

Comparative study on albumin, C-Reactive Protein (CRP) and D-dimer in chronic hemodialysis patients with COVID-19



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ABSTRACT

Background: Chronic kidney disease (CKD) patients on hemodialysis are more susceptible to COVID-19 infections. Mortality and morbidity rate are higher in this population. Thus, it is critical to understand which parameters are associated with mortality in this population. C-reactive protein (CRP), albumin, and d-dimer were shown in several studies to be associated with mortality in COVID-19-infected hemodialysis patients.

Methods: This study was a comparative observational, retrospective study from the medical records of Dr. Soetomo General Hospital in Surabaya, Indonesia. Chronic kidney disease patients on maintenance hemodialysis who tested positive for COVID-19 from June 2020 to January 2021 and underwent treatment in the isolation ward were included in this study. Data were analyzed using SPSS version 21.0 for Windows.

Results: The non-survivor groups have statistically significant lower albumin (2.78 (2.21-3.40) g/dL vs. 3.20 (2.45-3.80) g/dL; $p=0.040$) and higher CRP (10.40 (4.10-28.6) mg/L vs. 3.20 (0.10-80.0) mg/L; $p=0.020$) compared to the survivor group (Table 2). D-dimer value has no significant difference between the non-survivor and survivor groups (4,290 (190-18,310) ng/mL vs. 2,630 (190-19,430) ng/mL; $p=0.140$).

Conclusion: Non-survivor CKD patients with COVID-19 infections have significantly lower serum albumin and higher CRP concentrations. There is no significant difference in D-dimer concentrations in the survivor and non-survivor groups.

Keywords: Chronic Kidney Disease, COVID-19, CRP, Albumin, D-dimer.

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is disease caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) that originates in Wuhan, China.¹ Since March 11, 2020, the World Health Organization (WHO) declared this rapidly spreading viral disease a global pandemic.¹ COVID-19 has truly caused devastation worldwide, causing many healthcare facilities to be overwhelmed and resulting in millions of deaths.¹ Among millions infected, people with comorbidities are affected the most since they are more susceptible to infections and severe forms of COVID-19. Chronic kidney disease (CKD) is one of the many comorbidities impacted by COVID-19 infections.²

Chronic kidney disease is defined as abnormalities in kidney structure or function present for >3 months with health implications.³ CKD accounts for

one of many public health problems with a prevalence of 13.4% worldwide and it is estimated that between 4.9 to 7.1 million patients require renal replacement therapy.⁴ These numbers are mainly driven by many comorbidities that cause CKD, such as diabetes, hypertension, obesity and aging.⁴

CKD patients, particularly those on maintenance hemodialysis, are susceptible to COVID-19 infections because they must attend hospital dialysis up to three times a week.⁵ Mortality and morbidity rate of COVID-19 is seen higher in the dialysis population compared to the general population.⁶ Thus, it is critical to understand which parameters are associated with mortality in this population. C-Reactive Protein (CRP), albumin, and d-dimer were shown in several studies to be associated with mortality in COVID-19-infected hemodialysis patients.⁷⁻⁹

However, no study in Indonesia has explored how these variables may associate with mortality in hemodialysis populations with COVID-19 infections. This study aims to determine the association between CRP, albumin, d-dimer, and mortality in COVID-19 infections among CKD patients on hemodialysis.

MATERIALS AND METHODS

This was a comparative observational, retrospective study from medical records from Dr. Soetomo General Hospital in Surabaya, Indonesia. We included all chronic kidney disease patients on maintenance hemodialysis therapy who tested positive for COVID-19 from June 2020 to January 2021 and underwent treatment in the isolation ward. The hospital ethical committee approved the study protocol (1068/LOE/301.4.2/X/2022). The main outcome of this study is the mortality of hemodialysis patients with COVID-19.

The study included all chronic kidney disease patients on maintenance hemodialysis who tested positive for COVID-19 from June 2020 to January 2021 and underwent treatment in the isolation ward of Dr. Soetomo General Hospital. Patients must have the following laboratory values: CRP, albumin, and D-dimer. The exclusion criteria are ICU admission and incomplete laboratory data.

