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C-Reactive Protein (CRP) Levels in Stadium 5 Chronic Kidney Disease with Hemodialysis Regularly and Covid-19

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is kidney dysfunction that has occurred for more than 3 months. Patients with stage 5 CKD with hemodialysis (HD) regularly are prone to suffering from COVID-19 because hemodialysis patients can experience malnutrition, inflammation, and atherosclerosis. This study aims to determine CRP levels in stage 5 CKD with HD) regularly and COVID-19 at USU Hospital from June to October 2021.

Method: One of the inflammatory biomarkers that can be used in assessing C-Reactive Protein (CRP) levels, by looking at these levels it is expected to know how severe the inflammation of the disease is. This is an observational descriptive study with a total sampling technique. Data were obtained secondarily from the medical records of stage 5 chronic kidney disease patients with COVID-19 with HD regularly.

Result: Of the total 28 data, there were male 23 (82.1%) and female.5 (17.9%) patients. Most of them have aged 40-60 years old, and the clinical picture of patients was shortness of breath, with comorbid hypertension. In this study, the most HD duration was for 12-36 months and the highest level of CRP is > 200 mg/dl.

Conclusion: The patients with CKD with HD regularly and covid-19 have increased inflammatory markers of CRP

Keywords: CKD, Hemodialysis, CRP, Covid-19

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ABSTRAK

Latar Belakang*: Penyakit Ginjal Kronis (PGK) adalah disfungsi ginjal yang telah terjadi selama lebih dari 3 bulan. Pasien dengan PGK stadium 5 dengan hemodialisis (HD) secara teratur rentan menderita COVID-19 karena pasien hemodialisis dapat mengalami malnutrisi, peradangan, dan aterosklerosis. Penelitian ini bertujuan untuk mengetahui kadar CRP pada PGK stadium 5 dengan HD) secara rutin dan COVID-19 di RS USU terhitung pada Juni hingga Oktober 2021.*

Metode*: Biomarker inflamasi yang digunakan adalah penilaian kadar C-Reactive Protein (CRP), dengan melihat kadar tersebut diharapkan dapat mengetahui seberapa parah peradangan pada penyakit tersebut. Ini adalah penelitian deskriptif observasional dengan teknik total sampling. Data diperoleh sekunder dari rekam medis pasien penyakit ginjal kronis stadium 5 dengan COVID-19 dengan HD secara teratur.*

Hasil: *Dari total 28 data, ada pasien laki-laki 23 (82,1%) dan perempuan.5 (17,9%). Sebagian besar dari mereka telah berusia 40-60 tahun, dan gambaran klinis pasien adalah sesak napas, dengan hipertensi sebagai komorbid. Dalam penelitian ini, durasi HD paling banyak adalah selama 12-36 bulan dan tingkat CRP tertinggi adalah > 200 mg / dl.*

Kesimpulan: *Pasien dengan CKD dengan HD secara teratur dan covid-19 telah meningkatkan penanda inflamasi CRP*

Kata kunci*: PGK, Hemodialisis, CRP, Covid-19*

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1 Introduction

C-reactive protein (CRP) is a well-known biochemical marker of inflammation and has also been shown to be involved in several immunological functions.[1],[2] The usefulness of CRP measurements in the diagnosis of infection has been studied previously in several clinical settings [6],[3], and various studies have suggested that the CRP cut-off level for infection diagnosis is between 5 and 10 mg ⁄ dL.[4],[5] Chronic Kidney Disease (CKD) in the world is currently increasing and becoming a serious health problem, with the ranking of causes of death from 27th (1990) to 13th (2013).[6] According to data from the Indonesian Renal Registry (IRR) 2018, there were 132,142 active patients undergoing dialysis, the highest proportion of age is still 45-54 (30.31%) years old, the gender proportion of stage 5 CKD patients is slightly male patients (57%) than female (43%). The most CKD patients, the etiology or underlying disease of stage 5 CKD patients is hypertensive kidney disease (36%) and diabetic nephropathy (28%). The mortality rate due to hemodialysis still cannot be determined with certainty because of the lack of participation of hemodialysis units in the report data.[7] Patients with CKD have higher than expected mortality which can not only be explained by traditional risk factors of atherosclerosis like diabetes, hypertension, and dyslipidemia but other factors like inflammation, malnutrition, and

