



The Use of Eosinophil Count in Predicting the Need of Coronavirus Disease 2019 Patient for Treatment in Intensive Care Unit

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Abstract

BACKGROUND: Identification of coronavirus disease 2019 (COVID-19) patients who have the potential to become critical cases at an early stage and providing aggressive therapy can reduce the mortality rate.

AIM: This study aims to determine the diagnostic value and differences of eosinophil counts in patients with COVID-19 who require treatment in intensive care unit (ICU) and non-ICU.

METHOD: The prospective study was conducted on 382 patients with confirmed COVID-19 who were hospitalized from May to September 2020. Samples were obtained through consecutive sampling techniques. Mann–Whitney analysis was used to determine the difference of eosinophil counts in COVID-19 patients who require treatment in ICU and non-ICU. Receiver operating curve analysis was used to determine the diagnostic value of eosinophil count to predict the need of COVID-19 patients for treatment in ICU.

RESULTS: There is a significant difference in the absolute and percentage eosinophil count in COVID-19 patients who need treatment in ICU and non-ICU. The area under the curve of absolute and percentage eosinophil count to predict the need of COVID-19 patients for treatment in ICU is 0.659 and 0.738, respectively. The best cutoff value, sensitivity and specificity of absolute and percentage eosinophil count is $<0.025 \times 10^3 \mu\text{L}$ and $<0.25\%$; 77.7% and 78.3%; and 50.0% and 57.1%, respectively.

CONCLUSIONS: The eosinophil count can be used as a biomarker to predict the need of COVID-19 patients for treatment in ICU.

Edited by: Ksenija Bogojeva-Kostovska
Citation: Suastika NKW, Suega K. The Use of Eosinophil Count in Predicting the Need of Coronavirus Disease 2019 Patient for Treatment in Intensive Care Unit. Open Access Maced J Med Sci. 2021 Jul 22; 9(B):631-635. <https://doi.org/10.3889/oamjms.2021.6562>
Keywords: Biomarker; Coronavirus disease 2019; eosinophil; intensive care unit
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Received: 03-Jun-2021
Revised: 30-Jun-2021
Accepted: 12-Jun-2021
Copyright: © 2021 Ngakan Ketut Wira Suastika, Ketut Suega
Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists
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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 152 million people worldwide with more than 3 million deaths (data until May 3, 2021) [1]. The highest number of confirmed cases of COVID-19 occurred in the European and American regions [2]. The incidence of acute respiratory distress syndrome (ARDS) is quite high, between 17% and 29% of hospitalized COVID-19 patients [3], [4], [5]. Critical patients with ARDS require treatment in the intensive care unit (ICU). The mortality rate during 28 days of treatment in the ICU was very high, reaching 62% [6]. The relatively high number of critical cases in COVID-19 is a problem, especially in health facilities with a limited number of ICU [7], [8]. A biomarker is needed that can be used for risk stratification or early identification of patients who have the potential for worsening clinical conditions so that aggressive therapy can be given from the early of treatment.

Several inflammatory biomarkers such as ferritin [9], C-reactive protein (CRP) [10], and some cytokines [11] are associated with disease severity in

COVID-19. However, examining these inflammatory markers is time consuming and expensive. During this pandemic, biomarkers that provide fast and cost-effective results are needed. Eosinophil count is a potential biomarker for assessing disease progression in COVID-19. Studies show that there is a decrease in circulating eosinophils in some viral infections such as respiratory syncytial virus (RSV) pneumonia [12]. Experimental studies on mice infected with RSV and influenza have shown that eosinophils play a role in virus defense and are also responsible for organ damage due to the release of mediators [13], [14]. Eosinophils and neutrophils are also inflammatory cells that infiltrate the lungs in Middle East respiratory syndrome coronavirus infection [15].

In COVID-19 patients, eosinopenia is found in 47–66% of cases [16], [17]. A study by Xie *et al.* found that patients with low eosinophil counts had more complaints of fever and shortness of breath, worse chest radiology, and longer length of stay compared to normal eosinophil counts [18]. There are many studies on the role of lymphocytes and neutrophils, but few studies on the role and diagnostic value of eosinophils in COVID-19.

