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Original Article

Are Lymphocytes and Eosinophils Associated with the COVID-19 Severity: A Large, Retrospective Study

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Abstract

OBJECTIVE: Coronavirus disease 2019 is an ongoing disease with high morbidity and mortality. We aimed to investigate the relationship between demographics, lymphocytes, eosinophils, and the coronavirus disease 2019 severity at hospital admission.

MATERIAL AND METHODS: A retrospective, observational cross-sectional study was carried out with 5828 coronavirus disease 2019 patients between March 11, 2020, and November 30, 2020. Patients were divided into 3 groups according to where they were followed up as an indicator of disease severity, namely outpatients, inpatients, and critically ill patients. The patients' demographics and hemogram values on admission were recorded. The predictive accuracies of lymphocyte count, lymphocyte percentage, eosinophil count, and eosinophil percentage for predicting severity were determined using receiver operating characteristic curves. Logistic regression analysis was used to predict intensive care unit demand according to lymphocyte and eosinophil values.

RESULTS: Of the 5828 coronavirus disease 2019 patients, 4050 were followed up as outpatients, 1581 were hospitalized in a ward, and 197 were hospitalized in the intensive care unit. Lymphocyte count and lymphocyte percentage were significantly different between the groups, but the difference for eosinophil count and eosinophil percentage was not significant as it was for lymphocytes. Cutoff values for lymphocyte count (1.0×10^9/L), lymphocyte percentage (22%), eosinophil count (0.052×10^9/L), and eosinophil percentage (0.08%) were found to indicate a high risk for intensive care unit admission. Coronavirus disease 2019 patients >55 years of age, with a lymphocyte count $<1.0 \times 10^9$/L, a lymphocyte percentage <22%, and an eosinophil percentage <0.08% had a 2-fold higher risk of requiring intensive care unit management.

CONCLUSION: Lymphocyte counts and percentages are quick and reliable biomarkers for predicting coronavirus disease 2019 severity and may guide physicians for proper management earlier.

KEYWORDS: COVID-19, lymphocyte, eosinophil, intensive care unit, hospitalization
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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared to be a pandemic by the World Health Organization on March 11, 2020, and is an ongoing disease with high morbidity and mortality.[1,2] Using laboratory predictors of severity before any clinical deterioration occurs may be helpful for the selection and early intervention of these patients.

Lymphopenia, defined as a low count of lymphocytes, has been predicted to be associated with COVID-19 severity.[3-7] Allergic reaction characterized by eosinophils was inversely related to Angiotensin-converting enzyme 2 (ACE2) expression, and eosinophilia could be protective for COVID-19. Coronavirus disease 2019 causes eosinopenia , and the correlation of eosinopenia with severity has not been properly elucidated.[8] It is also unclear what the cutoff values for lymphocyte count, lymphocyte percentage, eosinophil count, and eosinophil percentage are for predicting disease severity. The lymphocyte count, lymphocyte percentage, eosinophil count, and eosinophil percentage are routinely, easily, and cheaply measured in complete blood counts.[3] Studies looking at the utility of these biomarkers as predictors of COVID-19 severity have thus far been limited and conducted with small population groups.

A better understanding of the relationship between lymphocytes, eosinophils, and disease severity on admission and identifying severe cases earlier may help direct appropriate clinical management of COVID-19 and decrease fatality rates.[3,4]

We aimed to investigate the relationship between demographics, lymphocytes, eosinophils, and the COVID-19 severity at hospital admission.

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MATERIAL AND METHODS

This retrospective, observational cross-sectional study was conducted at the University of Health Sciences, İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital between March 11, 2020, and November 30, 2020. The study protocol was approved by the ethics committee of University of Health Sciences, İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (date of approval/no.: 07.01.2021/116.2017.R-209) and was conducted in full accordance with the ethical principles stated in the Declaration of Helsinki. All data were collected retrospectively from the hospital database.

