

Factors Affecting The Survival Of Hd Patients With COVID-19

M. Feldi gazaly¹, Indah Septiani pasaribu²

^{1,2}Rumah sakit universitas Sumatera utara , Indonesia
feldydr@gmail.com¹, indahpasaribu195@gmail.com²

*(Korespondensi e-mail: feldydr@gmail.com)

Abstract

Maintenance hemodialysis (HD) patients experience an increased risk of exposure to COVID-19 and complications of COVID-19 due to comorbidity conditions and the obligation to routine hemodialysis. Patients undergoing HD with end-stage kidney disease (ESRD) are particularly susceptible to SARS-CoV-2 infection and have a high mortality rate. This study aims to assess the correlation of factor actors that affect the survival of HD patients with COVID-19. The design of this study is analytical research with a cross-sectional study retrospective approach. The study was conducted from August to December 2021 at the Medical Record Installation of USU Hospital Medan. The subjects of this study were all regular HD patients at USU Hospital Medan. To assess the relationship of the correlation factor actors that influence the survival of HD patients with COVID-19, the Pearson correlation test is used and if the data is not normally distributed, then the test used is the Spearman correlation test. The results of the analysis are said to be significant when $p < 0.05$, with a degree of confidence of 95%. Pearson's correlation values for Hb and platelets with mortality were -0.282 and -0.285 but with p-values above 0.05 so the results were insignificant. The Pearson correlation value for albumin with mortality is -0.462 with a p value of 0.013 which means that the test results are significant. Spearman's correlation values for leukocytes and D-Dimer with mortality were 0.296 and 0.307 but with a p-value above 0.05 so the results were insignificant. Spearman's correlation value for CRP with mortality is 0.383 with a p value of 0.044 which means the test results are significant. Albumin levels showed a significant correlation with mortality of HD patients with COVID-19. Meanwhile, CRP levels showed a significant positive correlation with mortality of HD patients with COVID-19.

Keywords : Mortality, COVID-19, Hemodialysis patients, albumin, CRP, hemoglobin, platelets, leukocytes, D-Dimer

Abstrak

Pasien hemodialisis rumatan (HD) mengalami peningkatan risiko paparan COVID-19 dan komplikasi COVID-19 akibat kondisi komorbiditas dan kewajiban rutin hemodialisis. Pasien yang menjalani HD dengan penyakit ginjal stadium akhir (ESRD) sangat rentan terhadap infeksi SARS-CoV-2 dan memiliki tingkat kematian yang tinggi. Penelitian ini bertujuan untuk menilai korelasi aktor faktor yang mempengaruhi kelangsungan hidup pasien HD dengan COVID-19. Desain penelitian ini adalah penelitian analitik dengan pendekatan retrospektif cross sectional study. Penelitian dilakukan pada bulan Agustus hingga Desember 2021 di Instalasi Rekam Medis RS USU Medan. Subyek penelitian ini adalah seluruh pasien HD reguler di RS USU Medan. Untuk menilai hubungan korelasi faktor faktor yang mempengaruhi kelangsungan hidup pasien HD dengan COVID-19, digunakan uji korelasi Pearson dan jika data tidak berdistribusi normal, maka uji yang digunakan adalah uji korelasi Spearman. Hasil analisis dikatakan bermakna bila $p < 0,05$, dengan derajat kepercayaan 95%. Nilai korelasi Pearson untuk Hb dan trombosit dengan mortalitas adalah -0,282 dan -0,285 tetapi dengan nilai p di atas 0,05 sehingga hasilnya tidak signifikan. Nilai korelasi Pearson untuk albumin dengan

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mortalitas adalah -0,462 dengan nilai p 0,013 yang berarti hasil uji signifikan. Nilai korelasi Spearman untuk leukosit dan D-Dimer dengan mortalitas adalah 0,296 dan 0,307 namun dengan nilai p di atas 0,05 sehingga hasilnya tidak signifikan. Nilai korelasi Spearman CRP dengan mortalitas adalah 0,383 dengan nilai p 0,044 yang berarti hasil uji signifikan. Kadar albumin menunjukkan korelasi yang signifikan dengan kematian pasien HD dengan COVID-19. Sementara itu, kadar CRP menunjukkan korelasi positif yang signifikan dengan kematian pasien HD dengan COVID-19.

