcitonin, ng/mL	0.7 (0.4–6.2)	0.6 (0.1–4.0)[c]	0.3
Ferritin, ng/mL	218 (64–7189)	239 (34–1797)[c]	0.8
LDH, U/L	244 (160–1443)	242 (165–728)	0.9
D-dimer, mg/L	1.8 (1.2–7.4)	2.2 (0.2–59)	0.9
BDG, pg/mL	26.4 (13.6–155.8)	4.7 (3.7–9.4)[c]	< 0.001

Note: The categorical variables are represented as numbers (percentages) and statistically analyzed using the Chi-squared test. The data with a normal distribution are expressed as the mean ± standard deviation and were statistically analyzed using a *t*-test. The data with a non-normal distribution are expressed as the median (range) and statistically analyzed using the Mann–Whitney U test.[a] The cycle threshold (Ct) values were identified by RT-PCR for SARS-CoV-2 upon diagnosis with COVID-19. Data are missing for 4[b] patients and 2[c] patients. BDG, (1, 3)-β-D-glucan; CAPA, COVID-19-associated pulmonary aspergillosis; COVID-19, coronavirus disease 2019; CCI, Charlson comorbidity index; CGN, chronic glomerulonephritis; CHF, chronic heart failure; Ct, cycle threshold; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CBVD, cerebrovascular disease; DKD, diabetic kidney disease; ESKD, end-stage kidney disease; GM, galactomannan; IHD, ischemic heart disease; LDH, lactate dehydrogenase; NS, nephrotic syndrome; RT-PCR, reverse transcription-polymerase chain reaction; PVD, peripheral vascular disease; WBC, white blood cell.

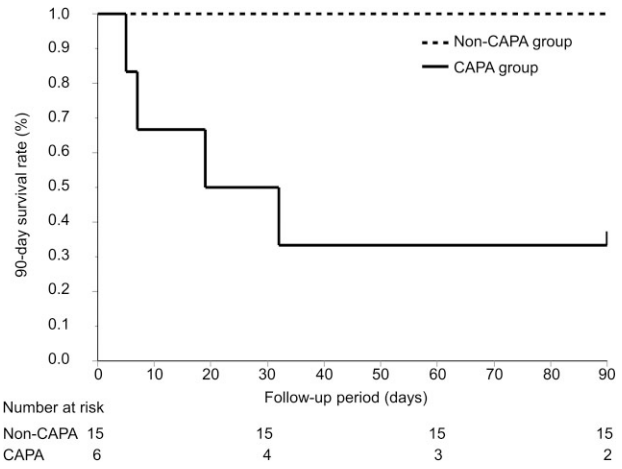

FIGURE 1: The 90-day survival rate after initiation of treatment in hemodialysis patients with COVID-19 (CAPA versus non-CAPA groups). The 90-day survival rate using the Kaplan–Meier method and comparative results of the log-rank tests are shown. CAPA, COVID-19-associated pulmonary aspergillosis.

in the non-CAPA group received CRRT with AN69ST membrane and PMX-DHP (Supplementary data, Table S1).

Clinical outcome

The 90-day survival rate after the initiation of treatment for COVID-19 was significantly lower in the CAPA than in the non-CAPA group ($P = 0.0002$, Figure 1) (90-day mortality rates, 66.6% versus 0%). The complications experienced after the initiation of treatment for COVID-19 are shown in the Supplementary data, Table S2.

Laboratory parameters, pharmacological treatment and clinical outcomes for aspergillosis in the CAPA group

The summarized baseline characteristics of the six patients in the CAPA group are shown in Table 2. Two patients had severe symptoms and four patients had moderate COVID-19. All the patients received antiviral treatment with remdesivir. The serum baseline BDG levels ranged from 13.6 to 29.6 pg/mL. In the CAPA group, four patients died due to respiratory failure (on Days 6 and 20), gastrointestinal bleeding (on Day 8) or sepsis (on Day 33); the RT-PCR for SARS-CoV-2 remained positive when they died. The remaining two patients survived and negative conversion of RT-PCR for SARS-CoV-2 was confirmed on Days 10 and 15. Negative conversion of the serum BDG was confirmed on Day 15 in one patient and the BDG remained positive on Day 64 in the other patient.