Using the hospital electronic system, patients coded U07.3 using the International Classification of Diseases, namely COVID-19, were enrolled in the study. A COVID-19 diagnosis was made according to the Republic of Turkey Ministry of Health COVID-19 (SARS-CoV-2 Infection) Guide, 2020. Cases diagnosed as COVID-19 with polymerase chain reaction (PCR) positivity in nasopharyngeal and/or nasal swab samples, or cases with a negative PCR but who were diagnosed with COVID-19 according to the National COVID-19 Guide with characteristic clinical, laboratory, and radiological findings, and who received COVID-19 therapy, were included in the study. All patients were over 18 years of age. Patients without hemogram values on the first day of hospital admission were excluded from the study. Patients were categorized into 3 groups according to where they were followed up as an indicator of disease severity, namely outpatients, inpatients, and critically ill patients. In the study center, COVID patient hospitalization and outpatient follow-up were determined using the Republic of Turkey Ministry of Health COVID-19 (SARS-CoV-2 Infection) Guide 2020.

Uncomplicated patients were followed up as outpatients. Criteria for these patients were:

a. Symptoms of fever, muscle/joint pain, cough, and a sore throat without respiratory distress (respiratory rate <24, SpO_2 >93% at room air).
b. No underlying comorbid disease (mainly cardiovascular disease, diabetes mellitus, hypertension, cancer, chronic pulmonary disease, and other immunosuppressive conditions) and patients under 50 years old.
c. A normal chest x-ray and/or thorax computed tomography.

MAIN POINTS

- Coronavirus disease 2019 (COVID-19) is an ongoing pandemic with high morbidity and mortality.
- Our results revealed that if the lymphocyte count on admission is below 1.0×10^9/L, and/or lymphocyte percentage is below 22%, eosinophil percentage is below 0.08%, and the patient age is over 55 years, there is a greater than 2-fold risk of intensive care unit demand.
- Lymphopenia showed a strong association with the severity of COVID-19, and lymphocyte values can facilitate earlier decision-making for the physicians on admission.

Criteria for ward hospitalization of COVID-19 patients were:

a. Symptoms such as fever, muscle/joint pain, cough, and a sore throat without respiratory distress (respiratory rate ≥30, SpO_2 <90% at room air).
b. Evidence of extensive bilateral pneumonia on chest x ray or thorax computed tomography.

Patients with COVID pneumonia were admitted to the intensive care unit (ICU) using the following criteria:

a. Dyspnea and respiratory distress (respiratory rate ≥30, PaO_2/FiO_2 <300, increasing oxygen need, SpO_2 <90%, or PaO_2 <70 mmHg despite 5 L/min nasal oxygen therapy).
b. Systolic blood pressure (SBP) <90 mmHg and 40 mmHg from usual SBP, mean arterial pressure <65 mmHg, and tachycardia >100/min.
c. Development of acute organ dysfunction such as acute renal injury, acute liver dysfunction, and immunosuppression.
d. High levels of troponin and arrhythmia.
e. Lactate >2 mmol/L.
f. Capillary refilling disorders and the presence of mottling.

Patient enrollment is summarized in a flowchart in Figure 1.

Data were obtained from the hospital electronic database. Patient characteristics and hemogram values on admission were recorded. A Coulter LH 780 Hematology Analyzer (Beckman Coulter Inc., Brea, Calif, USA) was used for complete blood counts (leukocyte, neutrophil, eosinophil, lymphocyte, and platelet) analysis.

Statistical Analysis

Patient demographics and all clinical data were summarized by descriptive analysis. The patient groups were designated according to place of admission, that is, outpatients, inpatients, or critically ill patients. The 3 study groups were compared using the analysis of variance–post hocTukey test for normally distributed continuous variables, i.e., age and hemogram values, and the values were defined as the mean and SD. If continuous variables were distributed non-normally, the Kruskal–Wallis test was used for analysis, and the values were defined as the median and interquartile range (25%-75%).