This study aims to determine the diagnostic value and differences of eosinophil counts in patients

with COVID-19 who require treatment in ICU and non-ICU.

Methods

Study design and sample

This prospective study was conducted on 382 patients who were treated at the Udayana University Hospital, Bali, Indonesia, from May 2020 to September 2020. Inclusion criteria were patients over 18 years of age who were confirmed COVID-19 through nasopharyngeal swab examination with the real-time reverse-transcriptase polymerase chain reaction method. Patients who had received steroid or antihistamine therapy before admission to the hospital, patients with a history of allergies, and patients who died within 24 h of treatment were excluded from the study.

The criteria for patients who need treatment in the ICU are patients with critical criteria according to the World Health Organization interim guidelines, including (1) patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 100$ mmHg) or need mechanical ventilation; (2) patients with sepsis characterized by impaired organ function, including decreased consciousness, decreased urine output, or acidosis; and (3) patients with septic shock (persistent hypotension even with fluid resuscitation, and requiring a vasopressor to maintain a mean arterial pressure ≥ 65 mmHg) [19].

This study protocol has received approval from the Institutional Review Board of the Faculty of Medicine, Udayana University (1010/UN1422.VII.14/LT/2020).

Data collection and instruments

Epidemiological, clinical characteristics (symptoms and signs, history of medication, and allergy), and laboratory data were obtained from patient medical records. Blood samples for laboratory examinations including a complete blood count are taken when the patient is admitted to the hospital. Patients were followed during hospitalization and recorded whether requiring treatment in the ICU or remaining in the general ward (non-ICU).

To detect SARS-CoV-2 from nasopharyngeal swab samples, Roche Diagnostic SARS-CoV-2 test was used. The absolute and percentage eosinophil count was obtained from a complete blood count that was checked with the Sysmex XN-series automated hematology analyzer.

Data analysis

Continuous variables are described into the median (interquartile ranges [IQRs]) while categorical

variables are described as percentages. To compare continuous variables, Mann–Whitney U-test analysis was used, while for categorical variables, we used Chi-square analysis.

Analysis using the receiver operating characteristic curve was used to obtain the area under the curve (AUC), sensitivity and specificity of the absolute and percentage eosinophil count to predict the need of COVID-19 patients for treatment in ICU. Eosinophil count variables and age were transformed into dichotomous variables based on the best cutoff values that had been found. To determine the effect of confounding variables, multivariate logistic regression analysis was used. All statistical analyzes used SPSS version 25.0 software. The results obtained were statistically significant if $p < 0.05$.

Results

Epidemiological, clinical characteristics, and complete blood count

Of the 382 patients, 31 patients (8.1%) required treatment in the ICU. The median age of the patients was 46 years (IQR 18–84 years). Most of the sample (63%) are male. A total of 97 (25.4%) patients had various comorbidities, mostly diabetes (44.3%) (Table 1). The absolute and percentage eosinophil counts were significantly lower in patients who require treatment in the ICU compared to non-ICU ($p < 0.001$). There are also significant differences in age, comorbidities, hemoglobin level, hematocrit, leukocyte, neutrophil, lymphocyte, and monocyte counts, however, there were no significant differences in sex and platelet counts in the two groups.

Eosinophil count to predict of patient need for treatment in the ICU

The percentage of eosinophil counts had a slightly better diagnostic value than the absolute eosinophil count. The area under curve of absolute and percentage eosinophil counts is 0.659 (95% CI 0.503–0.816) and 0.738 (95% CI 0.611–0.865), respectively. The best cutoff values obtained are: $<0.025 \times 10^3 \mu\text{L}$ for the absolute eosinophil count with a sensitivity of 77.7% and a specificity of 50.0%; $<0.25\%$ for the percentage eosinophil counts with a sensitivity of 78.3% and a specificity of 57.1% (Figure 1 and Table 2).

