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Does end stage renal disease increase severity of COVID-19?

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Background: End stage renal disease (ESRD) patients are vulnerable to contract corona virus disease-19 (COVID-19), and they have higher risk of deterioration and mortality rate compared to general population. There are studies on COVID-19 in end stage renal disease (ESRD) patients showing the low rates of deterioration, most of which did not develop into severe pneumonia.

Objective: Compare the clinical, laboratory, and radiological findings in COVID-19 patients with and without ESRD and to identify the mortality risk factors in those with ESRD.

Methods: We conducted a cross-sectional study involving 87 COVID-19 patients, consisted of 43 ESRD and 44 non-ESRD. Data taken included age, gender, the amount of co-morbid, oxygen saturation when they first arrived, COVID 19 symptoms (mild/moderate/severe-critical), and the data of patients who died.

Result: Severe-critical clinical manifestations of COVID-19 were more common in those with ESRD vs those without (p=0.012). However, the mortality was not significantly different. Absolute neutrophil count and neutrophil-lymphocyte ratio (NLR) were significantly higher in those with ESRD. As many as 24% COVID patients died, in which 11% are ESRD patients, and 13% non-ESRD. Multivariate analysis showed that NLR ≥1 had 1.3 times higher death risk compared to NLR<1.

Conclusion: Severe-critical clinical manifestations of COVID-19 were more commonly found in ESRD patients. The mortality rate was not significantly different between the ESRD and non-ESRD. In COVID-19 patients with ESRD, NLR ≥1 had 1.3 times higher death risk compared to NLR<1. High NLR is a risk factor for higher mortality in ESRD patients.

Keywords: COVID-19; ESRD; SARS-CoV-2; Ct-value; NLR.

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INTRODUCTION

Pre-exisiting chronic conditions in COVID-19 patients are associated with increased disease severity, morbidity and mortality.[1-5] ESRD is one of the chronic condition, that can put the patients in higher risk of deterioration and the increase of mortality. A study by Wang et al, 2020, found that patients with diabetes, cardiovascular disease (CVD) and chronic kidney disease (CKD) were associated with poor outcomes.[6] This might be caused by ESRD being the independent factor of mortality increase, immune response disorder, the decrease of cytokines and uremic toxin clearance, and comorbidity.[6,7] In New York, after massive tests were administered to the hemodialysis (HD) patients, 11%-26% were infected, 26% Italy, 24% Spain, and 3.5% Wuhan-China. The mortality rate based on the report from *European Renal Association-European Dialysis and Transplant Association* (ERA-EDTA) was 20% .[8] The mortality in New York reached 24-27%, in China 43%, Spain 10%, and there were 0% mortality in Canada and Turkey.[6,9]

Early study of COVID-19 in ESRD patients undergoing HD showed the low level of severity, with most of them not developing into severe pneumonia. This might be caused by the cellular immunity dysfunction, and the inability to form cytokine storm.[10,11] Chan L et al, 2021, stated that dialysis patients showed lesser and milder symptoms, which did not develop into severity, thus did not require more ICUs.[10] To this day, the studies related to the differences of clinical manifestation, laboratory result, radiological images, and mortality of COVID-19 in ESRD patients are still limited. The objectives of this study were to compare the clinical, laboratory and radiological findings of COVID-19 between patients with ESRD and non-ESRD and to identify the mortality risk factors in COVID-19 patients with ESRD.

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MATERIALS AND METHODS

This study was cross sectional, done by using consecutive sampling of the inpatient unit medical records from Lavalette Hospital, Malang, Indonesia. Data taken included age, gender, the amount of co-morbid (HT, DM, PVD, CAD, CVA, CLD, malignancy, CHF, COPD), oxygen saturation when they first arrived, COVID 19 symptoms (mild/moderate/severe-critical), and the data of patients who died.