The chi-square test was employed for dichotomous variables, that is, gender and the cutoff values group. Count and percentage were used when applicable. The receiver operating characteristic (ROC) curve was used to define the cutoff values for lymphocyte count and percentage and eosinophil count and percentage, and the area under curve (AUC) was obtained to determine optimal cutoff values. Logistic regression analysis was done for predicted ICU demand for lymphocyte and eosinophil values. The model included age, gender, and studied cutoff values for lymphocytes and eosinophils. P <.05 was accepted as statistically significant.

RESULTS

A total of 5828 patients with COVID-19 were assessed within the study period. Patients were categorized according to where they were followed up in the hospital. Four thousand

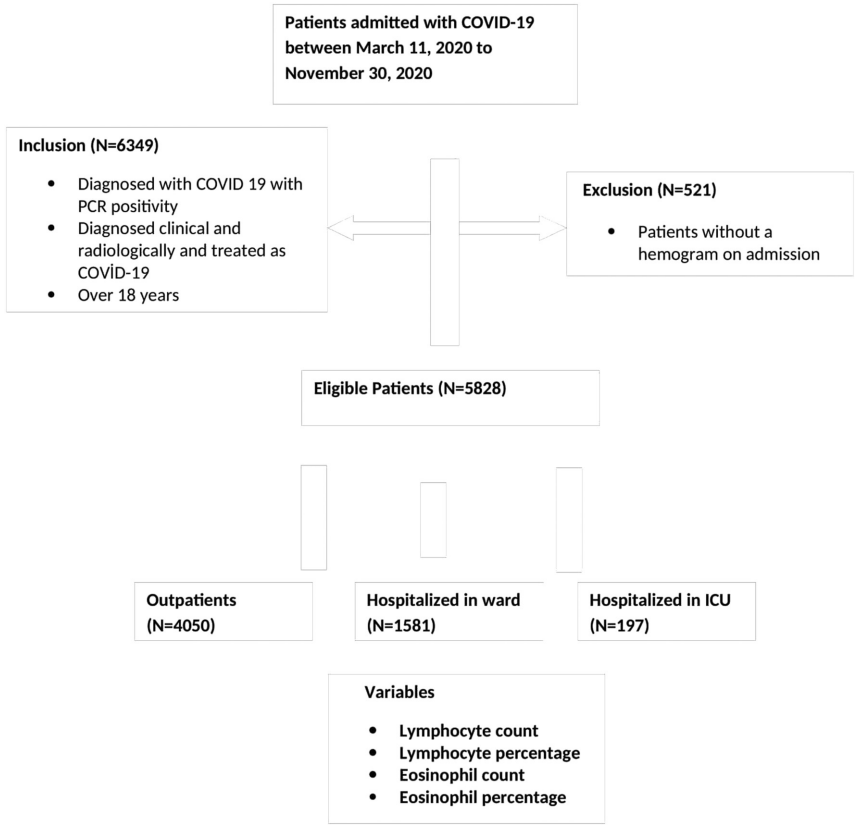

Figure 1. A flowchart of patients included in the study.

fifty patients were followed up as outpatients, 1581 patients were hospitalized in a ward, and 197 patients were hospitalized in the ICU (Figure 1).

Table 1 shows a comparison of demographics and hemogram values on the admission of the 3 groups. The older age and male ratio were significantly higher in ICU patients compared to outpatients and patients hospitalized in the ward. The median age was 46 (IQR, 35-60) years for outpatients, 56 (IQR, 44-68) years for inpatients, and 66 (IQR 55-77) years for critically ill patients. Lymphocyte count and percentage were significantly different between the groups. The median lymphocyte count was significantly lower in the ICU group [0.88 (0.54-1.63) × 10^9/L] compared with the outpatient [1.74 (1.26-2.34) × 10^9/L] and ward groups [1.43 (1.05-1.91) × 10^9/L], $P < .001$. Lymphocyte percentage was also significantly lower in the ICU group (10%) compared with the outpatient group (26%) and ward group (23%), $P < .001$. Our analysis revealed that eosinophil count and percentage in the ICU group (0.17 × 10^9/L and 0.14%, respectively) were lower than that in the outpatient (0.78 × 10^9/L and 1.06%, respectively) and ward groups, but the difference was not significant, as it was for lymphocytes. We found that the cutoff points for eosinophil cell count and percentage were 0.052 × 10^9/L and 0.08%, respectively, for predicting ICU follow-up.