Association between eosinophil counts with the patient need for treatment in the ICU

Multiple logistic regression analysis was used to determine the effect of age and comorbidity variables. We found that the percentage eosinophil count was independently associated with the need

Table 1: Epidemiological characteristics, eosinophil count, and other complete blood count parameters

Variable	Median (interquartile range)			p value
	All patients (n = 382)	Non-ICU (n = 351)	ICU (n = 31)	
Age, years	46 (18–84)	44 (18–84)	57 (32–75)	<0.001
Sex, n (%)				
Male	244 (63.9)	222 (63.2)	22 (71.0)	0.508
Female	138 (36.1)	129 (36.8)	9 (29.0)	
Comorbidities, n (%)				
Without comorbidities	285 (74.6)	274 (78.1)	11 (35.5)	<0.001
With comorbidities	97 (25.4)	77 (21.9)	20 (64.5)	
Hypertension	27 (27.9)	23 (29.9)	4 (20.0)	
Diabetes	43 (44.3)	31 (40.2)	12 (60.0)	
Congestive heart failure	9 (9.3)	7 (9.1)	2 (10.0)	
Coronary artery disease	11 (11.3)	11 (14.3)	0 (0)	
Asthma	4 (4.1)	3 (3.9)	1 (5.0)	
Chronic kidney disease	3 (3.1)	2 (2.6)	1 (5.0)	
Hemoglobin, gr/dl	13.9 (7.9–17.4)	13.9 (8.9–17.4)	13.1 (7.9–16.0)	0.028
Hematocrit, %	40.7 (24.2–50.2)	41.0 (24.2–50.2)	39.0 (32.9–47.2)	0.035
Leukocyte, × 10 ³ μL	6.79 (2.36–17.25)	6.72 (2.36–15.98)	7.67 (3.87–17.25)	0.008
Eosinophils				
Absolute, × 10 ³ μL	0.09 (0.00–1.53)	0.09 (0.0–1.53)	0.02 (0.0–0.1)	<0.001
Percent, %	1.2 (0.0–12.0)	1.4 (0.0–12.0)	0.2 (0.0–3.1)	<0.001
Basophils				
Absolute, × 10 ³ μL	0.01 (0.00–1.00)	0.01 (0.0–1.0)	0.01 (0.0–0.1)	0.02
Percent, %	0.2 (0.0–8.01)	0.2 (0.0–8.01)	0.1 (0.0–0.4)	<0.001
Neutrophil				
Absolute, × 10 ³ μL	4.2 (0.99–15.50)	3.99 (0.99–13.78)	6.38 (2.78–15.50)	<0.001
Percent, %	62.55 (0.2–95.2)	61.3 (33.9–93.5)	81.6 (67.3–95.2)	<0.001
Lymphocyte				
Absolute, × 10 ³ μL	1.55 (0.31–5.92)	1.61 (0.31–5.92)	0.82 (0.31–5.70)	<0.001
Percent, %	24.9 (1.29–53.6)	26.2 (1.4–53.6)	10.0 (1.29–24.0)	<0.001
Monocyte				
Absolute, × 10 ³ μL	0.58 (0.05–1.66)	0.58 (0.09–1.66)	0.46 (0.05–1.33)	0.017
Percent, %	8.9 (0.7–25.0)	9.1 (0.7–25.0)	6.4 (0.7–14.2)	<0.001
Platelet, × 10 ³ μL	241.5 (54–672)	242 (54–672)	224 (92–579)	0.45

Table 2: The cutoff value, sensitivity, specificity, and AUC of eosinophils count

Variable	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	95% CI	p value
Absolute eosinophils	<0.025	77.7	50.0	0.659	0.503–0.816	0.043
Percent eosinophils	<0.25	78.3	57.1	0.738	0.611–0.865	0.003

for COVID-19 patients for treatment in the ICU with an adjusted odds ratio (OR) of 3.31 (95% confidence interval [CI] 1.34–8.13), p = 0.009 (Table 3).

