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REVIEW

Therapeutic Apheresis and Dialysis

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Novel coronavirus disease in patients with end-stage kidney disease

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Abstract

The novel coronavirus disease outbreak started in Wuhan, China, in December 2019 and has since spread rapidly worldwide. As almost all patients with end-stage kidney disease have been treated with HD in Japan, they have a higher risk of infection than the healthy population. Moreover, the complications of renal failure, such as hypertension and cardiovascular diseases, appear to be a risk factor of death owing to novel coronavirus disease. The reported morbidity and mortality rates of novel coronavirus disease are significantly higher in dialysis patients than in the healthy population. No treatment for novel coronavirus disease has yet been developed; thus, countermeasures to prevent the spread of coronavirus disease in dialysis facilities must be rapidly established. The latest findings on novel coronavirus disease in patients with end-stage kidney disease and the guidelines for countermeasures against the spread of novel coronavirus disease worldwide are summarized in this review.

KEYWORDS

COVID-19, infection control, kidney failure, renal dialysis

1 | INTRODUCTION

As of October 5, 2020, the number of people who had been infected with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first emerged in Wuhan, China, in December 2019 as the etiological agent of novel coronavirus disease (COVID-19), had rapidly increased. More than 34.5 million people had already been infected, and >1.02 million patients died worldwide.[1] The fatality rate of the SARS-CoV-2 infection is estimated to be 2.9%,[1] and the incidence of COVD-19 has been recognized as a serious pandemic. SARS-CoV-2 belongs to the same β-CoVs as the SARS virus (SARS-CoV-1) and MERS virus (MERS-CoV) which broke out in 2003 and 2015, respectively.[2] As SARS-CoV-2 has 96.2% homology to a bat coronavirus, it has been thought to be derived from bats.[3] It enters cells via the angiotensin-converting enzyme 2 (ACE2), which is expressed on cell surfaces and serves as a receptor of the virus in humans.[4] ACE2 converts angiotensin 2 into angiotensin 1-7 and is highly expressed in the small intestine, testis, kidney, heart, thyroid, and adipose tissue.[5] Recently, high ACE2 expression level was also found in oral epithelial cells, especially in the tongue.[6] Previous studies suggested that continuous administration of ACE inhibitors (ACEIs) and angiotensin 2 receptor blockers (ARBs) could

increase the ACE2 expression level in rodents.[7] As ACEIs and ARBs have often been used in patients with ESRF, the increased risk of SARS-CoV-2 infection among these patients is concerning. Herein, we review the characteristics of and countermeasures against SARS-CoV-2 infection in dialysis patients.

2 | MORTALITY OF COVID-19 IN THE GENERAL POPULATION

Although approximately 80% of patients with SARS-CoV-2 infection have no or mild symptoms, the remaining 20% of patients develop severe pneumonia, of whom 25% die of multiple-organ failure due to respiratory failure or thrombosis. In agreement with this report, in Japan, the mortality rate of SARS-CoV-2-positive patients examined using polymerase chain reaction (PCR) was estimated to be 1.88% as of October 3, 2020.[1] However, the actual mortality rate cannot be estimated because a certain number of people with the infection have not been examined using PCR.

Price-Haywood et al reported the number of deaths due to COVID-19 from March 1, 2020, to April 11, 2020, in Louisiana, USA. According to this report, 326 of 3481 patients died, with a mortality rate of 9.4%. Moreover, black patients accounted for 70.6% of deaths. Goyal et al proposed that therapeutic intervention in the early phase can lower the mortality of COVID-19.[9] Thus, the medical insurance system in Japan, which enables people to consult a physician at a low cost, seems to be important to prevent the spread of COVID-19 and lower mortality. Faust et al stated that the current mortality of COVID-19 might have been overestimated, as it included SARS-CoV-2-positive patients who died of causes other than COVID-19, in addition to those who died of COVID-19 as the direct cause.[10] They estimated that the pandemic on the cruise ship "Diamond Princess" (1.8%) accounted for approximately 0.5% of the overall mortality rate of COVID-19 after adjustment for age. In the United States, 78 100 deaths due to COVID-19 occurred from March 1, 2020, to May 30, 2020. Weinberger et al, however, reported that the number of excess deaths had reached 122 300, which was 28% more than the actual number.[11] Although the mortality rate of COVID-19 depends on the status of the provision of medical care and the criteria for counting fatal cases, it is likely to be 5- to 50-fold higher than that of seasonal flu.

