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IMMUNE RESPONSE AND PROGNOSIS OF CHRONIC KIDNEY DISEASE PATIENTS UNDERGOING HAEMODIALYSIS AGAINST COVID-19: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Chronic kidney disease (CKD) patients are characterized by immune response dysfunction which increased susceptibility to infections. CKD is one of the Coronavirus disease-2019 (COVID-19) comorbidity that generally has a poor clinical outcome and patients undergoing hemodialysis had a 50% hospitalization rate and 20%-30% mortality rate. Seroconversion after confirmation of COVID-19 infection is close to 100% in the dialysis population, but the durability of the immune response and the extent as a protection against infection remains unclear. This study aimed to determine the immune response and prognosis of CKD patients undergoing hemodialysis against COVID-19. **Objective:** To determine immune response and prognosis of CKD patients undergoing hemodialysis against COVID-19. **Methods:** This is a systematic review study that used literature sourced from online journal databases on Google Scholar, PubMed, Cochrane, and Clinical Key sites. Literature that has passed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) staging and the journal quality review based on the Newcastle-Ottawa Scale (NOS) assessment then synthesized qualitatively and presented systematically. **Results:** Based on the data analysis, there were positive immune responses in 460 of 735 (62.6%) CKD patients undergoing hemodialysis against COVID-19 and a higher mortality rate (10.5%) than the control group (6.9%). **Conclusion:** The immune response and prognosis of CKD patients undergoing hemodialysis against COVID-19 were worse than the control group. Therefore, COVID-19 vaccination should be prioritized in CKD patients undergoing hemodialysis.
Keywords: *Chronic kidney disease, COVID-19, immune response, mortality.*

INTRODUCTION

Chronic kidney disease (CKD) is a kidney disorder characterized by structural or functional abnormalities of the kidney that persist for more than 3 months. CKD can be assessed by the glomerular filtration rate (GFR ≤ 60 ml/min/1.73 m2) or other evidence of damage such as increased albuminuria, urine sediment, electrolytes, or abnormal histology.[1]

CKD has been recognized as a leading public health problem worldwide. The global estimated prevalence of CKD is 13.4% (11.7-15.1%), and patients with end-stage kidney disease (ESKD) needing renal replacement therapy is estimated between 4,902 and 7,083 million.[2] In 2018, Riset Kesehatan Dasar (Riskesdas) reported an increase prevalence of CKD in 2018 to 0.38% compared to 2013 which was only 0.2%.[3]

Decreased kidney function and chronic inflammatory processes in patients with CKD can increase the risk of uraemia which then ends in immune response dysfunction and increases susceptibility to infection, including the risk of Coronavirus-2019 (COVID-19) infection.[4] Global population at high risk for infection with COVID-19 became 1.7 billion people, 349 millions of whom needed hospital treatment if infected and CKD was the most common risk factor for severe COVID-19 with 50% hospitalization rate and 20%-30% mortality rate.[5] Seroconversion after confirmation of COVID-19 infection is close to 100% in the dialysis population, but the durability of the immune response and the extent to which it can become immunity remains unclear.[6] Therefore, this study aimed to determine the immune response and prognosis of CKD patients undergoing haemodialysis against COVID-19.

METHODS

This is a systematic review study using literatures from online journal databases on Google Scholar, PubMed, Cochrane, and Clinical Key sites. Literature searched by using the mesh words (Chronic Kidney Disease) AND (Hemodialysis) AND (SARS-CoV-2 OR COVID-19) AND (Immune OR Immunology OR Prognosis OR Mortality). The relevant literatures were then reviewed for the quality of the journal using Newcastle-Ottawa Scale (NOS) assessment and the data found were then synthesized qualitatively and presented systematically.

Inclusion criteria were research conducted after 2020 with adult patients (> 18 years old) who have not received COVID-19 vaccination, there were measurements of innate and/or adaptive immunity after COVID-19 infection, and mortality rate as a

prognostic measurement. Reviews articles, commentary, and study conducted in animals were excluded in this study. This study had been approved by the Research Ethics Committee, Universitas Sumatera Utara no. 1187/KEP/USU/2021.

RESULTS

A total of 8 studies that have met the inclusion and eligibility criteria with seven studies investigated total and/or individual antibody (IgA/IgG/IgM) and one study measured ratio of T cells, NK cells, and B cells. All of the literature included mortality rates with six studies added severity of COVID-19 in CKD patients undergoing hemodialysis. The complete literature-search diagram with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) stages is displayed in Figure 1 and characteristics of the studies can be seen in Table 1.