Kata kunci : Mortalitas, COVID-19, Hemodialysis patients, albumin, CRP, hemoglobin, platelets, leukocytes, D-Dimer

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome due to coronavirus 2 infection (SARSCoV-2), has spread rapidly around the world and has become a global pandemic (F. Wang et al., 2021);(Aoun et al., 2021). On February 19, 2021, more than 100 million confirmed cases and more than 2 million deaths were found. Information about the epidemiology of COVID-19 in hemodialysis (MHD) maintenance patients is still limited. MHD patients may be at increased risk of COVID-19 infection due to various comorbidity conditions (Chen et al., 2021);(Albalate et al., 2020). All patients come in with lymphopenia, and the most common thoracic radiographic disorder is ground glass opacity (R. Wang et al., 2020);(Nassar et al., 2022).

Maintenance hemodialysis (HD) patients experience an increased risk of exposure to COVID-19 and complications of COVID-19 due to comorbidity conditions and the obligation to routine hemodialysis. In addition, the logistical aspect of HD can increase the risk of disease transmission (Ghonimi et al., 2021);(Zou et al., 2020). This includes frequent meetings in health care facilities with other patients and staff, the patient's physical proximity during HD, and transportation to or from HD sessions. Mortality in this very fragile population is quite high (21% of affected patients, which represents 4% of all patients in health centers) (Creput et al., 2020);(Haarhaus et al., 2021).

Patients undergoing HD with end-stage kidney disease (ESRD) are particularly susceptible to SARS-CoV-2 infection and have a high mortality rate (Mohtashami et al., 2022);(Kikuchi et al., 2021). Pasien HD with significant comorbidities, such as diabetes, hypertension, and cardiovascular disease and older age, experience a higher risk of becoming a disease that severe (Le et al., 2020);(Byeon et al., 2021). Second, HD patients have an abnormal immune system response due to a uremic state, resulting in impaired response and a pro-inflammatory state (Herrmann et al., 2022);(Del Valle et al., 2020). Due to the immunocompromised status, the clinical presentation may differ from that of the general population, which can increase the difficulty of diagnosis and treatment of HD patients (Neumann-Podczaska et al., 2020);(Zhang et al., 2020);(Kumar & Dey, 2020). Pasien HD must travel from home to hospital regularly and interact with doctors, nurses, medical workers and other patients in the common room for at least 12 hours each week, which can lead to widespread cross-contaminatio (Ok et al., 2021);(Ljungman et al., 2021);(Jakubíková et al., 2021).

METHOD

The design of this study is a descriptive study with a cross-sectional study retrospective approach. The study was conducted from August to December 2021 at the Medical Record Installation of USU Hospital Medan. The subjects of this study were all regular HD patients at USU Hospital Medan. Patients with incomplete data will be excluded from the study. The re-

search data is taken from the patient's medical records and then processed using the SPSS application. The study was conducted at the Internal Medicine Polyclinic of the University of North Sumatra Hospital. The research time is 1 year after obtaining approval from the Research Ethics Committee of the University of North Sumatra.

The participants involved in this study were patients who underwent regular HD and suffered from Covid 19. Exclusion criteria for HD patients traveling (temporarily) at USU Hospital Medan and incomplete medical record data. The research data is taken from the patient's medical records and then processed using the SPSS application. The normality test was carried out first with the Shapiro-Wilk test. To assess the correlation factor actors that affect the survival HD patients with COVID-19 used the Pearson correlation test and if the data is not normally distributed, then the test used is the Spearman correlation test. The results of the analysis are said to be significant when $p < 0.05$, with a degree of confidence of 95%.