Unfortunately, neither a vaccine nor an effective treatment for COVID-19 has yet been developed. Although several existing drugs have already been tried to overcome COVID-19, such as hydroxychloroquine,[12] lopinavir/ritonavir,[13] and interleukin-6 blocker,[14] effective agents have still have not been found. On the other hand, various ways of management have been performed for acute respiratory distress syndrome (ARDS) caused by COVID-19. Recent report suggests that lung protective ventilation defined as a low-volume, low-pressure ventilation strategy should apply in the early phase.[14] Furthermore, treatment with dexamethasone could lower mortality in the patients receiving either invasive mechanical ventilation or oxygen only without mechanical ventilation.[15] Since pulmonary vascular hypercoagulation has been indicated as cause of respiratory failure in COVID-19, management of ARDS should be performed with extreme caution to prevent ventilation-induced lung damage.

2.1 | Risk factors for COVID-19 advancing in severity in the general population

Liang et al reported several risk factors for the progression of COVID-19 to higher severity, such as illness in chest radiographic findings, advanced age, hemosputum, severe dyspnea, decreased level of consciousness, multiple medical histories, lymphocytopenia, elevated levels of lactate dehydrogenase, and direct bilirubin by analyzing the data of 1590 patients.[16] The Chinese Centers of Disease Control and Prevention estimated the mortality rate of COVID-19 in patients with cardiovascular disorders, diabetes, chronic respiratory disease, and hypertension to be 10.5%, 7.3%, 6.3%, and 6.0%, respectively, by analyzing 44 672 cases.[17] Reynolds et al, at New York University Hospital, found that 5894 of 12 594 patients were diagnosed as having COVID-19 by PCR examination, and 74% of them had hypertension.[18] They also reported that 63% of patients with severe COVID-19 had hypertension; however, no relationship was found between the risk of more severe COVID-19 and administration of ACEIs, ARBs, β1-blockers, Ca^{2+} channel blockers, or thiazide diuretics. Muncia et al compared the morbidity rate of hypertension between 6272 patients with and 30 759 patients without COVID-19 who were matched for age and sex.[19] The morbidity rate of hypertension was slightly higher in patients with (57.9%) than in those without COVID-19 (48.9%). They also reported that thiazide diuretic treatment tended to increase the risk of COVID-19, while administration of ACEIs or ARBs had no effect on the risk. Similarly, Zhang et al reported no relationship between ACEI/ARB exposure and COVID-19 severity.[20] As most of patients who receive antihypertensive drugs are elderly, their contribution to the risk of COVID-19 should be carefully estimated to avoid bias. Previous studies that mentioned the benefit of using

ACEIs/ARBs in improving the clinical outcomes of patients COVID-19 who have hypertension make treatment decision making more complicated.[21] The effect of the administration of antihypertensive drugs on the risk of COVID-19 is still unclear. Although whether uncontrolled BP is one of the risk factors of infection and/or more severe COVID-19 remains to be clarified, COVID-19 is likely to be closely related to cardiovascular diseases.

2.2 | Morbidity and mortality rates of COVID-19 in patients with end-stage kidney disease