The subjects were patients ESRD and non-ESRD patients with COVID-19 hospitalized between March to December 2020. COVID-19 diagnosis was based on clinical findings, radiological, laboratory examinations, and positive RT-PCR for SARS-CoV-2. The diagnosis of ESRD was based on the GFR calculation <15ml/min/1.73m^2 and abdominal ultrasonography (USG). COVID-19 symptoms were divided into mild (without viral pneumonia and hypoxia), moderate (clinical symptoms of pneumonia, with SpO2 ≥93%), severe (clinical symptoms of pneumonia, respiratory rate >30x/minute, respiratory distress, SpO2 <93%), critical (ARDS, sepsis, septic shock). The inclusion criteria was COVID-19 patients with 18 years as minimum age, with or without ESRD. The exclusion criteria was COVID-19 patients with acute renal failure. This study has been approved by the Health Research Ethical Committee from Dr. Saiful Anwar General Hospital, Malang, Indonesia.

The laboratory tests compared were complete blood counts (hemoglobin, leukocytes, platelets, neutrophils, lymphocytes, and NLR, using hematology analyzer Sysmex XN), and first-day RT PCR CT-value, negative RT PCR results on the seventh day, and chest X-Ray image (infiltrate/consolidation, bilateral/unilateral, peripheral/central, pleural effusion). The Ct-value was calculated using the patient's numerical result divided by the cutoff value, as the RT PCR cutoff value can vary depending on the reagent kit used.

To compare the variables in the two groups, statistical analysis was performed with the Chi-square or Fisher-exact test, Mann-Whitney, Kruskal-Wallis. Multivariate logistic regression analysis was used to determine the risk factors related to death. All tests were two-tailed, α=0.05.

RESULTS

Table 1 showed the basic characteristics of the subjects.

Each of the laboratory and radiological result was shown on Table 2. The clinical outcome was presented in Table 3.

Multivariate logistic regression analysis or risk factors related to the death of ESRD patients showed that NLR was the only factor affecting death (p=0.032). Odd ratio (OR) obtained were 1.331. Odd ratio value was on the confident interval (CI) range 95% (1.025-1.728).

DISCUSSION

A high clinical suspicion of COVID-19 in ESRD patients is necessary, because is common in ESRD patients whereas the febrile response may be blunted.[12] Clinical manifestations of COVID-19 patients with ESRD were more severe compared to non-ESRD.[13,14] There were 58.1% ESRD

Table 1. The basic characteristics of the subjects.

Characteristics	ESRD (n=43)	Non ESRD (n=44)	p-value
Age (mean, in years)	56.8	51.1	0.281
<65 yrs, n (%)	31 (46.3%)	36 (53.7%)	
≥65 yrs, n (%)	12 (60.0%)	8 (10.1%)	
Female, n (%)	23 (59.0%)	16 (41.0%)	0.108
Number of comorbidities per patient, n (%)			
≤1	2 (5.1%)	37 (94.9%)	-
2 to 3	36 (83.7%)	7 (16.3%)	<0.001
>3	5 (10%)	0 (0%)	<0.001
O2 saturation on the first day, n (%)			
<93%	21 (50.0%)	21 (50.0)	0.918
≥93%	22 (48.9%)	23 (51.1%)	
Hospitalization duration, in days (median (IQR))	15 (1-35)	13 (1-38)	0.782
COVID-19 symptoms, n (%)			0.035
Mild	2 (4.7%)	9 (20.0%)	
Moderate	16 (37.2%)	19 (42.2%)	0.106
Severe-critical	25 (58.1%)	17 (37.8%)	0.012
Mortality n (%)	10 (47.6%)	11 (52.4%)	0.849

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Table 2. Laboratory and radiological results.