The cutoff values for lymphocyte count, lymphocyte percentage, eosinophil count, and eosinophil percentage were analyzed by the ROC and AUC and are summarized in Figure 2 and Table 2, respectively. Being over 55 years was found to be a predictor of ICU admission. The greater AUC was obtained with lymphocyte count and lymphocyte percentage for ICU demand. The results of the ROC analysis revealed the cutoff values predictive for admission to ICU were 1.0 × 10^9/L for lymphocyte count, 22% for lymphocyte percentage, 0.052 × 10^9/L for eosinophil count, and 0.08% for eosinophil percentage (Table 2).

Table 3 summarizes the logistic regression analysis results showing that being over 55 years of age, lymphocyte count <1.0 × 10^9/L, lymphocyte percentage <22%, eosinophil count <0.052 × 10^9/L, and eosinophil percentage <0.08% were all predictors for ICU demand, although eosinophil count and male gender were not statistically significant (Table 3).

Table 4 shows the forward stepwise logistic regression analysis (likelihood ratio), where only 4 parameters were found to be predictive for ICU demand. The odds ratio (95% CI lower and upper values) for these parameters were as follows: lymphocyte count 1.0 × 10^9/L: 2.14 (1.55-3.00), lymphocyte percentage 22%: 2.53 (1.70-3.77); eosinophil percentage 0.08%: 2.57 (1.86-3.55), and age 55: 2.87 (2.03-4.04) (for each $P < .001$). Our results revealed that lymphopenia on admission had a strong association with COVID severity, but eosinopenia did not.

DISCUSSION

We reviewed and analyzed the association between demographics, the counts and percentages of lymphocytes, and eosinophils on admission of COVID-19 patients with disease severity. The findings revealed that COVID-19 patients over 55 years, with a lymphocyte count below 1.0 × 10^9/L, a lymphocyte percentage below 22%, and an eosinophil

Table 1. Comparisons of Demographics and Hemogram Values in COVID-19 Patients on Admission to the Outpatient Clinics, the Ward, or ICU

	Outpatients (A)		Inpatients (B)		Critically Ill Patients (C)		*P*		
	n	Values	n	Values	n	Values	A vs. B	B vs. C	A vs. C
Number of patients (n, %)	4050	69, 5%	1581	27, 1%	197	3, 4%			
Male (n, %)	2103	51, 9%	905	57, 2%	129	65, 5%	<.001	<.001	<.001
Age, years (Median 25%-75%)	4050	46 (35-60)	1581	56 (44-68)	197	66 (55-77)	<.001	<.001	<.001
Hemogram values									
Leucocyte count, 10^9/L	4050	7.3 (5.7-9.2)	1581	6.7 (5.0-8.7)	197	9.0 (6.8-12.8)	<.001	<.001	<.001
Neutrophil count, 10^9/L	4050	4.53 (3.37-6.13)	1581	4.23 (2.99-6.17)	197	7.26 (4.74-11.09)	.268	<.001	<.001
Neutrophil %	4050	63.40 (55.97-72.31)	1581	65.13 (57.73-74.16)	197	82.65 (70.33-91.26)	<.001	<.001	<.001
Erythrocyte count, 10^{12}/L	4050	4.73 (4.39-5.09)	1581	4.42 (4.04-4.81)	197	4.14 (3.55-4.63)	<.001	<.001	<.001
Hemoglobin, g/dL	4050	13.5 (12.3-14.7)	1581	12.5 (11.4-13.6)	197	11.5 (9.6-13.0)	<.001	<.001	<.001
Hematocrit, %	4050	41.1 (37.7-44.4)	1581	38.2 (34.8-41.6)	197	36.6 (30.3-40.1)	<.001	<.001	<.001
MPV	4050	7.9 (7.4-8.6)	1581	8.0 (7.4-8.7)	197	8.8 (7.9-9.5)	.046	<.001	<.001
Platelet count,10^9/L	4050	260 (210-314)	1581	292 (220-381)	197	259 (182-378)	<.001	.001	.192
Lymphocyte count, 10^9/L	4050	1.74 (1.26-2.34)	1581	1.43 (1.05-1.91)	197	0.88 (0.54-1.63)	<.001	<.001	<.001
Lymphocyte, %	4050	25.90 (17.78-32.49)	1581	23.10 (15.65-30.26)	197	10.23 (4.59-18.34)	<.001	<.001	<.001
Eosinophil count, 10^9/L	4050	0.078 (0.022-0.16)	1581	0.072 (0.021-0.159)	197	0.017 (0.003-0.084)	.269	.117	.020
Eosinophil, %	4050	1.06 (0.34-2.16)	1581	1.12 (0.29-2.45)	197	0.14 (0.02-1,.8)	.037	<.001	.010