Goicoechea et al reported that of 282 HD patients, 36 contracted COVID-19, of whom 11 died in one of the dialysis facilities in Spain (morbidity and mortality rates, 12.8% and 30.5%, respectively).[22] In Italy, of 209 dialysis patients, 55 contracted COVID-19, of whom 13 died in the dialysis facility (morbidity and mortality rates, 26.3% and 23.6%, respectively).[23] Keller et al reported on the impact of the first wave of COVID-19 on dialysis patients in the Alsace region of France. According to their report, 123 of 1346 dialysis patients were affected and 29 died (morbidity and mortality rates, 9.1% and 23.6%, respectively). The vast majority of deceased patients died 2 weeks after the onset of the symptoms.[24] In the Spanish facility, of 208 and 39 patients who were receiving HD and continuous ambulatory peritoneal dialysis (CAPD), 25 contracted COVID-19, of whom seven died (morbidity and mortality rates, 10.1% and 28.0%, respectively), while of 2500 kidney transplant recipients, 26 contracted COVID-19, of whom eight died (morbidity and mortality rates, 1.04% and 28.0%, respectively).[25] Furthermore, Manganaro and Baldovino surveyed the PCR positivity rate of COVID-19 in 5973 patients with end-stage kidney disease (ESKD) in the Piedmont and Aosta Valley, Italy.[26] As a result, 98 (3.4%) of 2893 HD patients, four (1.03%) of 387 patients with CAPD, and 26 (1.03%) of 2513 kidney transplant recipients were diagnosed as having COVID-19, with positivity rates 6- to 20-fold higher than the overall positivity rate in these districts (0.17%). In this report, the mortality rates of COVID-19 were calculated as 24.6% and 8.19% for ESKD patients and the general population in the district, respectively. In a pediatric kidney disease facility, on the other hand, four HD patients, four patients with CAPD, and 26 renal transplant pediatric patients had not acquired COVID-19. The mortality rates in dialysis patients were 28% and 27.3% according to reports from the United States and France, respectively.[27,28] According to the Japanese Society for Dialysis Therapy, as of October 2, 2020, 268 dialysis patients were diagnosed as having COVID-19 by PCR, of whom 38 died (mortality rate, 14.2%). Thus, the fatality rate due to COVID-19 in dialysis patients (14.2%-30.5%) is significantly higher than that in the general population (Table 1).

These results suggest that the morbidity rate of COVID-19 infection is clearly higher in dialysis patients than in the general population. On the other hand, that of kidney transplant recipients seems to be the same as in the general population. The mortality rate of COVID-19, however, in both dialysis patients and kidney transplant recipients were higher than that in the general population. To date, it has been considered that COVID-19 may increase the risk of long-term health problems mainly in respiratory, cardiovascular, and nervous systems. Since there is not enough clinical evidence to conclude the prolonged illness of COVID-19, it is necessary to take a careful look at symptoms of patients who have survived COVID-19. Especially, ESKD patients originally have high risk of cardiovascular disease. Moreover, it has been suggested that SARS-CoV-2 can infect specific kidney cells, such as parenchymal tubular epithelials and podocytes.[29] Thus, extreme caution should be exercised in the development of cardiovascular diseases and further renal dysfunction in ESKD patients who survived COVID-19. Taken together, caution is necessary for the prevention of COVID-19 in patients with ESKD.

2.3 | Precautions to prevent COVID-19 in patients with ESKD, especially those undergoing dialysis

As almost all patients with ESKD have various complications and suppressed immunoreactivity, infection is the prime cause of death in dialysis patients in Japan.[30] HD patients have to undergo dialysis for a prescribed period, three times a week, at dialysis facilities under any situation. Moreover, many patients adopt dialysis, and a staff simultaneously treats many patients on the same floor at dialysis facilities. These conditions may increase the risk of infection not only among dialysis patients but also among medical staff. In fact, 2.2% of the staff of dialysis facilities in the Piedmont and Aosta Valley, Italy, were diagnosed as having COVID-19 by PCR examination.[26] The incidence rate was approximately 10-fold higher in dialysis patients than in the general population in these districts.

In the case of dialysis patients with COVID-19, the problem would arise from the mode of visiting the dialysis facilities. Although not all dialysis patients have their own cars, they cannot use public transportations such as trains and buses when they have COVID-19. Moreover, the transfer services provided by the dialysis facilities

TABLE 1 Morbidity and mortality rates of COVID-19 in patients with end-stage kidney disease

Country and districts	Status	Morbidity rate (%)	Mortality rate (%)	Reference
Japan	Dialysis patients		14.2	[a]
Spain	Hemodialysis patients	12.8	30.5	22
	Hemodialysis and CAPD	10.1	28	25
	Kidney transplant	1.04	28	
Italy	Hemodialysis patients	26.3	23.6	23
Piedmont, and the Aosta Valley, Italy	Hemodialysis patients	3.4	24.6	26
	CAPD	1.03		
	Kidney transplant	1.03		
New York, USA	Hemodialysis patients		28	27
Paris, France	Hemodialysis patients		27.3	28
Alsace, France	Hemodialysis patients	9.1	23.6	24

