The Relationship Between C-Reactive Protein and Hemoglobin Levels with The Death of Chronic Kidney Disease Patients Undergoing Routine Hemodialysis Confirmed to Covid 19 at Ulin Hospital, Banjarmasin

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Abstract:

COVID-19 mortality is much higher in members of the population with multiple co-morbidities. Anemia is independently associated with all-cause mortality in patients hospitalized with COVID-19. C-Reactive Protein (CRP) levels are increased in patients with renal failure and are an independent predictor of cardiovascular mortality. This study used an observational case-control method. Data were taken consecutively using medical records of patients who died as a case group and lived as a control group with chronic kidney disease who underwent routine HD confirmed with COVID-19 at Ulin General Hospital, Banjarmasin. The number of subjects in this study was 92 patients. High CRP levels (>30 mg/L) significantly increased the risk of death by 4 times (OR 4.330; 95% CI 1.800-10.416; p = 0.001). Low hemoglobin levels (<10 g/dl) did not affect mortality in routine hemodialysis patients infected with COVID-19 (OR 0.643; 95% CI 0.281-1.471; p = 0.294). An increased CRP in COVID-19 patients is thought to indicate extensive inflammation in the infected lungs, then the condition of CKD patients undergoing routine hemodialysis with compromised immunity increases the risk of severity and mortality in this population. There is an effect of CRP levels on death from COVID-19 in Chronic Kidney Disease patients undergoing routine hemodialysis at Ulin General Hospital, Banjarmasin.

Keywords: C-Reactive Protein, Hemoglobin, Chronic Kidney Disease, Hemodialysis, COVID-19.

Introduction

The morbidity and mortality of COVID-19 are much higher in population members who show several co-morbidities.[1] Patients with chronic kidney disease usually have several co-morbidities, such as hypertension, diabetes, and cardiovascular disease. CKD is a global public health problem with a total of approximately 850 million CKD patients worldwide. The incidence of CKD in China is 10.8% and estimates show that 119.5 million Chinese adults have CKD.[2] People with CKD are highly susceptible to COVID-19. Hemodialysis patients need to visit the hemodialysis center regularly three times a week. Therefore, the hemodialysis center is a potential vector for the spread of this pandemic. In previous pandemic or disaster situations, the death rate in patients undergoing hemodialysis was much higher than in the general population.[3]

Early follow-up efforts for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) patients demonstrated the importance of knowing acute phase reactants for diagnosis and prediction of prognosis in severe coronavirus infections. It was reported that most SARS patients had elevated C-reactive protein (CRP).[4]

Anemia is a very common occurrence in CKD patients undergoing routine hemodialysis. Anemia is a global disease with below-normal hemoglobin levels which is related to the prognosis of many clinical diseases, including diseases with respiratory disorders such as COVID-19. Moderate-severe anemia also predicts a more severe outcome in COVID-19 patients. Anemia on admission and changes in hemoglobin levels during hospitalization may help further guide risk stratification and management of patients hospitalized with COVID-19.[5-6]

C-Reactive Protein (CRP) levels are increased in patients with renal failure and are an independent predictor of cardiovascular mortality.[7-9] Patients with chronic kidney disease (CKD) also have a high burden of cardiovascular disease and are at greater risk of death from cardiovascular disease. In patients with renal failure, there is a close pathophysiological relationship between cardiovascular disease, malnutrition, and inflammation. C-reactive protein (CRP) levels are a strong risk factor for cardiovascular events.[10-12]

CRP levels in COVID-19 patients with comorbid chronic kidney disease greatly affect the mortality rate because of its relationship with COVID-19 and chronic kidney disease. The increasing CRP value indicates the size of the lung lesions that occur in COVID-19 infection and increases the risk of cardiovascular disease in CKD patients who routinely carry out hemodialysis.

Research Method

This was a case-control study to assess prognostic factors such as *C-Reactive Protein* and Hemoglobin level in Chronic Kidney Disease on dialysis patients with COVID-19. This research was conducted in 2020-2022 at the Ulin Hospital Banjarmasin. The population in this study was a Chronic Kidney Disease on dialysis patient diagnosed with COVID-19 by RT-PCR swab method treated at Ulin Hospital, Banjarmasin. The inclusion criteria in this study were Adults (>18 and <80 years old) diagnosed with Chronic Kidney Disease on dialysis with COVID-19 using the RT-PCR swab method who are being treated at the Ulin Hospital in Banjarmasin. Exclusion criteria were adults diagnosed with Chronic Kidney Disease on dialysis COVID-19 patients with incomplete data and subjects with end-stage malignancy.