Table 3: The OR and adjusted OR of percentage eosinophils count, comorbid, and age

Variable	Odds ratio (95% CI)	p	Adjusted odds ratio (95% CI)	p value
Percentage eosinophils count	4.79 (2.25–10.18)	<0.001	3.31 (1.34–8.13)	0.009
Comorbidities	6.69 (3.07–11.04)	<0.001	3.85 (1.56–9.52)	0.003
Age	3.65 (1.53–8.69)	0.004	1.53 (0.56–4.16)	0.409

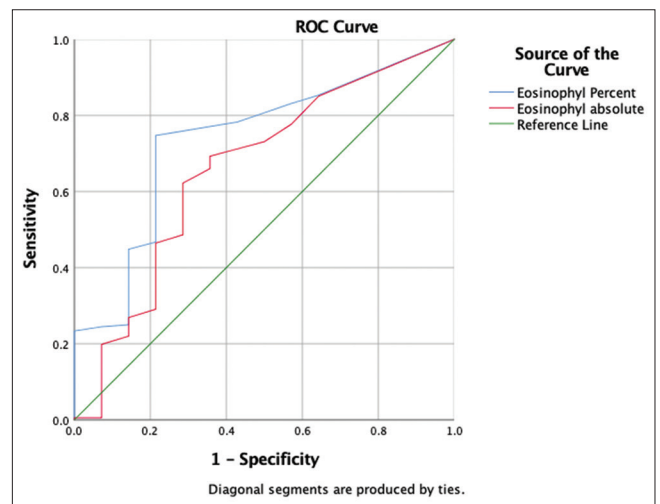


Figure 1: The ROC curve of absolute and percentage eosinophil counts to predict the need of Covid-19 patients for treatment in ICU

Discussion

Our study found significant differences in eosinophil counts in COVID-19 patients who need treatment in the ICU compared to non-ICU. This result is consistent with the study of Yan *et al.* who found that the eosinophils count was significantly lower in critical cases compared to moderate-severe cases. This study also found that the eosinophil count correlated with levels of D-dimer, urea, serum creatinine, serum aminotransferase, and lactate dehydrogenase [20]. Another study showed that eosinophil counts increased gradually, according to improve chest computerized tomography scans [18]. The eosinophil count was found to have decreased significantly in COVID-19 and returned to normal levels

gradually according to the improvement in the patient's condition, whereas, in patients with clinical deterioration, the eosinophil count continued to decline [21].

Our study found that the percentage eosinophil count has a better diagnostic value than the absolute eosinophil count. This can occur because the number of eosinophils relative to total white blood cells reflects the status of inflammation that occurs in COVID-19. Neutrophils will be recruited into the lungs in large numbers, followed by a shift with an increase in neutrophil production and a decrease in eosinophil production in the bone marrow [18]. Studies show that eosinophils and neutrophils are recruited into lung tissue starting in the early phase of viral infection and before the onset of respiratory symptoms [22]. Increased production of pro-inflammatory cytokines and decreased production of

anti-inflammatory cytokines will cause a large number of neutrophils, lymphocytes, and eosinophils infiltrate to the lungs and cause a decrease of eosinophils in peripheral blood [23]. Another mechanism may explain, stress conditions on lung injury causes increased production of corticosteroids by the adrenal glands and causes suppression of eosinophil release by bone marrow [24], [25]. Increased corticosteroids can also lead to decreased differentiation and survival of eosinophils and also stimulate the infiltration of eosinophils into the tissue [25], [26]. The eosinophil count was zero in 61% of patients who need treatment in the ICU [27]. This phenomenon was also observed in a study by Shaaban *et al.* in patients with sepsis who were treated in the ICU [28].

Our study found that a percentage eosinophil count <0.25% can predict the need of COVID-19 patients for treatment in the ICU with an AUC of more than 70%. Eosinophil counts can be used as a simple and effective biomarker and can be combined with other laboratory parameters for monitoring, evaluation, and predicting the prognosis of COVID-19 patients. Eosinophil counts as a biomarker have several advantages compared to other biomarkers such as D-dimer and CRP, they are cheap and can provide fast results, so they can be used as an option in hospitals with limited resources.

Our study has several limitations. First, examination eosinophil counts only once on admission to the hospital, not to be monitored regularly. Second, this study is a single center with a relatively small number of samples.

Conclusions

Eosinophil count can be used as a biomarker to predict the needs of COVID-19 patients for treatment in the ICU. Further studies are needed to determine the role of eosinophils in the pathogenesis mechanism of COVID-19 and their potential as therapeutic targets.

Acknowledgments

The author would like to thank to all management and medical personnel at the Udayana University Hospital, Bali, Indonesia.

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