In four patients, the administration of antifungal medication with MCFG was initiated on Day 1 (initiation of treatment for COVID-19) for fungal infection; subsequently, the serum GM was later found to be positive and the antifungal medication was continued.

In one patient with a high level of BDG (29.6 pg/mL), antifungal agents were not administered at the initiation of treatment for COVID-19 because the elevation of the serum BDG level was initially considered a false positive after IVIG administration. On Day 6, chest radiography revealed new pneumonia findings and the serum level of BDG was highly elevated (6321 pg/mL). We began administering MCFG as an antifungal treatment. However, a CT examination revealed multiple new nodules and consoli-

Table 2. Summarized baseline characteristics, laboratory parameters, pharmacological treatments, and clinical outcomes in hemodialysis patients with CAPA

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, years	89	73	62	77	61	73
Sex	Female	Male	Male	Female	Male	Male
HD vintage, years	4.4	4.1	19.1	36.5	23.4	4.2
Diabetes mellitus	Yes	Yes	No	No	No	Yes
Charlson Comorbidity Index	10	8	6	5	8	8
Severity of COVID-19	Severe	Severe	Moderate	Moderate	Moderate	Moderate
RT-PCR at diagnosis, (Ct)	17	22	31	24.95	21.48	32
RT-PCR at last point, (Ct)	None	30 (Day 16)	None	34 (Day 23)	Negative (Day 9)	Negative (Day 14)
Coinfections	No	No	No	Yes[b]	No	No
Mycological examinations						
BDG, pg/mL	16.5[a]	29.6	25.7	25.7	23.2	13.6
Serum GM, cut-off index	1.3[a]	5.0	1.4	0.6	0.6	1.3
Pharmacological treatment						
Antiviral agents	Remdesivir	Remdesivir	Remdesivir	Remdesivir	Remdesivir	Remdesivir
Dexamethasone						
Total dosage, mg	33	53.7	46.2	89.6	74.1	58.2
Duration, days	5	10	7	26	22	15
Antifungal medication	No	Yes	Yes	Yes	Yes	Yes
Type of antifungal agents	–	MCFG, VRCZ, AMPH-B	MCFG	MCFG	MCFG	MCFG, ITCZ
Start date	–	6th day	1st day	1st day	1st day	1st day
Length of stay in the ICU in days	6	20	8	33	12	17
Period of survival at the end-point in days	6	20	8	33	116	121
90-day survival	Dead	Dead	Dead	Dead	Alive	Alive
Major cause of death	RF	RF	GI	Sepsis	–	–

Note: [a]The patient was diagnosed with CAPA after death. [b]The patient had pyogenic spondylitis. AMPH-B, amphotericin B; BDG, (1, 3)-β-D-glucan; CAPA, COVID-19-associated pulmonary aspergillosis; COVID-19, coronavirus disease 2019; Ct, cycle threshold; GI, gastrointestinal bleeding; GM, galactomannan; HD, hemodialysis; ICU, dialysis intensive care unit; ITCZ, itraconazole; MCFG, micafungin; RF, respiratory failure; RT-PCR, reverse transcription-polymerase chain reaction; VRCZ, voriconazole.