The independent variables were levels of C-Reactive Protein and Hemoglobin. The dependent variables were survivor and non-survivor. The variables were categorized as high (>30 mg/dL) and low (≤30 mg/dL) C-Reactive Protein; low (<10 gr/dL) and high (≥10 gr/dL) Hemoglobin level.

The data collected were tabulated. Descriptive data of patients were presented in tables and percentages including patient

characteristics. Bivariate analysis with chi-square was used to determine the effect of CRP and Hemoglobin level on mortality in Chronic Kidney Disease on dialysis patients with COVID-19.

Results

The number of samples in this study was 92 subjects. The data that has been collected is checked first to ensure that all sample data has been filled in. Descriptive analysis is presented in this study based on age, gender, and characteristics of the subject data.

Table 1. Characteristics of research subject data.

Variable	Research Subject Population		
	Death (n=46)	Life (n=46)	p-value
Median age (years) (*mean*)	53,07	50,99	0,797
Gender			1,000
Male	25 (54,3%)	25 (54,3%)	
Female	21 (45,6%)	21 (45,6%)	
Comorbid			
Diabetes Mellitus	14 (30,4%)	17 (36,9%)	0,508
Hypertension	26 (56,5%)	32 (69,5%)	0,195
Heart Disease	3 (6,5%)	5 (10,8%)	0,459
Asthma	0	0	NA
COPD	1 (2,1%)	0	1,000
Cerebrovascular Disease	0	2 (4,3%)	0,495
Smoking	2 (4,3%)	4 (8,6%)	0,677

COPD: Chronic Obstructive Pulmonary Disease

Based on gender, the majority of the samples in this study were 50 (52%) male subjects, while 42 (45.6%) were female subjects. The highest mortality was found in the male sex, namely 25 (27.1%) of the sample. Based on Comorbidities, the majority of the samples in this study suffered from hypertension as many as 58 (60.4%) subjects, while 31 (33.6%) subjects had diabetes mellitus. The highest mortality was found in patients with hypertension, namely 26 (28.2%) subjects.

Table 2. Effect of *C-Reactive Protein* levels on Death.

C-Reactive Protein	Status		Total	Odd Ratio	p-value
	Death	Life			
High	29 (63%)	13 (28,2%)	42 (45,6%)		
Low	17 (36,9%)	33 (71,7%)	50 (54,3%)	4,330	0,001
Total	46	46	92		

Based on table 2, the majority of the samples in this study had a high CRP category with a total of 42 samples with 29 (63%) of them being the dead group and the remaining 13 (28.2%) from the living group. While the total samples with low CRP category were 50 samples with 33 (71.7%) of them from the living group and 17 (36.9%) from the dead group. Based on the chi-square test obtained a p-value of 0.001. This value is less than 0.05, which means that the hypothesis is accepted or has the conclusion that CRP has an effect on death in Chronic Kidney Disease patients undergoing routine hemodialysis confirmed with COVID-19 at Ulin Hospital, Banjarmasin.

The odds ratio for CRP levels to death is 4.330, meaning that patients with Chronic Kidney Disease who undergo routine hemodialysis confirmed for COVID-19 with high CRP levels have a significantly 4-fold risk of death compared to those with low CRP levels when admitted to the hospital.

Table 3. Effect of Hemoglobin levels on Death.

Hemoglobin	Status		Total	Odd Ratio	p-value
	Death	Life			
Low	23 (50%)	28 (60,8%)	51 (55,4%)		
High	23 (50%)	18 (39,1%)	41 (44,5%)	0,643	0,294
Total	46	46	92		

Based on table 3, the majority of the samples in this study had high Hemoglobin levels with a total of 41 subjects with 23 (50%) subjects from the dead group and 18 (39.1%) subjects from the living group. While the total number of a subject with low hemoglobin levels was 51 subject with 23 (50%) of them from the dead group and 28 (60.8%) from the living group. Based on the chi-square test obtained a p-value of 0.294. This value is greater than 0.05, which means that the hypothesis is not accepted or has the conclusion that hemoglobin levels do not affect death in Chronic Kidney Disease patients undergoing routine hemodialysis confirmed with COVID-19 at Ulin General Hospital, Banjarmasin.

