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Clinical and laboratory comparison between End-Stage Kidney Disease patients with and without COVID-19: a cross-sectional study in a top referred hospital of West Nusa Tenggara

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ABSTRACT

Background: The initial presentation of hospitalized End-Stage Kidney Disease (ESKD) patients with and without coronavirus disease 2019 (COVID-19) is similar and can overlap. We aimed to compare clinical dan laboratory characteristics of the COVID-19 positive and negative patients to help clinicians screen and differentiate hospitalized ESKD patients.

Methods: We reviewed data from the medical record of ESKD patients hospitalized between May 1st, 2020, and April 30th, 2021. The study comprised all suspected COVID-19 patients. The COVID-19 positive was based on results from RT-PCR for SARS-CoV-2. The bivariate analysis was used to compare the positive and negative groups. The association of all characteristics and diagnosis of COVID-19 were then evaluated by multivariable analysis.

Results: There was twenty-nine percent of confirmed COVID-19 in 176 ESKD patients. The proportion of dyspnea, pulmonary edema, pleural effusion, and cardiomegaly were lower in the COVID-19 positive group. Diastolic blood pressure, pulse rate, white blood cell differential counts, and potassium were lower in the COVID-19 positive group. Using a multivariate analysis, eosinophil count <0.04 x$10^3\mu$l (P<0.001, OR 3.50, 95%CI:0.123-0.665), monocyte count <0.69 x$10^3\mu$l (P=0.004, OR 2.54, 95%CI:0.166-0.931), and neutrophil-to-lymphocyte ratio (NLR) <3.13 (P=0.044, OR 3.18, 95%CI:0.102-0.968) were associated with the presence of COVID-19.

Conclusions: Leukocyte differential count and chest x-ray should be evaluated as an initial screening of COVID-19 in hospitalized ESKD. Low levels of monocyte and eosinophil count and mild elevation of NLR were associated with COVID-19 in ESKD patients.

Keywords: COVID-19, ESKD, eosinophil, monocyte, NLR

INTRODUCTION

A new coronavirus, first discovered in China at the end of December 2019, can spread from person to person. The causative agent of Coronavirus Disease 2019 (COVID-19) is Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[1] COVID-19 can affect various organs such as the lungs, kidneys, heart, blood, and gastrointestinal tract.[2] End-Stage Kidney Disease (ESKD) patients are a potential target of SARS-CoV-2 infections because they have impaired immune systems and many comorbidities.[3] Most developing countries have variable access to health care. Most hinterlands in this country do not have access to the diagnostic modality of COVID-19, such as Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and chest computed tomography scan. They also do not have isolation hemodialysis (HD) treatment.

During the pandemic, every hospitalized patient, including ESKD, should be screened for COVID-19.[4] Several studies have reported the characteristics and outcomes of COVID-19 in ESKD or dialysis patients.[3,5–9] However, there is limited information on the differences between positive and negative COVID-19 in the ESKD population. A study showed that the most common symptoms of COVID-19 in ESKD patients were fatigue and anorexia, just like uremic symptoms.[9] Uremic patients tend to exhibit less prominent or more significant variations in clinical symptoms of COVID-19.[2] ESKD patients might be missed in the process of differentiation and screening, so the diagnosis of COVID-19 in this population can be challenging. Identifying ESKD patients admitted to resource-limited hospitals is crucial because of solely uremic complications or COVID-19 infection. Patients with COVID-19 need more resources such as an isolation room, portable dialysis machine, negative pressure room, dedicated staff, and personal protection equipment.[10] Therefore, we conducted this retrospective study of hospitalized ESKD patients in our hospital and compared the COVID-19 positive and negative groups. Risk factors associated with COVID-19 in ESKD patients were further explored. The result of this study might guide first-line clinicians in diagnosing COVID-19 in ESKD patients in resource-limited settings.