COVID-19, coronavirus disease 2019; ICU, intensive care unit; MPV, mean platelet volume.
Results are presented as median (25%-75%).

percentage below 0.08%, had a greater than 2-fold risk of ICU demand.

Previous studies have shown that the severity of COVID-19 increases with increased age.[5] A meta-regression analysis showed that lymphopenia was affected by age, but not by gender, in patients with poor outcome.[5] Our findings revealed that age and male ratio differed significantly between patients in outpatients, the ward, and ICU, but male ratio was not found to be an independent variable for ICU demand. We also found that being over 55 years of age was a predictor for ICU demand.

Lymphopenia is a common finding in patients with COVID-19 and is believed to indicate a defective immune response to the virus.[9] The cutoff values for lymphopenia range from 0.5 to 1.5 × 10^9/L in different studies[7] and is defined as an absolute lymphocyte count below 1.0 × 10^9/L in some studies.[10-12] Lymphopenia has been reported in 35%-75% of COVID-19 patients and found to be a frequent feature of severe disease.[13] The study reported it to be the most common hematological abnormality, present in up to 83% of hospitalized patients with COVID-19.[12] The meta-analysis noted that lymphopenia, defined as a lymphocyte count of less than 1.5 × 10^9/L, is associated with a 3-fold increased risk of severe COVID-19 infection.[3] In another meta-analysis, it was indicated that lymphopenia, defined as a lymphocyte count <1.1 × 10^9/L, was associated with severe COVID-19.[11] Zhang et al[13] found a median lymphocyte count of 1.3 × 10^9/L in discharged patients but a value of 0.56 × 10^9/L in those COVID-19 patients whose condition had deteriorated following hospital admission. Our results showed the cutoff value for lymphocyte count was 1.49 × 10^9/L for outpatients versus 1.26 × 10^9/L for COVID-19 patients hospitalized in the ward. A lymphocyte count of more than 1.49 × 10^9/L may be helpful for physicians in cases with possible non-severe COVID-19 that may be followed as outpatients, whereas patients with a lymphocyte count of lower than 1.26 × 10^9/L can be hospitalized in a ward for possible worsening of the disease.

Fan et al[14] reported that lymphopenia, with a median lymphocyte count of 0.4 × 10^9/L, featured prominently in the