RESULT

Table 1. Demographic and Comorbidity Data

| | Total (N = 28) | Live (n=21) | Die (n = 7) | p value² |
|-------------------------------------|---------------------------|------------------------|------------------------|--------------------------------|
| Age, years | 53 (14-65) | 53 (14-64) | 54 (39-65) | 0.473 |
| Gender, n (%) | | | | |
| Woman | 7 (25) | 7 (33.3) | 0 (0) | 0.141 |
| Man | 21 (75) | 14 (66.7) | 7 (100) | |
| Blood pressure | | | | |
| Systole | 130 (110-165) | 130 (110-160) | 150 (130-165) | 0.061 |
| Diastole | 90 (70-95) | 90 (70-95) | 90 (80-95) | 0.976 |
| Old HD, months | 12 (1-72) | 18 (1-72) | 3 (1-60) | 0.155 |
| URR | 75.41 (63.5-84.38) | 76 (63-84) | 70.5 (63-78) | 0.00 |
| History of Hypertension, n (%) | 26 (92.9) | 20 (95.2) | 6 (85.7) | 0.444 |
| History of Diabetes, n (%) | 14 (50) | 9 (42.9) | 5 (71.4) | 0.385 |
| History of Other Diseases | 3 (10.7) | 2 (9.5) | 1 (14.3) | |
| Heart Disease, n (%) | 1 (3.6) | 1 (4.8) | 0 (0) | 1.00 |
| Follicular lymphoma grade II, n (%) | 1 (3.6) | 1 (4.8) | 0 (0) | 1.00 |
| Glomerulonephritis, n (%) | 1 (3.6) | 0 (0) | 1 (14.3) | 0.25 |

Table 1 shows that out of a total of 28 patients, 7 people (25%) died. Male patients were found to be more numerous than women in a ratio of 3:1. There was no general average difference between living and deceased patients. Almost all patients have hypertensive comorbidities, followed by diabetes mellitus in half of patients. The URR test had significant differences between the two groups, where the surviving group had a higher value than the deceased group.

Table 2. Basic Laboratory Data

| Variable | Total (N = 28) | Live (n=21) | Die (n = 7) | p value |
|-----------------------------------|-----------------------|----------------------|---------------------|---------|
| SpO2, % | 98 (94-99) | 98 (95-99) | 98 (94 – 99) | 0.319 |
| Hemoglobin, g/dL | 9.25 (7-13.5) | 9.3 (7.7-13.5) | 8.9 (7.0-11.0) | 0.00 |
| Leukocytes, x 10 ³ /mL | 11.8 (4.48-28.62) | 11.7 (4.48-18.03) | 17.6 (5.39 – 28.62) | 0.124 |
| Platelets, x 10 ³ /mL | 251 (80 – 451) | 267 (127 – 451) | 205 (80 – 416) | 0.00 |
| Album, g/dL | 3.05 (2.28-3.5) | 3.1 (2.28 – 3.5) | 2.9 (2.3 – 3.2) | 0.00 |
| CRP, mg/dL | 75.7 (12.4 – 252.8) | 67 (12.4 – 252.8) | 120 (20 – 211.60) | 0.047 |
| D-dimer, ng/mL | 1000 (20.87 – 15.710) | 900 (20.87 – 2680) | 2730 (250 – 15710) | 0.111 |
| Urea, mg/dL | | | | |
| Pre HD | 133.45 (56.12 – 305) | 131.2 (59.6 – 224.5) | 197.7 (56.12 – 305) | 0.277 |
| Post HD | 40.95 (18 – 76) | 34.1 (19.1 – 60.5) | 52 (18 – 76) | 0.053 |
| Creatinin, mg/dL | 9.625 (0.84-24.19) | 8.9 (0.8 – 19.7) | 9.9 (3.8 – 24.1) | 0.00 |

Laboratory examinations in both groups are shown in table 2. The results obtained that hemoglobin, platelet, albumin, CRP, and creatinine levels showed significant differences between the deceased and survival groups ($p < 0.05$). The living group had higher average hemoglobin, platelet, and albumin levels, while creatinine levels were lower than the deceased group. In the deceased group, the increase in CRP levels was almost twice as high as in the live patient group.