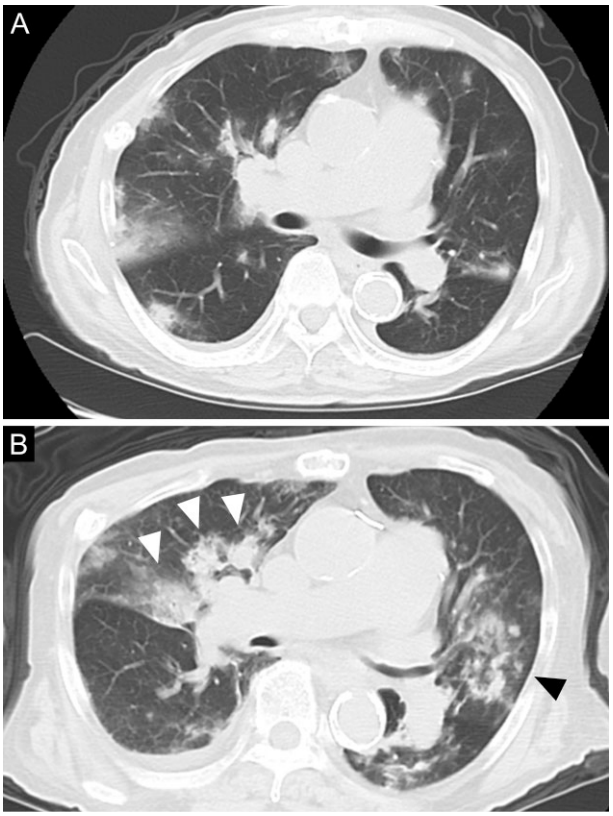

FIGURE 2: Computed tomographic (CT) image of COVID-19-associated pulmonary aspergillosis (CAPA). **(A)** CT examination revealed ground glass opacities with predominant peripheral distribution in a 73-year-old man (Patient 2 in Table 2) upon diagnosis with COVID-19 (Day 1). **(B)** CT examination revealed new nodular shadows (white arrows) and consolidation (black arrow) in the bilateral lobes in the same patient upon diagnosis with CAPA (Day 9).

dation (Figure 2) and we changed the antifungal treatment to a combination therapy of VRCZ and AMPH-B on Day 10. On Day 14, the serum GM test result was positive and the patient was diagnosed with CAPA. On Day 16, the RT-PCR results for SARS-CoV-2 remained positive (Ct value = 30). Respiratory function subsequently deteriorated and the patient died on Day 20.

The remaining patient died of respiratory failure on Day 6. Because of the rapid course of events after the initiation of COVID-19 treatment, the serum GM and stored serum were measured and she was diagnosed with CAPA after death.

DISCUSSION

In this study, we evaluated CAPA in patients undergoing HD. We investigated the prevalence and clinical outcomes of CAPA in patients undergoing HD. The log-rank test revealed that the 90-day survival rate after the initiation of treatment for COVID-19 was significantly lower in the CAPA than in the non-CAPA group and the 90-day mortality rates were 66.6% and 0% in the CAPA and non-CAPA groups, respectively.

Mortality due to infectious diseases is the second leading cause of death [18]. Respiratory virus infection is believed to prompt the development of IPA by causing direct damage to the airway epithelium [19]. Therefore, HD patients may be susceptible to aspergillosis after ICU administration because ESKD patients have immunocompromised host factors. In the general population, the prevalence of CAPA was reported to range from 0 to 33% [5, 10]. Recently, a nationwide questionnaire-based study from the Japanese Respiratory Society showed that the prevalence of CAPA was 0.54% (9/1664 patients) and the authors concluded that the low prevalence of CAPA in Japan might be due to the following reasons: (i) the low incidence of COVID-19 in Japan; (ii) the fact that CAPA was not diagnosed according to specific criteria; and (iii) the fact that a routine mycological workup was not performed [19]. We found that the prevalence of CAPA was 28.6% (6/21 patients), which is much higher than in a Japanese study and relatively high compared to the figure reported in previous studies from other countries [5, 10, 19]. Although the true prevalence of CAPA in HD patients remains controversial, clinicians should consider the possibility of testing for CAPA in the treatment of COVID-19 in HD patients.