METHODS

It is a cross-sectional analytic study. Data were extracted from patients' medical records in West Nusa Tenggara General Hospital (WNTGH) between May 1, 2020, and April 30, 2021. WNTGH is the top referral hospital in West Nusa Tenggara Province, located in Lombok Island, Indonesia. All ESKD patients with suspected COVID-19 were included in this study. Criteria of suspected COVID-19 were based on the COVID-19 management guidelines from the Indonesia Ministry of Health's 5th revision of 2020, including any upper respiratory tract infection symptoms and history of contact with COVID-19 cases. Exclusion criteria included patients discharged against medical advice and patients with incomplete RT-PCR results. The diagnosis of COVID-19 is based on the WHO interim guidance and the Indonesian guideline of COVID-19 management.[4,11] The ESKD patients were divided into two groups based on the result of the RT-PCR test. Positive cases are defined as suspected COVID-19 with a single positive RT-PCR test. Negative cases are suspected COVID-19 with negative in two consecutive RT-PCR tests 24 hours apart. The data collected included demographics, history of contact, routine hemodialysis status, underlying ESKD,

characteristics at presentation such as comorbidities, complications, symptoms, and signs, and laboratory and chest x-ray findings. The normal ranges of laboratory data were based on institutional standards. Three researchers collected medical record data. Discrepancies in the data were confirmed and discussed between the three researchers.

In the analysis, differences in quantitative parameters between COVID-19 and non-COVID-19 groups were assessed by the independent t-test, or the Mann-Whitney U test, whereas differences in qualitative parameters in both groups were assessed by the X2 test, or Fisher's exact test, as appropriate. Table 1 shows the risk factors associated with COVID-19 as dichotomous independent variables. The correlation between the risk factors and diagnosis of COVID-19 was analyzed by Spearman's correlation and continued by logistic regression. All data analyses were performed by SPSS statistical software package (version 25.0; Chicago, IL), and a p-value < 0.05 was considered significant.

RESULTS

During one year of the pandemic, 176 ESKD patients were hospitalized and suspected of COVID-19 after excluding six patients who refused the RT-PCR test and were discharged against medical advice. Fifty-one of them tested positive for COVID-19 based on RT-PCR, and ten of the confirmed patients died. So, the incidence of COVID-19 in our center was 29%, with a mortality rate of 19.6%. There were 51% males with a median age of 50 years. The most common etiology of ESKD was diabetic kidney disease. The three significant complications on admission were pulmonary edema (49%), hyponatremia (20%), and hyperkalemia (19%). Ninety of ESKD patients were already on maintenance HD, the median HD vintage was 11 months, and 59% had AV shunt access.

Clinical comparison

There was no significant difference between the COVID-19 and negative groups in this study regarding demographics, history of routine HD, comorbidity, and underlying ESKD. There were significant differences between the COVID-19 positive and negative groups regarding admission signs, symptoms, and complications (Table 1). Patients with COVID-19 had a lower prevalence of dyspnea (21% vs. 79%, P=0.003), a lower diastolic blood pressure (82 vs. 89 mmHg, P=0.025), a lower pulse rate (88 vs. 100 x/minutes, P=0.003), a higher temperature (36.7 vs. 36.5 °C, P=0.049) than patients without COVID-19. Admission complication of pulmonary edema was less common in ESKD patients with COVID-19 than without COVID-19 (19% vs. 81%, P=0.003).

Table 1. Demographics and clinical characteristics of ESKD patients

Characteristics	**Total (n=176)**	**COVID-19 positive (n=51)**	**COVID-19 negative (n=125)**	**P value**
Age, yr*	50 ± 13	53 ± 13	49 ± 14	0.053

Men	89 (51)	23 (26)	66 (74)	0.354
History of contact	23 (13)	10 (44)	13 (56)	0.100
Routine Hemodialysis	90 (51)	25 (28)	65 (72)	0.720
Comorbidity	156 (89)	45 (29)	111 (71)	0.915
Diabetes	49 (28)	15 (31)	34 (69)	0.766
Hypertension	125 (71)	37 (30)	88 (70)	0.776
Cardiovascular disease	47 (27)	9 (19)	38 (81)	0.083
Others	36 (21)	7 (19)	29 (81)	0.157
Admission symptoms				
Fever	33 (19)	13 (39)	20 (61)	0.143
Cough	63 (36)	22 (35)	41 (65)	0.194
Dyspnea	109 (62)	23 (21)	86 (79)	0.003
Rhinorrhea	6 (3)	2 (33)	4 (67)	0.811
Abdominal pain	28 (16)	8 (29)	20 (71)	0.959
Myalgia	20 (11)	7 (35)	13 (65)	0.528
Fatigue/malaise	97 (55)	28 (29)	69 (71)	0.971
Nausea/vomiting	50 (28)	16 (32)	34 (68)	0.578
Other symptoms	22 (13)	8 (36)	14 (64)	0.414
Admission vital signs				
Systolic blood pressure, mmHg*	157 ± 34	150 ± 33	160 ± 35	0.077
Diastolic blood pressure, mmHg*	87 ± 17	82 ± 15	89 ± 17	0.025
Pulse rate, beats per minute†	98 (83-108)	88 (77-104)	100 (89-108)	0.003
Respiration rate, breaths per minute†	24 (20-28)	22 (20-26)	24 (20-28)	0.150
Temperature, °C†	36.6 (36.3-36.9)	36.7 (36.5-37.0)	36.5 (36.3-36.8)	0.049
Pulse oximetry, %†	97 (94-98)	97 (95-98)	97 (94-98)	0.279
Admission physical examination				
Conjunctival anemia	139 (79)	38 (27)	101 (73)	0.353
Crackles on auscultation	91 (52)	23 (25)	68 (75)	0.263
Ascites on percussion	17 (10)	3 (18)	14 (82)	0.401
Edema of lower extremities	31 (18)	5 (16)	26 (84)	0.082