Table 3. Normality Test Table of Factors Affecting Mortality of HD Patients with COVID-19

| | Kolmogorov-Smirnov P-value | Shapiro-Wilk P-value |
|-----------|-------------------------------|-------------------------|
| Hb | 0,200 | 0,282 |
| Leukocyte | 0,200 | 0,045 |
| Platelets | 0,200 | 0,480 |
| Albumin | 0,031 | 0,051 |
| D-Dimer | 0,001 | 0,001 |
| CRP | 0,200 | 0,010 |

In this study with a total sample of 28, the normality test used was Shapiro-Wilk. Normality test results for Hb, platelets, and albumin are above 0.05, which means that the data is distributed normally so that a Pearson correlation test will be carried out. Normality test results for leukocytes, D-Dimer, and CRP are below 0.05, which means that the data is not normally distributed so the Spearman correlation test will be carried out.

Table 4. Table of Pearson Correlation Test Results of Factors Affecting Mortality of HD Patients with COVID-19

| | Pearson Correlation Value | P-value |
|--------------------------|---------------------------|---------|
| Hb with mortality | -0,282 | 0,146 |
| Platelets with mortality | -0,285 | 0,142 |
| Albumin with mortality | -0,462 | 0,013 |

In table 4, pearson correlation values for Hb and platelets were obtained with mortality being -0.282 and -0.285 but with a p value above 0.05 so the results were insignificant. The pearson correlation value for albumin with mortality is -0.462 with a p value of 0.013 which means that the test results are significant.

Table 5. Table of Spearman Correlation Test Results of Factors Affecting Mortality of HD Patients with COVID-19

| | Spearman Correlation Value | P-value |
|---------------------------|----------------------------|---------|
| Leukocytes with mortality | 0,296 | 0,126 |
| CRP with mortality | 0,383 | 0,044 |
| D-Dimer with mortality | 0,307 | 0,112 |

In table 5, Spearman correlation values for leukocytes and D-Dimer were obtained with mortality being 0.296 and 0.307 but with a p value above 0.05 so the results were not significant. Spearman's correlation value for CRP with mortality is 0.383 with a p value of 0.044 which means the test results are significant.

DISCUSSION

T-cell immunity is a major factor in recovery from SARS-CoV infection. Since the status of uremia is associated with impaired function of lymphocytes and granulocytes, abnormalities of the immune system can alter the response to SARS-CoV infection. This is of particular concern to patients who are routinely hemodialysis due to the high risk of exposure. COVID-19 positive dialysis patients experienced lymphopenia and serum levels of inflammatory T cells, helper T cells, killer T cells, natural killer cells, and cytokines and clinical diseases were lower compared to non-HD patients with COVID-19 (Kumar & Dey, 2020). COVID-19-related mortality rates range from 1.4 to 8% in the general population. A recently published meta-analysis of 29 international studies showed that the overall mortality rate was 22.4%, and fever was the dominant clinical manifestation in HD patients with COVID-19 (Adam & Alarifi, 2021).

The unfavorable prognostic effects of male sex and metabolic syndrome in SARS-CoV-2 infection have been attributed to a low-level chronic inflammatory state and an irregular immune response, which triggers a "cytokine storm" so that SARS-CoV-2 infection becomes lethal. Old age is also associated with a pro-inflammatory and procoagulant condition called inflammatory," shedding light on the strong correlation between age and death from COVID-19. Premature aging in hemodialysis patients caused by uremic states, intestinal dysbiosis, and oxidative stress (Long et al., 2022).