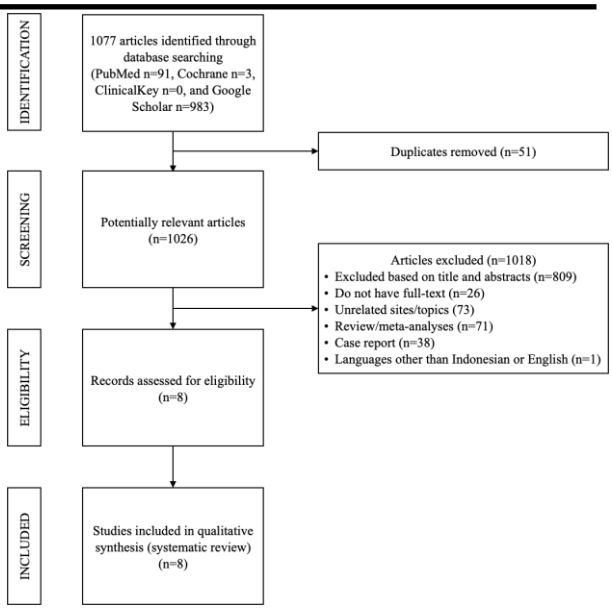

Figure 1. PRISMA flow diagram

Table 1. Study characteristics

Study	Title	Sample	
		Patient	Control
Ma et al.[7] (2020)	Epidemiological, Clinical, and Immunological Features of a Cluster of COVID-19–Contracted Hemodialysis Patients	42	33
Beppu et al.[8] (2021)	Hemodialysis patients with coronavirus disease 2019: reduced antibody response	34	68
Wickens et al.[9] (2021)	Investigating the utility of COVID-19 antibody testing in end-stage renal disease patients receiving hemodialysis: a cohort study in the United Kingdom	32	-
Forbes et al.[10] (2021)	Persistence of antibody response to SARS-CoV-2 in a cohort of hemodialysis patients with COVID-19	122	-
Clarke et al.[11] (2021)	Longevity of SARS-CoV-2 immune responses in hemodialysis patients and protection against reinfection	356	-
Ahmed et al.[12] (2021)	Outcomes of patients with end stage kidney disease on dialysis with COVID-19 in Abu Dhabi, United Arab Emirates; from PCR to antibody	152	-
Alcazar-Arroyo et al.[13] (2021)	Rapid decline of anti-SARS-CoV-2 antibodies in patients on hemodialysis: the COVID-FRIAT study	91	-
Prendecki et al.[14] (2021)	SARS-CoV-2 Antibody Point-of-Care Testing in Dialysis and Kidney Transplant Patients With COVID-19	39	-
Total		868	101

Note: HD= Hemodialisys; LFIA= Lateral Flow Immunoassay; RT-PCR= Reverse Transcription-Polymerase Chain Reaction; SARS-CoV-2= Severe Acute Respiratory Syndrome Coronavirus 2; IgG= Immunoglobulin G; FRIAT= Fundación Renal Íñigo Álvarez de Toledo.

Analysis of immune response of CKD patients undergoing hemodialysis against COVID-19 can be seen in Table 2. The results of seven different studies showed the presence of positive

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antibodies in 460 of 735 CKD patients who underwent hemodialysis and were infected with COVID-19 with a percentage of 62.6%. The seroconversion results for the SARS-CoV-2 specific antibody were quite varied because the timing of the serological tests and the severity of COVID-19 were found to be different in each literature.

Table 2 Immune response of CKD patients undergoing hemodialysis against COVID-19

Study	Age	Serology Test	Type of Immune Response	Sample	Sero-conversion	COVID-19 Severity	
						Non-severe	Severe
Beppu et al.[8] (2021)	66,3 (17.2)**	CLIA	Anti-S IgG	21/34 (61.8)	7-13 days	21	13
Wickens et al.[9] (2021)	62 (54-57)*	CLIA	Anti-S IgG	31/32 (96.9)	22 (16-36) days*	29	3
Forbes et al.[10] (2021)	63 (53-72)*	ECLIA	Anti-N IgM + IgG	122/122 (100)	122 (91-145) days*	113	9
Clarke et al.[11] (2021)	65 (55-73)*	CMIA	Anti-N IgG	129/356 (36.2)	0-7 days	nr	nr
Ahmed et al.[12] (2021)	53 (44-60)*	CMIA	Anti-RBD IgG	64/87 (73.6)	85 (16) days**	136	16
Alcazar-Arroyo et al.[13] (2021)	65,5 (14.8)**	ELISA	(Anti-S + Anti-N) IgA + IgM and/or IgG	55/65 (84.6)	4 weeks	nr	nr
Prendecki et al.[14] (2021)	64 (58-76)*	LFIA	Anti-RBD IgG	38/39 (97.4)	35 (30-39) days*	36	3
Total				460/735 (62.6)			

Note: HD= Hemodialysis; CLIA= Chemiluminescence Immunoassay; CMIA= Chemiluminescent Microparticle Immunoassay; ELISA= Enzyme-linked Immunoassay; ECLIA= **Electro-Chemiluminescence Immunoassay;** LFIA= Lateral Flow Immunoassay; nr= not reported.
*Median [interquartile range (IQR)], **Mean ± standard deviation (SD)

In Ma et al[7] study that can be seen in Table 3, there was a measurement of the Peripheral Blood Mononuclear Cells (PBMC) profile of CKD patients undergoing hemodialysis with COVID-19 and control groups. In this study, it was found that the number of T cells, CD4+ T cells, CD8+ T cells, NK cells, and B lymphocytes was lower than the control group with p value < 0.05 which showed significant results.