Notes: Data are given as n (%) or mean ± standard deviation* or median (IQR)†.

P values comparing COVID-19 positive and COVID-19 negative are from the independent t-test*, the Mann-Whitney U test†, $\chi 2$, or Fisher's exact test.

Laboratory and chest X-ray comparison

Regarding laboratory parameters, ESKD patients with COVID-19 had lower white blood cell counts, neutrophil counts, monocyte counts, basophil counts, eosinophil counts, and potassium levels than patients without COVID-19 (Table 2). As for chest X-ray findings, ESKD patients with COVID-19 revealed less proportion of pulmonary edema (18% vs. 82%, P=0.007), pleural effusion (17% vs. 83%, P=0.021), and cardiomegaly (22% vs. 78%, P=0.017). There was no significant difference in the proportion of ground-glass opacification, infiltration, or consolidation between the two groups (28% vs. 72%, P=0.422).

Table 2. Laboratory findings of ESKD patients

Laboratory findings	**Total (n=176)**	**COVID-19 positive (n=51)**	**COVID-19 negative (n=125)**	**P value**
White blood cells, 10^3 μl	10.5 (8.1-15.7)	9.5 (6.3-13.7)	11.0 (8.5-16.6)	0.015
Hemoglobin, g/dl	8.0 (6.8-9.5)	8.7 (7.0-9.9)	7.8 (6.7-9.2)	0.058
Thrombocyte, 10^3 μl	213 (156-280)	200 (146-267)	230 (159-306)	0.109
Neutrophil, 10^3 μl	8.33 (5.48-13.64)	6.99 (4.43-11.52)	8.86 (6.24-14.11)	0.017
Lymphocyte, 10^3 μl	1.05 (0.79-1.46)	1.12 (0.78-1.49)	1.02 (0.79-1.46)	0.557
Monocyte, 10^3 μl	0.69 (0.50-1.00)	0.57 (0.42-1.00)	0.73 (0.54-1.00)	0.021
Basophil, 10^3 μl	0.04 (0.02-0.06)	0.03 (0.01-0.05)	0.04 (0.02-0.06)	0.004
Eosinophil, 10^3 μl	0.12 (0.02-0.36)	0.08 (0.02-0.23)	0.15 (0.03-0.36)	0.047
Neutrophil-Lymphocyte ratio	7.3 (4.5-15.2)	6.5 (3.0-13.6)	8.3 (5.1-15.6)	0.063
estimated Glomerular Filtration Rate, ml/1,73m^2/minute	4.3 (2.7-6.7)	5.0 (3.5-8.5)	4.1 (2.6-6.1)	0.038
Glucose, mg/dl	119 (100-158)	119 (90-158)	119 (103-157)	0.821
Aspartate transaminase, U/L	27 (18-47)	27 (17-54)	27 (18-46)	0.951
Alanine transaminase, U/L	24 (15-40)	24 (15-37)	24 (15-43)	0.565
Sodium, mmol/L	134 (130-137)	132 (129-135)	135 (130-137)	0.062
Potassium, mmol/L	5.1 (4.4-5.9)	4.6 (4.0-5.5)	5.2 (4.5-6.0)	0.008

Chloride, mmol/L*	104 (100-108)	104 (98-107)	105 (101-109)	0.151
C-reactive protein, mg/L†	41 (11-120)	53 (9-120)	37 (12-111)	0.236

Notes: Data were collected from 163 patients* or from 160 patients†.
Data are given as median (IQR).
P values comparing COVID-19 positive and COVID-19 negative are from the Mann-Whitney U test.