Abbreviation: CAPD, continuous ambulatory peritoneal dialysis.
[a]Report by the Japanese Society for Dialysis Therapy as of October 2, 2020.

may not be used by the infected patients depending on the contract with the operating company. Therefore, they would be robbed of their opportunity to visit dialysis facilities. To solve this problem, dialysis patients diagnosed as having COVID-19 by PCR examination should be immediately hospitalized in a hospital with a dialysis facility. From another point of view, a specific transfer service for patients with COVID-19 may also be useful for dialysis patients. Securing the mode of visiting dialysis facilities for patients with COVID-19 is necessary.

Second, dialysis facilities must reschedule the treatment for patients with COVID-19 to avoid close contact with other people. However, Rombola and Brunini reported that 37 of 230 dialysis patients contracted COVID-19, of whom seven died not of pneumonia due to COVID-19 but of hyperkalemia, heart failure, and cerebrovascular disease, which are symptoms related to renal failure.[31] Seidel et al also suggested that cardiorenal syndrome strongly associated with death of HD patients after infection with SARS-CoV-2 in HD outpatient centers in Germany.[32] Therefore, rescheduling and/or decreasing the duration or time of dialysis can endanger a patient's life. Dialysis facilities must exert maximum effort to segregate patients with COVID-19 and treat them on schedule as much as possible.

In relation to the above-described situation, overcoagulated state and thrombi have often been observed in patients with COVID-19.[33] Liu et al reported that treatment with dipyridamole, an inhibitor of platelet aggregation often used to treat renal diseases, decreased the mortality rate of COVID-19 patients by one-third as compared with the untreated group.[34] They suggested that dipyridamole can improve the conditions of patients with COVID-19 by suppressing the proliferation of SARS-CoV-2 and inhibiting platelet aggregation. Low-molecular-weight heparin used as an anticoagulant in Europe has also been proposed as a useful agent for the treatment of COVID-19 by exhibiting antivirus, anticoagulant, and immunostimulating activities.[35] Hoffmann et al reported that camostat, a protease inhibitor, can prevent the entry of SARS-CoV-2 into cells.[4] In Japan, research has been conducted to demonstrate the usefulness of nafamostat mesilate for COVID-19 treatment (unpublished). Nafamostat mesilate is often used as an anticoagulant in HD patients; however, approximately 40% of it is extracted by single circulation into the dialyzer. Thus, dipyridamole and low-molecular-weight heparin may be more useful for the treatment of COVID-19 in dialysis patients. Further investigation is necessary to validate their effects on COVID-19.

2.4 | Countermeasures to prevent COVID-19 infection in dialysis facilities

On April 3, 2020, the Japanese Society of Dialysis Physicians published a countermeasure against the spread of COVID-19 in dialysis facilities (fourth edition).[36] According to this guideline, dialysis patients should perform the standard precautionary measures, carefully prevent aerosol and/or contact infection, and be prechecked and triaged before visiting the dialysis facilities when they have symptoms such as fever. Moreover, this guideline has described methods for putting on and removing personal protective equipment (PPE), cleaning equipment after termination of dialysis for patients with confirmed and/or suspected COVID-19, and risk assessment of medical staff.

Ikizler and Kliger proposed that control of inventory of medical materials, labor management, shifting the place of dialysis from the facilities to the patient's home, including CAPD, and defining a protocol for transferring the patient with COVID-19 are essential to minimize the risk of infection at dialysis facilities.[37] If the COVID-19 pandemic is prolonged, a lack of PPE would be a menace to hospitals. They suggested that the priority of usage and the rule for recycling PPE should be considered in individual facilities. As 10% of the medical staff had been infected with COVID-19 in the dialysis facilities in Italy, securing a sufficient number of medical staff has been difficult. Thus, we have to confirm the ability and adjust the alternative schedule of the medical staff in individual facilities in advance. Moreover, they described the need to promote shifting the place of dialysis from facilities to the patient's home by performing surgery for the insertion of a CAPD catheter as much as possible.