predisposition to infection are also believed to have substantial contributions to the development of cardiovascular diseases as well as morbidity and mortality.[8],[9] Patients on chronic hemodialysis are at greater risk of morbidity and mortality as compared with the general population.[10],[11] Among the several associated factors of atherosclerosis, more attention has been given to the contribution of inflammation and its consequence in hemodialysis patients. The impact and the adverse effects of the inflammatory response have been also investigated in several organs and this issue is used to explain several symptoms and signs of apparently non-inflammatory and inflammatory conditions such as osteoarthritis and chronic obstructive pulmonary disease.[11],[12] In CKD patients with high CRP levels, there is an inflammatory process triggered by uremia that affects the occurrence of malnutrition and atherosclerosis,[13] Another process during the dialysis process is due to exposure of the dialyzer membrane and dialysate.[14] According to a study by Bernardo et al, CRP levels were found with a median value of 6.50 mg/L (3.57-8.32mg/L) in stage 5 CKD patients without hemodialysis while in CKD patients with hemodialysis (HD), CRP levels were found with a median value of 9.60 mg/L (6.62-16.38 mg/L).[15] Patients with CKD with HD regularly who have comorbidities can increase the risk when hospitalized with COVID-19. A significant difference was found between the levels of inflammatory markers of patients who survived and those who died. CRP levels were significantly higher in hemodialysis CKD patients with COVID-19 who died (median value of 14.2 mg/dl) compared to patients who survived (median value of 9.3 mg/dl).[16] The cause of inflammation on morbidity and mortality in hemodialysis patients is multifactorial, the purpose of the study is to determine CRP levels in stage 5 CKD patients with HD regularly and COVID-19.

2 Method

This research was conducted at the University of North Sumatra Hospital (USU Hospital). The time of the research was carried out from June to October 2021. The sampling technique in this study used total sampling. In this technique, the total population is the number of samples. In this study, the samples taken were all patients with stage 5 CKD with COVID-19 who underwent regular hemodialysis at USU Hospital and met predetermined criteria. The inclusion criteria were, patients with chronic kidney disease undergoing regular hemodialysis, patients with COVID-19 disease, and patients who had their CRP levels checked. Exclusion criteria, namely incomplete medical record data. This study uses secondary data in the form of patient medical records

3 Result

There were male 23 (82.1%) and female.5 (17.9%) patients. Based on Table 1, most age of stage 5 CKD patients undergoing HD with COVID-19 are 40-60 (53.6%) years old.

Table 1 Frequency Distribution by Age

Age (years)	Total Patients (n=28)	Percentage (%)
<20	1	3.6
20-40	4	14.3
40-60	15	53.6
>60	8	28.6

In Table 2, there are the most clinical feature is shortness of breath by 100%, followed by fever at 96.4%, cough at 92.9%, and nausea and vomiting at 7.1%.

Table 2 Frequency Distribution Based on Clinical Features

Clinical Overview	Total Patients (n=28)	(%)
Fever	27	96.4
Nauseous	2	7.1
Vomit	2	7.1
Out of breath	28	100
Cough	26	92.9

Table 3 shows that the highest proportion of comorbid in CKD with HD regular patients and COVID-19 is hypertension 85.7%, T2DM (64.3%), and CHD (3.6%)

Table 3 Frequency Distribution Based on Comorbidity

Comorbid	Total Patients (n=28)	(%)
Hypertension	24	85.7
DM	18	64.3
CHD	1	3.6

Based on Table 4, the highest duration of hemodialysis in stage 5 of CKD with HD regular patients and COVID-19 is 12-36 (35.7%) month group.

Table 4 Frequency-Based Distribution Hemodialysis Duration

HD duration (months)	Total Patients (n=28)	(%)
< 3	8	28.6
3-12	7	25.0
12-36	10	35.7
> 36	3	10.7

In table 5. The higher level (90-200 mg/dl) is in 9 patients, the highest level of CRP (> 200 mg/dl) in patients, and the normal CRP level (<90 mg/dl) in 17 patients.

Table 5 Distribution of CRP Levels in CKD Patients with COVID-19 undergoing Regular HD

CRP (mg/dl)	Total Patients (n=28)	(%)	Died (n=7)
<90	17	60.7	1
90-200	9	32.1	5
> 200	2	7.1	1

4 Discussion

4.1 Frequency Distribution Based on Age

The youngest age of a patient with stage 5 CKD undergoing HD with COVID-19 is 14 years old, while the oldest age is 80 years. According to the IRR, there were 132,142 active patients undergoing dialysis in 2018, the highest proportion was still in the 45-54 year category with 30.31%. But in the research of Aydin Bahat et al., it was found the mean age was 60.5 years (median: 65 years). The mean age was following other studies (range between 57 and 66 years.[17] Meanwhile, in Creput et al study, it was found that the average age was 66.5 years (range 31-89 years).[18] According to Fisher et al's research, the dominant group in the study was men at 61%. And the study by Creput et al is also appropriate, namely that the majority (79%) of the 38 patients with CKD were positive for COVID-19 and underwent regular HDis male.[18] This is according to IRR data in 2018, with the proportion of sex of stage 5 CKD patients slightly more male patients with a value of 57% than female patients with a value of 43%. This proportion is under the profile of HD patients found in several other countries.[7] These study results are appropriate with other studies

4.2 Frequency Distribution Based on Clinical Features

The most common clinical picture in this study was shortness of breath at 100%, followed by fever with a percentage of 96.4% and cough with a percentage of 92.9%. According to research by Sosa et al, most patients in his study showed symptoms of fever by 71.1% and cough by 53.2%.[19] However, according to research by Aydin Bahat et al, the most common clinical features were dyspnea (in 14 patients, 56%), fever (in 13 patients, 52%), and cough (in 12 patients, 48%). It was also found that the most common symptoms of COVID-19 were dyspnea, fever, and cough in the study. This is similar to other HD and non-HD studies studied showing that the clinical picture is not different in HD patients.[17] From the above data, it can be concluded, that the most common clinical features obtained in stage 5 CKD patients with COVID-19 who undergo regular HD are shortness of breath, fever, and cough.