Uni- and Multivariable analyses of COVID-19 positive and negative groups

Based on the difference between the COVID-19 positive and negative groups (Table 1 and 2), we assessed symptoms of dyspnea, the complication of lung edema, white blood cell counts, monocyte counts, eosinophil counts, NLR, and chest X-ray findings such as pulmonary edema, pleural effusion dan cardiomegaly by univariable analyses for the risk developing COVID-19. Less dyspnea, monocytopenia, low eosinophil count, and mild elevation of NLR were associated with COVID-19. We further analyzed using a multivariable logistic regression model for symptoms of dyspnea, monocyte group, eosinophil group, and NLR group. Among these factors, monocyte count <0.69 x$10^3\mu$l (P=0.004, OR 2.54, 95%CI:0.166-0.931), eosinophil count <0.04 x$10^3\mu$l (P<0.001, OR 3.50, 95%CI:0.123-0.665), and NLR <3.13 (P=0.044, OR 3.18, 95%CI:0.102-0.968) were associated with the presence of COVID-19 (Table 3).

Table 3. Multivariable Analyses of Odds Ratio for mortality of COVID-19 in ESKD patients

Variable	Multivariable analysis		
	OR	**P value**	**95% CI**
Neutrophil-to-lymphocyte ratio <3.13	3.18	0.044	0.102-0.968
White blood cell count <10.0 x$10^3\mu$l	1.08	0.866	0.376-2.281
Symptoms of dyspnea	2.27	0.048	0.195-0.994
Chest X-ray pulmonary edema	1.47	0.404	0.274-1.685
Chest X-ray pleural effusion	1.38	0.503	0.282-1.860
Chest X-ray cardiomegaly	1.63	0.225	0.277-1.352
Complications of lung edema	1.41	0.463	0.280-1.784
Monocyte count <0.69 x$10^3\mu$l	2.54	0.004	0.166-0.931
Eosinophil count <0.04 x$10^3\mu$l	3.50	<0.001	0.123-0.665

Notes: OR - odds ratio; CI - confidence interval.

DISCUSSION

Several studies reported different incidences of COVID-19 in HD patients, such as 2.2% in Wuhan,[8] 4.6% in Canada,[12] and 19,6% in the United Kingdom.[13] The prevalence of COVID-19 in our center was higher than in other studies since we included only symptomatic and suspected patients who come to the hospital. Over 85% of HD patients have one or more comorbid conditions.[3,8]

Like this study, Valeri et al. reported that almost all patients had hypertension, 69% diabetes, and 46% coronary artery disease.[7] The main complication at admission in this study was pulmonary edema. It might result from patient factors such as inadequate HD, non-compliance to routine HD schedule, or fear of contracting COVID-19 in the hospital.[14]

Our findings showed a statistically significant difference between the COVID-19 positive and negative groups in terms of diastolic blood pressure levels, pulse rate, and temperature levels. However, these results were relatively not crucial in clinical settings. Despite the proportion of dyspnea being lower in the COVID-19 positive group, respiratory rates and oxygen saturation were similar between the two groups in this study. The main symptoms of COVID-19 were less common in the HD population than in non-HD patients,[9] which was in line with this study. In contrast, a study in India showed that 50% of confirmed COVID-19 in HD patients,[5] and 38% of HD patients in Romania complained of dyspnea.[3] Immune response in uremic conditions may alter the response to SARS-CoV-2 infection.[2] Happy hypoxia in COVID-19 may also be present in the infected ESKD population. Patients may not complain of shortness of breath despite hypoxia requiring oxygen therapy.[5]

Based on multivariate analysis, our findings revealed that low eosinophil counts were associated with the diagnosis of COVID-19 in ESKD patients. Eosinophils are a subset of leukocytes that have long been associated with allergic diseases and parasitic infections. Recent studies have demonstrated the role of eosinophils in the immune response to viruses, particularly RNA viruses. Toll-like receptor 7 (TLR7), which functions to recognize RNA viruses, is abundant on the surface of eosinophil cells. Eosinophil counts have been associated with early markers of SARS-CoV-2 infection and the severity of COVID-19.[15] The eosinophil counts are an effective and efficient indicator in diagnosing COVID-19. A study reported that 71.7% of COVID-19 patients had low eosinophil counts, and the proportion was more remarkable than patients with pneumonia due to other causes.[16] Another study showed that eosinophils counts were lower in COVID-19 patients, then slowly increased to the average level in recovered patients. But, the number continued to decrease in deteriorated patients.[17]