Laboratory Results	ESRD	Non ESRD	p-value
Laboratory,median (IQR)			
Hb (g/dL)	8.3 (3.4-13.6)	13.8 (6.1-16.10)	<0.001
Leukocytes, (/µL)	7920 (2930-34850)	8170 (2040-23460)	0.61
Platelets, (/µL)	183x10³ (53x10³ - 433x10³)	281x10³ (42 x10³ -512 x10³)	<0.001
Neutrophils (/µL)	6225.1 (4561.9-7381.4)	5964.1 (3153.6-7328.5)	0.049
NLR	6.33 (2.11- 24.27)	4.54 (0.74-16.92)	0.024
Lymphocytes	12.10 (3.8-27.3)	17 (5.3-52.6)	0.058
Chest x ray, n (%)			
Infiltrate	41 (51.9%)	38 (48.1%)	0.11
Consolidation	5 (71.4%)	2 (28.6%)	0.212
Bilteral	29 (58%)	21 (42%)	0.045
Unilateral	12 (40%)	18 (60%)	0.23
Peripheral	16 (53.3%)	14 (46.7%)	0.542
Central	34 (60.7%)	22 (39.3%)	0.003
Pleural Effusion	4 (100%)	0 (0%)	0.047
SARS-CoV-2 PCR			
CT value Day 1, median (IQR)	0.86 (0.49-1)	0.91 (0.54-0.99)	0.075
CT value Day>7, mean (IQR)	0.98 (0.62-1)	0.99 (0.87-1)	0.261
Negative PCR on Day 7, N (%)	24 (57.1%)	18 (42.9%)	0.834

Table 3. Clinical outcome.

	ESRD patients (n=43)	Non ESRD (n=45)	p-value
Hospitalization duration, median (IQR) day	15 (1-35)	13 (1-38)	0.782[b]
Deaths n (%)	10(47.6)	11 (52.4)	0.849[a]
CT value Day 7, median (IQR)	0.917 (0.62-1.00)	0.964 (0.87-1.00)	0.261[b]
Negative PCR negatif Day 7, n (%)	24 (57.1)	18(42,9)	0.834[a]

patients with severe-critical COVID-19 symptoms. This might be caused by the high comorbidity in ESRD patients, worse nutritional status, anemia, which caused the group to undergo clinical deterioration.[10] Despite the worse clinical manifestation in ESRD patients, the mortality rate was not significally different compared to non ESRD (47.6% vs 52.4% ; p=0.849). Kooman stated that the case mortality rate in ESRD patient is 30%.[15]

In this study, the average of lymphocyte counts in ESRD patients was lower than non-ESRD, but not significant. However, Ma *et al* stated a contrasting result.[16]

Ct-value in ESRD patients were insignificantly lower compared to non-ESRD. High Ct-value shows lower viral load on the surface close to viral shedding.[17] Other references stated that Ct-value is not correlated directly or indirectly with the degree of severity. Ct-value can be opposite to the viral load and transmissibility.[18-20]

The CXR (chest x-ray) results for COVID-19 patients with ESRD showed more unilateral and central infiltrate image, compared to non-ESRD. Generally, CXR in COVID-19 pneumonia patients show patchy or diffuse reticulonodular opacity and consolidation, with basal, peripheral, and predominant bilateral with 68.1% sensitivity, but can be unilateral.[21,22]

Neutrophil to lymphocyte ratio (NLR), is one of of the systematic inflammatory response indicators.[23] Universally, COVID-19 patients with ESRD have lymphopenia and 21% higher mortality rate.[24] In this study, NLR value affects the mortality (p=0.032). Odd ratio (OR) obtained were 1.331 which means that patients with NLR =1 have 1.331 times more mortality risk compared to NLR <1. The previous study found that elevated NLR can be used as independent prognostic biomarker and evaluate the severity of clinical symptoms for COVID-19 patients. The NLR limit of 3.3 showed a prognostic change in clinical symptoms from mild to severe.[25]

This study has several limitations such as not provided comorbidity detail, baseline eGFR before infected COVID. The futere investigation are needed to improve the evidence.

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CONCLUSION

ESRD patients have higher severe-critical clinical manifestations compared to non-ESRD, however there is no difference in mortality between the two groups. High NLR is a risk factor for higher mortality in ESRD patients.

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