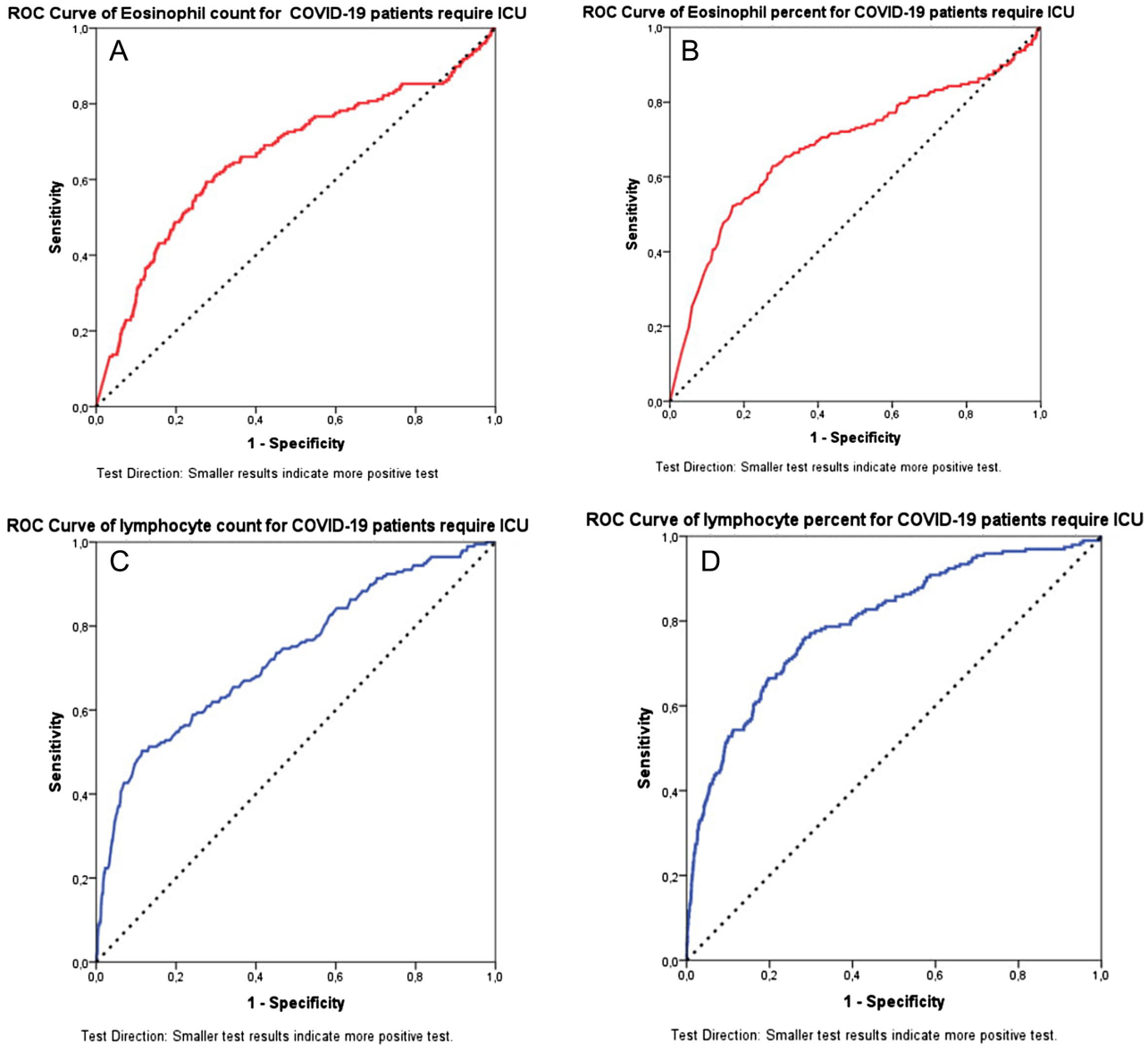

Figure 2. Receiver operating characteristic (ROC) curve analysis of (A) eosinophil count for predicting intensive care unit (ICU) demand, (B) eosinophil percent for predicting ICU demand, (C) lymphocyte count for predicting ICU demand, and (D) lymphocyte percent for predicting ICU demand.

COVID-19 ICU group, compared to 1.2 × 10^9/L in the non-ICU group. They proposed that a lymphocyte count of <0.6 × 10^9/L may be predictive for early admission to ICU. Tanriverdi et al[15] noted that lymphocyte count was significantly lower in the deceased group (1.5 × 10^9/L) compared to survivors (0.83 × 10^9/L).