Discussion

C-Reactive Protein is a type of protein produced by the liver that functions as an early marker of infection and inflammation. In blood, the normal concentration of CRP is less than 1 mg/dL; however, CRP increases rapidly within 6 to 8 hours and gives its highest peak within 48 hours of disease onset. Its half-life is approximately 19 hours and concentrations decrease as the inflammatory phase ends and the patient recovers. CRP prefers to bind to phosphocholine which is highly expressed on the damaged cell surface. This binding activates the classical complement pathway of the immune system and modulates phagocytic activity to clear microbes and damaged cells from the organism. When inflammation or tissue damage resolves, CRP concentrations fall, making it a useful marker for monitoring disease severity.[13]

A 2020 systemic review by Henry et al. is a meta-analysis that highlights possible biomarkers related to the severity of COVID-19, including:[14] Hematologic changes: leukocytosis and neutrophilia, lymphopenia, thrombocytopenia, decreased eosinophil count, and anemia; Biochemical changes: hypoalbuminemia, increased alanine and aspartate transaminase, total bilirubin, nitrogenous waste products, lactate dehydrogenase, creatinine kinase, creatinine kinase-myocardial band, troponin, and myoglobin; Coagulation changes: quantitative increase in D-dimer, and prothrombin time; Inflammatory syndrome: increased, CRP, ESR, ferritin, IL-6, IL-8, IL-10, and procalcitonin.

The results of this study are supported by several studies with similar populations. An increase in CRP in COVID-19 patients is thought to indicate extensive inflammation in the infected lungs, then the condition of CKD patients undergoing routine hemodialysis with compromised immunity increases the risk of severity and mortality in this population.[15]

In a study in Qatar by Savas et.al, found a significant association of increased CRP with the mortality of routine hemodialysis patients infected with COVID-19 (p=0.004). significant effect on mortality compared to CRP levels which increased upon admission in routine hemodialysis CKD patients infected with COVID-19 (p=0.020).[16] A study conducted by

Yonglong et.al., in China, found that a mild to moderate increase in CRP with a median of 16.95 mg/L was significantly associated with mortality in hemodialysis CKD patients infected with COVID-19 (p=0.006).[15] Research conducted in Germany by Lisa et.al., found increased CRP levels (≥ 30 mg/l, aOR 3.44, 95% CI 1.13–10.45, p = 0.029) significantly associated with mortality in hemodialysis patients infected with COVID-19. Anemia, thrombocytopenia, increased LDH levels, and increased CRP levels are early detection parameters to predict mortality in hemodialysis CKD patients infected with COVID 19.[17]

In a study by Tanuj et.al., which was conducted in India found factors that were independently associated with the death of hemodialysis patients infected with COVID-19, including age over 60 years, neutrophil-lymphocyte ratio (NLR) >6, CRP >20 mg/L, serum LDH >250 IU/L, CT Grades 3 and 4 and needed assisted breathing. Biochemical tests for systemic inflammation in the form of increased CRP increased LDH, and increased NLR was found to be independent predictors of death.[16]

Kenan et.al., found in their study that lymphocyte and hemoglobin levels were low, while CRP and ferritin levels were high at initial admission to the hospital in routine hemodialysis patients confirmed with COVID-19. High CRP and Ferritin levels were also found in patients who died (p. =<0.001 and p=<0.05). Cytokine storm is the cause of increased CRP levels, lymphopenia, and leukopenia which are related to the severity of COVID-19 patients.[18]