The death rate of COVID-19 infection varies between countries, ranging from 35.4 per million inhabitants (Southeast Asia) to 904.4 per million inhabitants (Americas). Chronic kidney disease is associated with an increased risk of COVID-19 infection. Patients undergoing hemodialysis (HD) are patients with immune dysregulation due to uremia, comorbidities, and biocompatibility related to dialysis procedures so that the incidence of viral infections, especially COVID-19, is found to be high among HD patients. A systematic

review and meta-analysis of 29 international studies, on 3,261 confirmed cases of COVID-19, drawn from 396,062 HD patients, found that the incidence of COVID-19 infection was 7.7% and the mortality rate was 22.4% where these results were higher than those of the general population. The increased risk of COVID-19 was found to be 15.4 times compared to the normal population, with patients also older than the general population. The median age of patients was slightly greater (63.5 years) in non-Asian patients compared to Asian patients (61.8 years). Some of the risk factors for high mortality in HD patients, including greater age, male sex, underlying heart or lung disease, diabetes and hypertension and the use of mechanical ventilation. Cough is associated with the risk of death in HD patients and fever predicts death in HD patients. Other prognostic factors include *vintage* dialysis, thrombocytopenia, lymphopenia, and elevated levels of LDH or CRP (Bobdey et al., 2021).

Albalate conducted a study with 90 HD patients of which 37 (41.1%) patients were infected with COVID-19. Fever is the most commonly found symptom, 50% of patients have lymphopenia and 18.4% <95% saturation O₂. Sixteen (43.2%) patients required hospitalization and 6 (16.2%) died. ⁷ Ghonimi studies showed 76 out of 1064 dialysis patients were diagnosed with COVID-19 (average age 56±13.6 years, 56 hemodialysis and 20 peritoneal dialysis, 56 patients were male). During the study period, 7.1% of all dialysis patients were infected with COVID-19. Male patients had twice the incidence of COVID-19 compared to women (9% versus 4.5%; p<0.01, respectively). The most common symptoms were fever (57.9%), cough (56.6%), and shortness of breath (25%). Pneumonia is diagnosed in 72% of dialysis patients with COVID-19. High severity was manifested with 25% of patients requiring intensive care, 18.4% with ARDS, 17.1% requiring mechanical ventilation, and 14.5% requiring inotropes. The average length of hospital stay is 19.2 ± 12 days. Deaths from COVID-19 are 15% (Ghadamgahi et al., 2021).

Dialysis patients are a particularly vulnerable population and hemodialysis centers are high-risk areas in the COVID-19 epidemic. "Idiopathic" lymphopenia and/or elevated levels of C-reactive protein should lead the physician to a diagnosis of COVID-19 and, if possible, should be followed by diagnostic testing with reverse transcriptase-polymerase chain reaction as well as strengthening contamination barrier measures. ³ The incidence rate, based on PCR testing, varies between 2% and 20%, with considerable regional variation. The average cumulative incidence of <10% in dialysis patients, based on testing of IgG antibodies, while T cell immunity showed a higher cumulative incidence than reflected by antibody serology. The case fatality rate in the HD cohort varied between 20% and 35% in previous reports, which is more than double higher for COVID-19 in the general population, identifying HD patients as a high-risk population (Aoun et al., 2021).

Compared to the group of HD patients with COVID-19 who died, the living group had a higher albumin level (*weighted mean difference* (WMD) of 3.82.95% CI [1.98, 5.66], p<.0001, I² = 55%), a lower leukocyte count (WMD 1.45.95% CI [-2.16, - 0.75], p<.0001, I² = 50%) and higher platelet counts (WMD 16.06, 95% CI [0.86, 31.26], p=0.04, I²= 0%). The hemoglobin level and platelet count did not show significant differences between the survivors and non-survivors (hemoglobin: WMD 0.18.95% CI [- 4.72,2.56], p=.56, I²= 38%). A higher leukocytes and platelets, and hypoalbuminemia were associated with higher mortality rates in HD patients. Platelet activation plays an important role in inflammation. Low platelet levels contribute to the severity of COVID-19. Damaged lung tissue will lead to platelet activation and thrombus formation, leading to platelet consumption. As the number of leukocytes increases, it may be commonly associated with bacterial co-infection that exacerbates the disease. In HD patients, albumin is an indicator of the patient's nutritional status and is associated with complex malnutrition-inflammatory syndrome, which is also an important risk factor for cardiovascular death (Chen et al., 2021).