We identified a lymphocyte count of 1.0 × 10^9/L as predictive of a 2.10-fold admission to the ICU. Monitoring the lymphocyte count on admission may help with early identification of patients who may need ICU care before clinical deterioration. Physicians should take care of patients with a lymphocyte count below 1.0 × 10^9/L and be aware of the potential

Table 2. Cutoff Values of Lymphocyte Count, Lymphocyte Percentage, Eosinophil Count, and Eosinophil Percentage for ICU Follow-up, as Determined with ROC Analysis

		95% CI					
Variables	**AUC**	**Lower Limit**	**Upper Limit**	***P***	**Cutoff**	**Sensitivity, %**	**Specificity, %**
Eosinophil count, 10^9/L	0.66	0.61	0.72	<.001	0.052	66	60
Eosinophil percentage	0.68	0.64	0.73	<.001	0.078	70	60
Lymphocyte count, 10^9/L	0.73	0.69	0.77	<.001	1.0	52	84
Lymphocyte percentage	0.80	0.76	0.83	<.001	0.22	80	60

AUC, area under curve; ICU, intensive care unit; ROC, receiver operating characteristic.

Table 3. Logistic Regression Analysis of the Parameters Included in the Model for Intensive Care Unit Demand

		95% CI		
	Odds Ratio	Lower	Upper	*P*
Age >55 years	2.868	2.033	4.047	<.001
Lymphocyte percentage <22%	2.383	1.593	3.564	<.001
Eosinophil percentage <0.08%	2.366	1.627	3.440	<.001
Lymphocyte count <1.0 × 10^9/L	2.100	1.489	2.961	<.001
Male gender	1.363	0.999	1.859	.051
Eosinophil count <0.052 × 10^9/L	1.177	0.799	1.733	.409

Table 4. Forward Stepwise Logistic Regression Analysis (Likelihood Ratio) Result for Prediction of ICU Demand

		95% CI		
	Odds Ratio	Lower	Upper	*P*
Lymphocyte count <1.0 × 10^9/L	2.14	1.53	3.00	<.001
Lymphocyte percentage <22%	2.53	1.70	3.77	<.001
Eosinophil percentage <0.08%	2.57	1.86	3.55	<.001
Age >55 years	2.87	2.03	4.04	<.001

ICU, intensive care unit.

severity and the need for ICU. Potential fatalities may be prevented with the timely management of these patients.

Lymphocyte percentage has been reported to decrease as the severity of disease increases.[16] While lymphocyte percentage was found to be 31% in non-severe patients, it was found to be 19% in severe patients.[16] Zhang et al[17] reported lymphocyte percentages as 20% in all COVID-19 patients, 25% in the non-severe group, 14% in the severe survival group, and 8% in the non-survival group.

According to our analysis, a lymphocyte percentage below 22% was predictive for ICU demand. Lymphocyte percentage, together with lymphocyte count, appears to present a useful, easy biomarker for predicting disease severity.

Eosinopenia has been observed in nearly 80% of COVID-19 patients on admission, with a median eosinophil count of 0.015 × 10^9/L.[18] The pathophysiology for eosinopenia in COVID-19 is not clear, but it is considered multifactorial, like reduced production and release of eosinophils from bone marrow and increased apoptosis induced by type 1 interferons during COVID-19 infection.[18]

Peripheral blood eosinophils are reduced at the early stage of COVID-19, regardless of the severity of the disease.[19] The usefulness of eosinopenia as a diagnostic and prognostic indicator has been investigated, but there is conflict regarding the association between eosinopenia and unfavorable disease progression.[18] Eosinopenia has been suggested to have a prognostic value in COVID-19 and an association with disease severity.[19,20] An early prediction of severity using eosinophil count on admission before clinical deterioration may be important to improve the prognosis of patients with COVID-19.[20] Xie et al[19] reported a low eosinophil count as an absolute number below 0.02 × 10^9/L.