In the general population, the overall mortality rate of CAPA is reported to be approximately 50.0% [10, 11] and the mortality rate of patients with CAPA is reported to be higher than that of patients without it [5, 11]. In HD patients, the overall mortality rate of COVID-19 is reported to be approximately 25.0% [20]. The mortality rate of CAPA in HD patients is 66.7%, which is higher than in the general population [10, 11]. Furthermore, the 90-day survival rate after the initiation of treatment for COVID-19 was lower in the CAPA than in the non-CAPA group ($P = 0.0002$). The trend was similar to that of the general population [5, 11]. However, further studies are required to confirm these findings.

Several studies have reported the following CAPA risk factors in the general population: age, low serum albumin level, high frailty, chronic obstructive pulmonary disease, diabetes mellitus, the need for invasive mechanical ventilation (severity of COVID-19) and immunosuppressive treatment, including steroids and azithromycin [12, 13, 21]. In the present study, BMI ($P = 0.03$), serum albumin level ($P = 0.03$) and the proportion of patients with mild COVID-19 symptoms ($P = 0.03$) were lower in the CAPA group. These findings suggest that malnutrition may be associated with CAPA in HD patients as well as in the general population. Although the proportion of IHD was higher in the CAPA group, no previous reports have evaluated the association between CAPA and IHD. Moreover, we could not demonstrate any association between dexamethasone and CAPA because we used dexamethasone in most HD patients with COVID-19. However, dexamethasone may remain harmful in HD patients because it is a long-acting glucocorticoid that leads to infection, gastrointestinal bleeding, hyperglycemia and venous thromboembolism [22]. In the present study, gastrointestinal bleeding was observed in two patients and one of the two patients died due to gastrointestinal bleeding. Therefore, clinicians may need to modify the type and amount of steroids used [23].

In the present study, the mean baseline BDG level was significantly higher in the CAPA than in the non-CAPA group, suggesting that the baseline BDG level is a useful pan-fungal marker for screening at the initiation of COVID-19 treatment [24]. Although the insensitivity of serum biomarkers remains a clinical concern, the combination of serum BDG and GM may be useful for the diagnosis of CAPA in HD patients.

Although triazoles are the most frequently administered treatment for CAPA [8], the therapeutic strategy for it has not yet been fully established [10]. In an observational study evaluating whether antifungal prophylaxis prevents CAPA in critically ill patients, 57% of patients received antifungal prophylaxis within the first 48 h after ICU admission [25] and a significant reduction was observed in the incidence of CAPA in patients who received antifungal prophylaxis. However, the administration of intravenous VRCZ is not approved for HD patients because it carries the risk of the accumulation of sulfobutylether