Data were collected from the medical records. Data collected included demographics, comorbidities, clinical features, and laboratory. Purposive sampling techniques were used in the collection of the samples. Demographic data are presented with frequency distributions for qualitative data and summarized as mean or median for quantitative data. CRP, albumin, and D-dimer value are analyzed for distributions. If the distribution is normal, an unpaired T-test will be performed. Otherwise, the Mann-Whitney test will be performed. All statistical analyses were performed using SPSS Software version 21.0 for Windows. Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 54 patients are included in the analysis of the study. There are 13 non-survivor patients (24.00%) and 41 survivor patients (76.00%). The mean age of the non-survivor and survivor patients are 53.08 ± 12.3 and 49.41 ± 8.8 . Male patients account for 46% and 53% for the non-survivor and survivor groups. The most common comorbidities in both groups are diabetes and hypertension. The two groups have no significant difference statistically in demographics and comorbidities. The demographics and comorbidities of the patients included in the study can be seen in [Table 1](#).

Thirteen patients (24.00%) died of COVID-19 among the included hemodialysis patients during the study period. Mann-Whitney test was performed to determine the median difference in albumin, CRP and d-dimer value between the non-survivor and survivor groups. The non-survivor groups have a statistically significant lower albumin (2.78 (2.21-3.40) g/dL vs. 3.20 (2.45-3.80) g/dL; $p = 0.040$) and higher CRP (10.40 (4.10-

Table 1. Demographics of COVID-19-infected CKD patients on hemodialysis

Variables	Non-Survivor (N=13)	Survivor (N=41)	P
Age (Years) (Mean±SD)	53.08±12.3	49.41±8.8	0.134 ^a
Sex, n (%)			
Male	6 (24.00)	19 (76.00)	0.991 ^b
Female	7 (24.14)	22 (75.86)	
Comorbidities, n (%)			
Diabetes	7 (29.17)	17 (70.83)	0.434 ^b
Hypertension	7 (18.42)	31 (81.58)	0.134 ^b
Thyroid Disease	0 (0.00)	0 (0.00)	-
Obesity	0 (0.00)	0 (0.00)	-
Retinopathy	0 (0.00)	1 (100.00)	0.570 ^b
HIV/AIDS	00 (0.00)	00 (0.00)	-
Hepatitis B or Chronic liver disease	2 (66.67)	1 (33.33)	0.076 ^b
History of Stroke	1 (50.00)	1 (50.00)	0.382 ^b
Chronic Obstructive Pulmonary Disease	1 (100.00)	0 (0.00)	0.073 ^b
Coronary Artery Disease	0 (0.00)	1 (100.00)	0.570 ^b
Age >65 years	3 (75.00)	1 (25.00)	0.039 ^{b*}

^aUnpaired T-Test; ^bChi-Square; *Statistically significant if p-value less than 0.05

Table 2. The median difference in albumin, CRP, and d-dimer value in COVID-19-infected CKD patients on hemodialysis

Variables	Median (Min-Max)	p
Albumin (g/dL)		
Non-survivor	2.78 (2.21-3.40)	0.040 [*]
Survivor	3.20 (2.45-3.80)	
CRP (mg/L)		
Non-survivor	10.40 (4.10-28.6)	0.020 [*]
Survivor	3.20 (0.10-80.0)	
D-dimer (ng/mL)		
Non-survivor	4,290 (190-18,310)	0.140
Survivor	2,630 (190-19,430)	

^{*}Mann-Whitney Test: statistically significant if p-value less than 0.05

28.6) mg/L vs. 3.20 (0.10-80.0) mg/L; $p = 0.020$) compared to the survivor group ([Table 2](#)). D-dimer value has no significant difference between the non-survivor and survivor group (4,290 (190-18,310) ng/mL vs. 2,630 (190-19,430) ng/mL; $p = 0.140$). The median comparison of albumin, CRP and d-dimer value between the non-survivor and survivor groups can be seen in [Table 2](#).

DISCUSSION

This study explored the laboratory parameters, albumin, CRP, and D-dimer, associated with COVID-19 mortality in hemodialysis patients. To the best of our knowledge, this is the first study to explore the association between these three parameters and COVID-19 mortality in CKD hemodialysis patients in Indonesia.