Our study also revealed that monocytopenia and mild elevated NLR were a good indication of COVID-19 in ESKD patients. Monocytes might play an essential role in the host's defense against COVID-19. The severe COVID-19 patients exhibit higher levels of monocyte counts.[18] In contrast, our study showed that monocyte count $<0.69\ x10^3\mu l$ indicated COVID-19 in ESKD patients. The expected value of NLR in a healthy population is 1.0-2.3. NLR is said to be low if the level is < 0.7 and high if the level is >3.00.[19] A study demonstrated the use of NLR with a cut-off value of 5.87 to support the diagnosis of COVID-19.[20] A meta-analysis study reported that higher NLR levels were found in advanced COVID-19 stages while lower NLR levels were found in early COVID-19 stages. NLR has good accuracy for diagnosis and good predictive ability of death in COVID-19.[21]

Pulmonary edema was infrequent chest x-ray findings in the COVID-19 positive group in this study. Pulmonary edema in the population of HD patients was associated with readmission and rehospitalization. A cohort study in the United States reported that 23% of HD patients had repeated hospital admissions in the past month, and 44% were associated with pulmonary edema. Factors

influencing pulmonary edema in HD patients are dialysis vintage <1 year, chronic obstructive pulmonary disease, dialysis non-compliance, and congestive heart failure.[22] On the contrary, SARS-CoV-2 infection might directly cause pulmonary edema through the increased effect of bradykinin on its receptors in the lung. It is known that Angiotensin-Converting Enzyme 2 (ACE-2) converts angiotensin II to angiotensin 1-7, which has a vasodilating effect by stimulating Nitric Oxide (NO) synthase. ACE-2 also hydrolyzes the active metabolite of bradykinin, namely des-Arg^{9}-bradykinin. The bind between des-Arg^{9}-bradykinin and the bradykinin type 1 receptor (BKB1) on pulmonary endothelial cells causes fluid extravasation and edema. Suppression of ACE-2 by the SARS-CoV-2 virus increased the number of bradykinin metabolites, increasing BKB1 receptor activation and pulmonary edema.[23] Pulmonary edema was infrequent in other studies or even normal chest x-ray findings in 7-19% of cases.[7,9]

The proportion of pleural effusion and cardiomegaly was lower in the COVID-19 positive group in this study. The feature of pleural effusion might rule out COVID-19 in hospitalized ESKD patients. The prevalence of pleural effusion in COVID-19 patients was only 9.55%. Pleural effusion was associated with an increased risk of disease severity and death in COVID-19.[24] The prevalence of cardiomegaly in regular HD patients in Mali is 55.68%. This feature was associated with hypertension-related kidney disease and left ventricular hypertrophy.[25] Cardiomegaly in patients without other comorbidities can be a feature of COVID-19 due to pericardial effusion or myocarditis.[26]

This study had some limitations—first, a limited number of cases from one single center. Second, not all patients documented CRP levels since this retrospective study. Third, the dynamics of clinical and laboratory changes during hospitalization were not analyzed, so the data on admission may differ from each stage of the disease. However, it is the first study of COVID-19 in this country's population with kidney disease. It also provides clinical features of COVID-19 at the first visit in hospitalized ESKD patients that may be useful in the screening and differentiation.

CONCLUSIONS

ESKD patients with COVID-19 were less dyspnea and showed less frequent chest x-ray patterns of pulmonary edema, pleural effusion, and cardiomegaly. The COVID-19-positive patients presented with lower leukocyte, eosinophil, monocyte, and NLR. Eosinophil count <0.04 x$10^{3}\mu$l, monocyte count <0.69 x$10^{3}\mu$l, and NLR <3.13 indicated COVID-19 that can help clinicians screen and differentiate hospitalized ESKD patients in resource-limited settings. Further studies are needed to determine the dynamics of COVID-19 in ESKD during hospitalization.

AUTHOR CONTRIBUTION

All authors contributed by preparing the proposal, data collection, data analysis, writing and revising the manuscript, and approving the final version for publication.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

ETHICAL STATEMENT

The West Nusa Tenggara General Hospital Ethics Committee approved this research with ethical clearance reference number 070.1/21/KEP/2020.

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