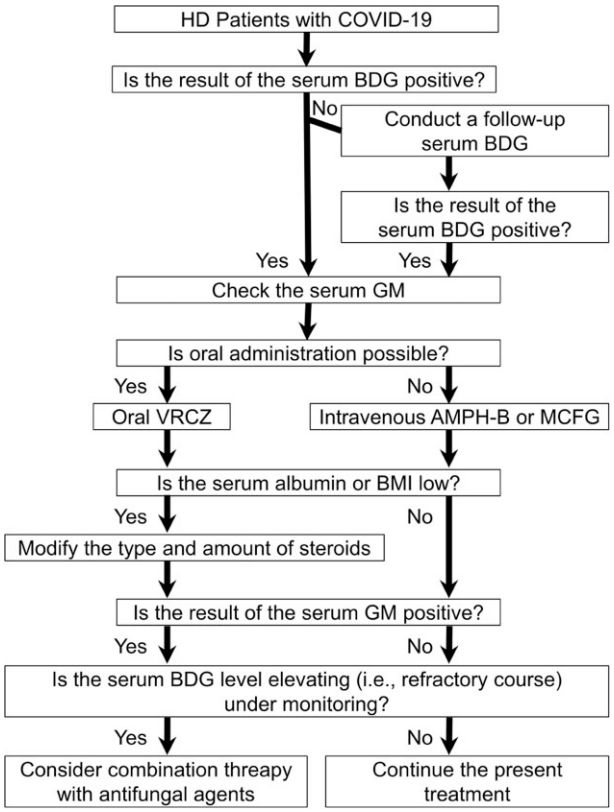

FIGURE 3: The strategy of mycological workups and treatment in hemodialysis patients with CAPA. AMPH-B, amphotericin B; BDG, (1, 3)-β-D-glucan; BMI, body mass index; CAPA, COVID-19-associated pulmonary aspergillosis; COVID-19, coronavirus disease 2019; GM, galactomannan; HD, hemodialysis; MCFG, micafungin; VRCZ, voriconazole. care unit; Max, maximum.

beta-cyclodextrin sodium [26] and an oral suspension of VRCZ is not approved. Moreover, peak plasma concentrations of oral VRCZ close to a steady state are achieved 5–7 days after multiple oral administration [27]. Taken together, we recommend that oral VRCZ should be initiated as a first-line antifungal agent in HD patients when serum BDG is positive and the patients can take it internally. We recommend the administration of intravenous AMPH-B or MCFG in cases in which HD patients are unable to take medication and it is difficult to use VRCZ owing to drug–drug interactions. When GM is confirmed, the serum BDG should be monitored and the combination of antifungal agents can be effective in patients with elevated serum BDG levels (i.e. refractory course) (Figure 3).

The present study has several limitations. First, this was a retrospective study conducted at a single center, so the sample size was small. Therefore, the small number of subjects caused the data to lack sufficient power for accurate multivariate testing for the assessment of the risk factors of CAPA and the efficacy of antifungal agents. Second, the true incidence of CAPA was uncertain because we did not perform a necropsy. Such procedures are invasive and arouse fears surrounding aerosol generation. The proposed case definition that we used to define probable IPA in HD patients with COVID-19 can improve the early diagnosis of CAPA and help practitioners avoid underestimating the frequency of CAPA. Despite these limitations, few previous studies have reported CAPA in HD patients [6–8]. Therefore, the present study is valuable in relation to the existing information in the field.

CONCLUSIONS

CAPA is a fatal complication in HD patients and the general population. A mycological workup conducted at the initiation of COVID-19 treatment is effective for the diagnosis of CAPA and early detection may contribute to improving a patient's prognosis. Our findings can guide clinical management practices for CAPA in HD patients.

DATA AVAILABILITY STATEMENT

The data and materials used are available upon request.

SUPPLEMENTARY DATA

The supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

M.Y. and M.B. performed the statistical analyses and took responsibility for the content of the manuscript. M.Y., M.B. and H.K. contributed substantially to the study's design. M.Y., M.B., S.M., H.T., S.H., N.S. and S.S. collected the data. M.Y., M.B. and H.K. contributed significantly to writing the manuscript. M.Y., M.B., S.M., K.T., A.K., H.T., S.H., N.S., S.S., M.M., S.T., T.M. and H.K. provided intellectual content of critical importance to the work described. All the authors followed the patients and approved the final manuscript.

CONFLICT OF INTEREST STATEMET

None to declare.

REFERENCES

1. Zhu N, Zhang D, Wang W *et al*. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382: 727–733
2. Chung EYM, Palmer SC, Natale P *et al*. Incidence and outcomes of COVID-19 in people with CKD: a systematic review and Meta-analysis. *Am J Kidney Dis* 2021; 78(6): 804–815
3. Hilbrands LB, Duivenvoorden R, Vart P *et al*. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant* 2020; 35: 1973–1983
4. Chong WH, Neu KP. Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. *J Hosp Infect* 2021; 113: 115–129
5. Yusuf E, Seghers L, Hoek RAS *et al*. Aspergillus in critically ill COVID-19 patients: a scoping review. *J Clin Med* 2021; 10: 2469
6. Bartoletti M, Pascale R, Cricca M *et al*. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. *Clin Infect Dis* 2020; 71: 899–901
7. Xu J, Yang X, Lv Z *et al*. Risk factors for invasive aspergillosis in patients admitted to the intensive care unit with Coronavirus disease 2019: a multicenter retrospective study. *Front Med (Lausanne)* 2021; 8: 753659