In a study in Turkey by Ebru et.al., found that at admission CKD patients infected with COVID-19 who lived had significantly lower levels of CRP, Ferritin, and D Dimer compared to those who died (p=0.001, p=<0.001, p=0.001 sequentially). CRP level > 88 mg/L (HR: 4.590; 95% CI, 1.722–12.236; p = 0.002) was significantly associated with death from COVID-19 infection in hemodialysis patients. Most of the literature finds an association between CRP and mortality in hemodialysis patients during COVID-19. However, the underlying chronic inflammatory process may influence the sensitivity and specificity of inflammatory markers such as CRP for predicting disease severity. The results of the study revealed that CRP is a sensitive biomarker for mortality (81%) but not specific enough (66%).[19]

Research by Andrei et.al., which was conducted in Romania found no significant association in the CKD population infected with COVID-19 (p=0.194).[20] Samia et.al., in their study in Pakistan, found an increase in disease severity markers such as CRP, troponin I, and ferritin in deceased patients, but not significantly related to the study population of chronic kidney disease patients infected with COVID-19 (p=0.178).[21]

Hemoglobin levels have not been shown to have an effect on mortality in the routine hemodialysis CKD patient population infected with COVID-19. Based on the data, the subjects who died were the same as those who were alive, namely 50%, while the data for living subjects with hemoglobin less than 10 gr/dl was approximately 60.8%. Several studies have shown that there is no significant effect in this population on mortality. This is thought to be because in CKD patients who are infected with COVID-19, other factors are more influential in mortality than hemoglobin. Subjects with low hemoglobin levels were found to be more in the living group, presumably because patients infected with COVID-19 have a higher risk of thrombosis, while the condition of routine hemodialysis CKD patients tends to be anemia which reduces the risk of thrombosis when infected with COVID-19.[18,20]

Kenan et.al., in a study, found low hemoglobin and lymphocyte levels, high CRP and ferritin levels at the time of admission to the hospital but did not find a specific relationship between initial admission hemoglobin levels to the death of routine hemodialysis patients infected with COVID 19 (p=0.8).[18]

In a study in Romania by Andrei et.al., found no specific relationship between hemoglobin levels and mortality in routine hemodialysis patients infected with COVID-19 (p=0.207). Another interesting finding was that the risk of death was seen in increasing hemoglobin levels (Exp(b) = 1.260). Based on the literature data shows a relationship between higher hemoglobin concentrations and the risk of poor outcomes in CKD patients. Several studies have shown that increased concentrations of Hb, hematocrit, and erythrocytes may be associated with the risk of thrombosis. In addition, it is known that COVID-19 patients show an increased risk of thrombosis. In patients with moderate to severe forms of COVID-19, elevated Hb levels in this study were associated with an increased risk of death, due to the exponential risk of thrombosis.[21]

In a study by Savas et.al., which was conducted in Qatar found age, hemoglobin level (p=0.04), disease severity, CRP levels, and routine hemodialysis were significantly related to outcomes (death or ICU admission).[16]

Lisa et.al., in their study, found predictive factors for mortality in CKD patients infected with COVID-19, including old age, increased lactate dehydrogenase > 2 × upper limit of normal, thrombocytopenia, anemia (Hb < 10 g/dl, aOR 3.21, 95% CI 1.17–8.82, p = 0.024) and very elevated c-reactive protein (CRP) (≥ 30 mg/l, aOR 3.44, 95% CI 1.13–10.45, p = 0.029). Anemia, thrombocytopenia, very high levels of LDH, and CRP (> 30 mg/dl) at admission are factors that predict a more severe course of COVID-19 in patients with renal impairment. Assessment of age, anemia, thrombocytopenia, LDH, and CRP upon early detection of SARS-CoV-2 is critical for predicting mortality in CKD patients, which may facilitate risk stratification for COVID-19 in high-risk CKD patients as early as possible.[17]

The limitations of this study are: (1) Only use patient data at the time of admission to the hospital, so the data analyzed is limited, (2)Did not assess the condition of the degree

of COVID-19 at the time of admission which could affect the variables studied, (3) It has not been possible to match the research samples, because chronic kidney disease patients undergoing hemodialysis have various comorbidities and diseases, making it difficult to find a subject with the same characteristics in large numbers.

Conclusions

This study found that increased CRP levels upon admission had an influence on the risk of death in patients with chronic kidney disease routine hemodialysis with COVID-19. Further studies are recommended to determine several markers to predict the risk of death in patients with chronic kidney disease routine hemodialysis with COVID-19.

Acknowledgements

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