4.3 Frequency Distribution Based on Comorbidity

According to the study of Fisher et al, it was found that the proportion of comorbidities in CKD patients with COVID-19 who underwent Regular HD was hypertension (90%), DM (67%), CHD (55%), and pulmonary disease (35%).[16] Also according to a study by Ozturk et al, the

underlying disease in the study was hypertension (62.8), and DM (33.4%).[20] According to research by Creput et al, the underlying diseases in these patients were hypertension (95%), dyslipidemia (66%), diabetes (45%), ischemic heart disease (45%), obesity (26%), and heart rhythm dysfunction (13%).[18] In this case, according to IRR data in 2018, there were 132,142 active patients undergoing dialysis in 2018, most of whom were patients with chronic kidney disease with the proportion of the etiology or underlying disease of these stage 5 CKD patients being hypertensive kidney disease (36%) and diabetic nephropathy (28%).[7]

4.4 Frequency Distribution Based on Hemodialysis Period

Based on the table that has been presented, in this study the length of hemodialysis in stage 5 CKD patients with COVID-19 who underwent HD regularly with the highest percentage value of 35.7% in the 12-36 months. According to research by Ozturk et al, of 390 people undergoing HD, the median length of hemodialysis was around 3.4 years.[20] These study results are appropriate with other studies

4.5 Frequency-based distribution of CRP levels in CKD with HD regularly and COVID-19

In the study, the highest CRP (> 200 mg(dl) levels were in 2 patients, while according to Smolander et al, CRP levels in HD CKD patients with COVID-19 who died were in the range of 86-329 mg/L.[21] In Fisher et al, a significant difference was found between the levels of inflammatory markers of patients who survived and patients who died. CRP levels were significantly higher in CKD with HD regular and COVID-19 who died with a median value of 14.2 mg/dl compared to patients who survived with a median value of 9.3 mg/dl.[16] Based on research by Aydin Bahat et al, by examining 25 CKD patients with HD with 12 positive patients with COVID-19, high CRP levels were found with an average value of 95.6 mg/L (median: 80.7 mg/L). Meanwhile, when viewed in the group that died, high CRP levels were found with a mean value of 169 mg/L (median: 77 mg/L). Then analyzing the factors associated with intensive care and death in patients, it was found that elevated CRP was the most common abnormal laboratory parameter in patients in this study. In a general population study, COVID-19 disease severity, requiring intensive care, and mortality are associated with leukocytosis, lymphopenia, elevated neutrophils, thrombocytopenia, and elevated CRP and in HD-specific patients, mortality rates have been reported only concerning elevated CRP so far.[17] Stage 5 CKD with regular HD is prone to inflammation. Coupled with patients diagnosed with COVID-19 shows an increased vulnerability in these patients. Based on the research of Kooman et al, in all HD patients, there is a disruption of the immune response in patients on dialysis, both Natural Killer Cells, CD4 + and $CD8^+$ responses. Moreover, the condition of uremia in patients triggers a chronic immune response that reduces $CD4^+$, and $CD8^+$ cells, and inflammatory conditions, which can be the beginning of a hyperinflammatory response. HD is closely related to the persistent inflammatory process that occurs due to blood contact with dialysis membranes, dialysate fluid, vascular access, as well as hepatitis B and C infection, which can activate the inflammatory response resulting in

hyperinflammation as well. In other words, it may be hypothesized that the inability to eliminate the SARS-CoV-2 virus is due to subsequent hyperactivation of the already chronic stimulated innate immune system. So there can be very high inflammation in HD CKD patients with COVID-19.[22][12] And according to a study by Tortonese et al. HD in CKD patients can also be potentially exposed to the SARS-CoV-2 virus by going to dialysis centers which increases the risk of exposure. So it can be concluded that in this study, there is a high increase in CRP in CKD with HD regularly and COVID-19 which indicates very high inflammation in patients.[23] These study results are appropriate with other studies

5 Conclusion

Of the patients of CKD with HD regularly and COVID-19, most of them have aged 40-60 years old, male while 17.9%, of the most common clinical picture of patients in this study were shortness of breath, and comorbid hypertension. In this study, the most hemodialysis duration was for 12-36 months and the highest level of CRP is > 200 mg/dl. The patients have increased inflammatory markers of CRP and the mortality not only increased CRP level but due to many risk factors.

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