Table 3 Comparison of PBMC in CKD patients undergoing hemodialysis and control group

Study	Parameter (/µl)	HD patients with COVID-19, n=19	HD patients without COVID-19, n=19	Non-HD patients with COVID-19, n=19	Healthy volunteers, n=19
Ma et al.[7] (2020)	T cells	422 (309-819)	594 (397-1045)	884 (684-1166)	1452 (1327-1839)
	Th cells	207 (187-337)	272 (231-531)	527 (395-579)	794 (696-926)
	Killer T cells	143 (110-171)	143 (114-394)	335 (200-692)	585 (457-626)
	NK cells	99 (48-196)	108 (55-259)	138 (99-178)	215 (181-466)
	B cells	35 (32-56)	56 (29-83)	109 (83-175)	315 (150-388)

Note: HD= hemodialysis; NK cells= Natural Killer cells; Th cells= T helper cells
Data are median [interquartile range (IQR)], p < 0,05

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There are 6 literatures that include mortality rates and add severity of COVID-19 in CKD patients undergoing hemodialysis. Severe symptoms of COVID-19 were assessed based on the patient's need for ICU care or information as measured by the SpO_2 value, P/F ratio, and type of oxygen therapy. There were 31 out of 421 (7.4%) CKD patients undergoing hemodialysis who died due to COVID-19 (Table 4).

Table 4 Mortality of CKD patients undergoing hemodialysis against COVID-19

Study	Hemodialysis patients	COVID-19 Severity		Mortality (%)
		Non-severe	Severe	
Ma et al.[7] (2020)	42	37	5	2 (4.8)
Beppu et al.[8] (2021)	34	21	13	6 (17.6)
Wickens et al.[9] (2021)	32	29	3	6 (9.4)
Forbes et al.[10] (2021)	122	113	9	0 (0)
Ahmed et al.[12] (2021)	152	136	16	14 (9.2)
Prendecki et al.[14] (2021)	39	36	3	3 (7.7)
Total	421			31 (7.4)

The mortality rate of CKD patients undergoing hemodialysis and infected with COVID-19 compared to the control group was later found in a study conducted by Beppu et al[8] and Ma et al[7] (Table 5). It was found that the mortality rate in CKD patients undergoing hemodialysis was higher than the control group with a percentage of 10.5% compared to 6.9%. This shows that the prognosis of CKD patients undergoing hemodialysis and infected with COVID-19 is worse than the control group.

Table 5 Comparison of mortality of CKD patients undergoing hemodialysis with control group

Study	Hemodialysis patients		Control	
	Death	Presentation (%)	Death	Presentation (%)
Ma et al.[7] (2020)	2/42	4.8	0/33	0
Beppu et al.[8] (2021)	6/34	17.6	7/68	10.3
Total	8/76	10.5	7/101	6.9

DISCUSSION

Using eight studies with 969 samples, we discovered four studies[9,10,13,14] that have higher seropositivity than the others, but the time required to achieve this seropositivity was much longer (Table 2). The highest seroconversion was shown in a cohort study conducted by Forbes et al[10], where all patients were able to form antibodies against COVID-19 within 4 months (Table 2). The delay in antibody response also stated in De-Vriese et al[15] and Labriola et al[16], concluded that hemodialysis patients managed to produce IgG antibodies within 3 weeks after the onset and remained stable (plateau) thereafter. Beppu et al[8] showed the lowest seroconversion which was 36.2%, and also the highest percentage of severe COVID-19 patients with a percentage of 38.2% (Table 2). The low and delayed antibody response are associated with the worsening of the patient's clinical manifestations, as mentioned in the study of Lucas et al[17] that stated death in CKD patients undergoing hemodialysis and infected with COVID-19 had a delay in the production of anti-spike IgG and neutralizing antibodies before the second week after onset compared to patients who recovered.

The study conducted by Ma et al[8] found that the number of T cells, $CD4^+$ T cells, $CD8^+$ T cells, NK cells, and B lymphocytes was significantly lower than the control group with p value < 0.05 (Table 3). The dysfunction of the immune system makes CKD patients undergoing hemodialysis take longer to form SARS-CoV-2 specific antibodies and lower PBMC profile that are responsible for worsening the patient's condition and causing death.

This study has several limitations, including the literature that does not provide

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controls, does not have the same timing of serological measurements and assays used, including different type of antibodies and target antigens. Researchers also did not identify other risk factors that could influence changes in the immune response (e.g. immunosuppressive treatment) and there are studies that were incomplete in providing the severity of COVID-19 and studies that lose more than 20% of the sample.

CONCLUSION

The systematic review showed that the immune response and prognosis of CKD patients undergoing haemodialysis against COVID-19 were worse than the control group. Therefore, COVID-19 vaccination should be prioritized in CKD patients undergoing hemodialysis.

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