Basile et al suggested that dialysis for patients with COVID-19 should be performed with full-barrier precautions, the medical staff separated into several teams, and each team corresponding to the patients divided according to the risk of the COVID-19 without transferring the members between teams.[38] In addition, they recommended that outpatient dialysis facilities should not provide dialysis, except that the negative-pressure rooms can be utilized for patients with COVID-19.

The measures taken at dialysis facilities worldwide were well summarized in previous literature[39] and are shown in Table 2. Education for patients and medical staffs is a key factor for preventing and mitigating further spread of COVID-19. Since patients on in-center HD are particularly vulnerable to COVID-19, management of medical staff, such as creating a COVID-19 team and backup list of staff is also important. In particular, thoroughness of constant mask wearing within the dialysis facilities for patients and medical staff is necessary. If a staff member contacts patients with confirmed and/or suspected COVID-19 without either of them wearing a mask or a face shield, the staff should be restricted from working for 14 days. This restriction for working is also required in case the initial symptoms of a cold have been observed in the medical staff. Then, vacancies must immediately be filled from backup lists. Although it is difficult to create backup lists, cooperation with neighboring hospitals and dialysis facilities would make it possible. Furthermore, registration of retired medical staff as backup members by respective association can solve the problem of shortage of manpower.

In addition, patients with confirmed and/or suspected COVID-19 should be segregated from other patients in the dialysis facilities. The separation of a flow line and dialysis room for patients with or without confirmed and/or suspected COVID-19 would be considered as the

TABLE 2 Comparison of COVID-19 guidelines provided for different geographic regions in the world (modified in part from Kliger et al.[39])

			USA	Europe	India	Japan
Education	Patients	Basic hygiene and disease education	◦	◦	◦	◦
	HCWs	PPE training and evaluation	◦	NA	NA	◦
Screening		Symptom check on arrival	◦	◦	◦	◦
		Temperature check on arrival and departure	◦	◦	◦	◦
		Screening diagnostic test in all patients on dialysis	NSG	NSG	NSG	NSG
Management	Administrative	COVID-19 teams	◦	◦	◦	◦
		Backup lists	◦	NA	NA	◦
	Facility workflow	Dedicated space and shift	◦	◦	◦	◦
		Surgical face mask to all patients	◦	◦	◦	◦
		Routine cleaning and disinfection procedure	◦	◦	◦	◦
	Supply chain	Recycling of PPE	◦	◦	NA	NA
Others		Transportation	◦	NSG	NSG	◦
		Return-to-work for HCWs	◦	NSG	NSG	◦
		Clinical management of patients under investigations	RS	RS	RS	◦

Notes: USA: Centers for Disease Control and Prevention; Europe: European Dialysis and Transplant Association; India: Indian Society of Nephrology; Japan: Japanese Society of Dialysis Physicians.

Abbreviations: ◦, availability of a recommendation; HCWs, health care workers; NA, not available; NSG, no specific guidelines; RS, region-specific with different recommendations.

most effective measure. To achieve complete separation, utilization of negative-pressure rooms for dialysis patients with confirmed and/or suspected COVID-19 would be recommended as described in a previous report.[36] Secondly, all infected patients should keep a distance of at least two meters in the dialysis facilities. A curtain enclosing the distance between them would provide a brief spatial isolation. In the case it is impossible to take the above measures, dialysis facilities should try to stagger dialysis times for patients with or without confirmed and/or suspected COVID-19 to ensure the temporal isolation.

Almost no outpatient dialysis facilities in Japan have both negative-pressure rooms and/or private rooms for performing dialysis with segregation. Therefore, currently, medical staff have no choice but to perform dialysis while wearing an N-95 mask, goggles, a medical gown, and gloves in partitioned spaces. Moreover, strict triage should be performed before the patients visit the facilities and immediately check for COVID-19 in dialysis patients by PCR examination.

3 | CONCLUSION

The mortality rate of COVID-19 seems higher in patients with end-stage kidney disease than in the general population. As medicines and vaccines for COVID-19 have not been established yet, COVID-19 transmission should be prevented during the treatment of dialysis patients. The crisis caused by COVID-19 should be overcome by exerting maximum efforts such as education for patients and medical staff, and improving medical equipment and facilities. To match the new lifestyle of coexisting with COVID-19, the treatment method for patients with end-stage kidney disease might need to be changed.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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