Ebrahimi assessed that 428 HD patients with COVID-19 who were eligible for the analysis, 221 (52%) had died. Cox-adjusted PH results showed that the number of ultrafiltration volumes (UF) (HR = 1.146, P = 0.049), the number of WBC (HR = 1.039, P = 0.001), the number of RBCs (HR = 0.817, P = 0.044), MCHC (HR = 0.887, P = 0.001), and serum albumin (HR = 0.616, P <0.001) had a significant effect on mortality. The log-normal model of AFT shows that WBC (ETR = 0.982, P = 0.018), RBC (ETR = 1.131, P = 0.023), MCHC (ETR = 1.067, P = 0.001), and serum albumin (ETR = 1.232, 0.002). has a significant influence on survival time. As the number of WBC increases, the survival time of patients undergoing HD decreases. For each unit increase in the number of WBC (within 103/mikl), the survival time of HD patients was reduced by about 2%. Anemia and low hemoglobin levels are indicators of lower survival in HD patients. for every 10⁶ per microliter increase in the number of RBCs, the patient's survival time increased by 13%. As serum albumin increases, the probability of survival as well as survival time increases. Due to the increase in g/dl in serum albumin, the survival time of HD patients increased by about 23%.^{11th}

Higher white blood cell counts, longer PT times, and higher D-dimer levels were also found in hemodialysis patients with poor prognosis after being infected with the coronavirus. These results suggest that severe inflammatory damage and activation of the coagulation system results in a poor prognosis. Hepatocyte damage was also observed in hemodialysis patients who died of COVID-19. In addition, hemodialysis patients are also accompanied by damage to cardiomyocytes, which is mainly manifested by an increase in the level of troponin I. Nevertheless, only some hemodialysis patients with an increase in troponin I develop into acute myocardial infarction. But a report by Zou et al, shows after treatment with anti-bacterial, antiviral, anticoagulation, and platelet aggregation inhibition, this patient eventually recovered.⁹ Factors associated with an increased risk of death were identified as being over 70, having a long dialysis duration, oxygenation requirements, high CRP in laboratory data at diagnosis, high BMI, and complications of peripheral artery disease. In dialysis patient reports in the United States, complications of peripheral artery disease were identified as an important risk factor. In addition, hypercoagulation and vascular damage have been reported to be involved in the pathogenesis of COVID-19, and thrombosis and increased inflammatory response with CRP have been reported to be associated with worsening symptoms.

Aoun's study showed the mortality rate of HD patients with COVID-19 was 23.8% after an average duration of 6 (IQR, 2 to 10) days. Adjusted regression analysis showed a higher risk of death among older patients (odds ratio = 1.038; 95% confidence interval: 1.013, 1.065), patients with heart failure (odds ratio = 4.42; 95% confidence interval: 2.06, 9.49), coronary artery disease (odds ratio = 3.27; 95% confidence interval: 1.69, 6.30), multimorbidity (odds ratio = 1.593; 95% confidence interval: 1.247, 2.036), fever (odds ratio = 6.66; 95% confidence interval: 1.94, 27.81), CRP above 100 mg/L (odds ratio = 4.76; 95% confidence interval: 1.48, 15.30), and pneumonia (odds ratio = 19.18; 95% confidence interval: 6.47, 56.83). Hypotension during dialysis was a poor prognostic factor in our patients consistent with the results of a study of 108 patients from London. *Cut off* CRP above 100 mg/L as a bad prognostic marker. This is in line with French research from the Paris region that found an association between CRP > 175 mg/L and higher mortality. This is also in keeping with research from Wuhan, China, and from Turkey that identified high CRP as a predictor of higher mortality. These studies also found a low neutrophil/lymphocyte ratio as a predictor of mortality (Aoun et al., 2021).

CONCLUSION

Albumin levels showed a significant correlation with mortality of HD patients with COVID-19. Meanwhile, CRP levels showed a significant positive correlation with mortality of HD patients with COVID-19.

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