In a study by Zhang et al.[17] the median eosinophil count was 0.01 × 10^9/L in 289 COVID-19 patients and did not significantly differ between the non-survival, severe but survival, and non-severe groups. However, the eosinophil percentage was found to differ between the non-survival (0.00%) and non-severe groups (0.30%). In another study, eosinophil counts and percentages were found to be lower in severe COVID-19 patients compared with non-severe ones.[16] Sun et al[16] reported that while the eosinophil count was 0.16 × 10^9/L, and eosinophil percentage was 2.35% in non-severe patients with COVID-19, the eosinophil count and percentage was lower in the severe cases (0.03 × 10^9/L and 0.44%, respectively). Sun et al[21] also reported that eosinophil count was significantly lower in critically ill patients compared to those with mild disease (0.09 × 10^9/L and 0.14 × 10^9/L, respectively).

The utility of eosinophils to predict COVID-19 severity is not clear. Our analysis revealed that eosinophil count and percentage in the ICU group (0.17 × 10^9/L and 0.14%, respectively) was lower than in the outpatient (0.78 × 10^9/L and 1.06%, respectively) and inpatient group, but the difference was not significant, as it was for lymphocytes. We found the cutoff points for eosinophil cell count and percentage were 0.052 × 10^9/L and 0.08%, respectively, for predicting ICU follow-up. However, eosinophil count was not found to be an independent predictor of ICU need.

A systematic review suggested that eosinopenia may not be associated with unfavorable progression of COVID-19.[22] A meta-analysis including 17 articles with 3396 (ranging from 12 to 1099) patients who were 720 in severe and 2676 in non-severe groups reported that decreased eosinophils in severe cases need more investigations through future studies.[23] Our results indicate that, unlike lymphopenia, eosinopenia does not have a strong association with COVID severity.

There are some limitations in this study. Firstly, it was of a retrospective nature. Nonetheless, the COVID-19 pandemic presents an urgent situation that cannot wait for prospective studies, and a retrospective study with a large sample size can provide valuable clinical information. Secondly, other patient data, such as previous history, comorbidities, and smoking history, were not recorded in the hospital database, although these values are not the primary information required for our study. Thirdly, this study is a single-centered study. Nonetheless, it was conducted in the largest chest disease teaching and research hospital in our country and reflects the whole population. All patients were evaluated by a pulmonary specialist.

The strength of this study lies in the large study population; the number of patients is indeed greater than many meta-analyses. In addition, data values were obtained using an electronic system to prevent human data entry errors. The study results are reliable and could be used to compare with other study results.

CONCLUSION

The present study findings revealed that lymphopenia showed a strong association with the severity of COVID-19 regardless of gender. Lymphocyte values can be obtained easily, cheaply, quickly, and routinely and facilitate earlier decision-making for the physicians on admission. Our results indicate that if the lymphocyte count on admission is below 1.0 × 10^9/L, and/or lymphocyte percentage is below 22%, eosinophil percentage is below 0.08%, and the patient age is over 55 years, there is a greater than 2-fold risk of ICU demand. These values may thus guide physicians to make early decisions for appropriate management in place regarding disease severity on admission.

COVID-19 Interest Group

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences, İstanbul Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 07.01.2021, Number: 116.2017.R-209).

Informed Consent: Owing to the retrospective nature of the study, informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.D., Z.K., N.D.K.; Design – D.D., Z.K., N.D.K.; Supervision – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G.; Resources – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G., COVID-19 Interest Group; Materials – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G., COVID-19 Interest Group; Data Collection and/or Processing – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G., COVID-19 Interest Group; Analysis and/or Interpretation – D.D., Z.K., N.D.K., N.A., T.Y.; Literature Search – D.D., Z.K., N.D.K.; Writing – D.D., Z.K., N.D.K., N.A., T.Y.; Critical Review – D.D., Z.K., N.D.K., N.A., T.Y., G.G., H.B.T., F.M.T., H.G., COVID-19 Interest Group.

Declaration of Interests: The authors declare that they have no competing interest.

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