SARS-CoV-2 primary target receptor is the ACE2 receptors, which are abundant in the kidney, even more than in the lungs, particularly on the brush border apical membrane of the proximal tubule.¹⁰ Thus, making the kidney susceptible to injury from COVID-19 infection. It is yet to be understood whether the virus directly damages renal cells or whether kidney injury is secondary to cytokine syndrome.¹¹ There are numerous possible pathophysiology mechanisms in which kidney injury may occur. These include acute lung injury leading to hypoxemia in the kidney medulla, sepsis, cardiorenal syndrome, cytotoxic effects leading to tubular and podocyte injury, coagulopathy, microangiopathy, and rhabdomyolysis.¹⁰

Patients with CKD have marked alterations in the immune system,

which can be seen as persistent systemic inflammation leading to acquired immunosuppression.¹² B and T cell phagocytic dysfunction along with increased pro-inflammatory cytokines concentrations and inflammatory monocytes are associated with alterations of the immune system in CKD patients.¹³ CKD is also marked with chronic inflammation, which is contributed by comorbidities, oxidative stress, infections, and hemodialysis related factors such as biocompatibility and quality of dialysate.¹¹ The immune-deficient state makes CKD patients more susceptible to infection.¹¹ Along with persistent systemic inflammation and inflammation caused by the virus, hyperinflammation may occur, resulting in tissue injury and death.¹¹ In addition, CKD is often associated with comorbidities such as diabetes, cardiovascular disease, anemia, malnutrition, and others may further aggravate the tissue injury seen in COVID-19 infections.¹¹

Patients with CKD are often seen with reduced serum albumin due to protein-energy wasting, defined as a state of metabolic alterations characterized by loss of protein and energy stores.¹⁴ Furthermore, those on maintenance hemodialysis may lose up to 6-8 g of total amino acids during each dialysis due to the dialyzer membrane, which triggers an inflammatory state.¹⁴ Our study found that the non-survivor group had lower serum albumin than the survivor group. This result is similar to a study by Acharya et al., which reported that lower serum albumin at presentation was associated with serious outcomes, including kidney injury, cardiac injury, hypercoagulability, physical incapacity, encephalopathy and higher mortality, even after adjusting for age, sex and comorbidities.¹⁵ Inflammation, in general, has a catalytic effect on serum albumin.⁸ Therefore, low serum albumin is an independent risk predictor for poor outcomes.⁸ As demonstrated in our study, patients with lower serum albumin and in the presence of COVID-19 infection are associated with mortality.

C-reactive protein is an acute-phase inflammatory protein produced in response to acute inflammatory reactions.¹⁶ CRP has a role in activating the classical pathway of

complement activation. Thus, CRP is not merely a marker of inflammation but also contributes to inflammatory processes in COVID-19 infections.¹⁷ Our study shows an association between a higher level of CRP and mortality in hemodialysis patients with COVID-19 infections. A single-center study in Malaysia also reveals the same results; CRP levels on admission and day 7 of hospitalization were associated with mortality in CKD patients with COVID-19 infections.⁷

D-dimer is a byproduct of fibrin degradation that is used to measure thrombosis. In COVID-19, an increase up to 3 to 4-fold in D-dimer concentrations is associated with poor prognosis.⁹ In our study, both groups demonstrated increased D-dimer concentrations beyond the normal range. However, there are no significant differences between the non-survivor and survivor groups in d-dimer concentrations. A systematic review and meta-analysis reported that d-dimer is seen higher in populations with severe COVID-19.¹⁸ Our study did not include those patients admitted into the ICU; thus, the same result is not seen. Unlike our study, a single-centered study in China reported that D-dimer, along with fever and dyspnea, is an independent predictor of mortality in hemodialysis patients with COVID-19.¹⁹ Previous studies also found that D-dimer was related to the mortality of patients in several conditions.²⁰⁻²²

Our study does not include patients admitted to the ICU; thus, the relationship between these three parameters and severe COVID-19 in patients with CKD is not explored. Further studies with larger sample sizes and case-control studies are needed to find stronger associations and predictors between albumin, CRP and d-dimer with mortality.

CONCLUSION

Non-survivor CKD patients with COVID-19 infections have lower serum albumin and higher CRP concentrations. There is no significant difference in D-dimer concentrations in the survivor and non-survivor groups.

CONFLICT OF INTEREST

There is no conflict of interest.

ETHICS CONSIDERATION

The hospital ethical committee approved the study protocol (1068/LOE/301.4.2/X/2022).

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AUTHOR CONTRIBUTION

All authors equally contribute to the study from the conceptual framework, data acquisition, and data analysis until reporting the study results through publication.

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