8. Salmanton-Garcia J, Sprute R, Stemler J *et al*. COVID-19-associated pulmonary aspergillosis, March–August 2020. *Emerg Infect Dis* 2021; 27: 1077–1086
9. Roudbary M, Kumar S, Kumar A *et al*. Overview on the prevalence of fungal infections, immune response, and microbiome role in COVID-19 patients. *J Fungi (Basel)* 2021; 7: 720
10. Verweij PE, Bruggemann RJM, Azoulay E *et al*. Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis. *Intensive Care Med* 2021; 47: 819–834
11. Singh S, Verma N, Kanaujia R *et al*. Mortality in critically ill patients with Coronavirus disease 2019-associated pulmonary aspergillosis: a systematic review and meta-analysis. *Mycoses* 2021; 64: 1015–1027
12. Prattes J, Wauters J, Giacobbe DR *et al*. Risk factors and outcome of pulmonary aspergillosis in critically ill Coronavirus disease 2019 patients—a multinational observational study by the European Confederation of Medical Mycology. *Clin Microbiol Infect* 2021; S1198-743X(21): 00474–2
13. Delliere S, Dudoignon E, Fodil S *et al*. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. *Clin Microbiol Infect* 2020; 27(5): 790.e1–790.e5
14. Wu Z, McGoogan JM Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323: 1239–1242
15. Verweij PE, Rijnders BJA, Bruggemann RJM *et al*. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. *Intensive Care Med* 2020; 46: 1524–1535
16. Cruz DN, Perazella MA, Bellomo R *et al*. Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. *Crit Care* 2007; 11: R47
17. Sessler CN, Gosnell MS, Grap MJ *et al*. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; 166: 1338–1344
18. Hanafusa N, Nakai S, Iseki K *et al*. Japanese society for dialysis therapy renal data registry—a window through which we can view the details of Japanese dialysis population. *Kidney Int Suppl (2011)* 2015; 5: 15–22
19. Takazono T, Mukae H, Izumikawa K *et al*. COVID-19 associated pulmonary aspergillosis: a nationwide survey by the Japanese Respiratory Society. *ERJ Open Res* 2021; 7(4): 00402–2021
20. Jager KJ, Kramer A, Chesnaye NC *et al*. Results from the ERA-EDTA registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. *Kidney Int* 2020; 98: 1540–1548
21. Chauvet P, Mallat J, Arumadura C *et al*. Risk factors for invasive pulmonary aspergillosis in critically ill patients with Coronavirus disease 2019-induced acute respiratory distress syndrome. *Crit Care Explor* 2020; 2(11): e0244
22. Fardet L, Kassar A, Cabane J *et al*. Corticosteroid-induced adverse events in adults: frequency, screening and prevention. *Drug Saf* 2007; 30: 861–881
23. Pinzon MA, Ortiz S, Holguin H *et al*. Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia. *PLoS One* 2021; 16(5): e0252057
24. Alanio A, Delliere S, Fodil S *et al*. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *Lancet Respir Med* 2020; 8(6): e48–e49
25. Hatzl S, Reisinger AC, Posch F *et al*. Antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients: an observational study. *Crit Care* 2021; 25: 335
26. von Mach MA, Burhenne J, Weilemann LS. Accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium in critically ill patients treated with intravenous voriconazole under renal replacement therapy. *BMC Clin Pharmacol* 2006; 6: 6
27. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/Pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; 45: 649–663