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ORIGINAL ARTICLE

The Relationship Between Blood Eosinophil Levels and COVID-19 Mortality

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ABSTRACT

Aim: COVID-19 is a global pandemic caused by severe acute respiratory syndrome (SARS-COV-2). The objective of this study is to determine the relationship between blood eosinophil levels and the severity and mortality of COVID-19. **Methods:** The data of 678 patients were retrospectively collected from the electronic database of a hospital by researchers between March 2020 and December 2021. This is a descriptive study, and no specific sampling method was employed. The data were evaluated based on three groups of patients (moderate, severe, and chronic). Eosinophil values within the first 24 hours following hospital admission were obtained. The data was analyzed through IBM SPSS Statistics (20.0) software. Parametric tests were used for the statistical evaluations when the normality assumptions were met. Mann-Whitney U was used for two independent groups and multivariate logistic regression analysis was used to identify the relations. p-value < 0.05 was considered statistically significant. **Results:** In our study, it was found that eosinophil levels did not have an effect on disease severity (p=0.941). The COVID-19 related mortality rate was 14.6%, and the rate of severe/critical disease progression was 27.3%. Upon examining hematological parameters, it was observed that critical cases had significantly higher NEU values (p=0.001) and PCT values (p=0.024). LYM (p=0.007), HGB (p=0.029), PLT (p=0.023), HCT (p=0.005), MCV (p=0.039), MCH (p=0.048), MCHC (p=0.001), and RDW (p=0.023) were significantly lower in the severe group. It was determined that age, HCT, MCV, MCHC, urea, uric acid, sodium and potassium parameters were not significant risk factors for mortality (p>0.05). A reduction in MCHC (OR: 0.996; p=0.007) and sodium (p=0.031) demonstrated a mitigating effect on disease severity. The predictive effect of other parameters was found to be statistically insignificant. **Conclusion:** The effect of eosinophil levels on the severity and mortality of COVID-19 has not been found, whereas a decrease in MCHC and sodium levels showed a mitigating effect on disease severity. Further research is needed to investigate the clinical significance of these indicators in COVID-19 patients.

Keywords: COVID-19, Disease Severity, Eosinophils, Mortality

ÖZET

Amaç: COVID-19, şiddetli akut solunum yolu sendromu SARS-COV-2'nin neden olduğu küresel bir pandemidir. Bu çalışmanın amacı, kan eozinofil düzeyleri ile COVID-19'un şiddeti ve mortalitesi arasındaki ilişkiyi belirlemektir. **Yöntem:** 678 hastanın verileri, Mart 2020 ile Aralık 2021 tarihleri arasında araştırmacılar tarafından bir hastanenin elektronik veri tabanından geriye dönük olarak toplandı. Bu tanımlayıcı bir çalışmadır ve özel bir örnekleme yöntemi kullanılmamıştır. Veriler, hastaların üç grubuna (orta, şiddetli ve kronik) dayanarak değerlendirildi. Hastaneye yatışı takip eden ilk 24 saat içinde alınan eozinofil değerleri elde edildi. Veriler, IBM SPSS Statistics (20.0) yazılımı kullanılarak analiz edildi. Normal dağılım varsayımlarının karşılandığı durumlarda parametrik testler kullanıldı. İki bağımsız grup için Mann-Whitney U testi ve ilişkileri belirlemek için çok değişkenli lojistik regresyon analizi kullanıldı. p değeri <0,05 istatistiksel olarak anlamlı kabul edildi. **Bulgular:** Çalışmamızda eozinofil düzeylerinin hastalık şiddetinde etkili olmadığı bulunmuştur (p=0,941). COVID-19'a bağlı ölüm oranı %14,6, şiddetli/kritik hastalık seyri oranı ise %27,3 olarak bulunmuştur. Hematolojik parametreler incelendiğinde, kritik vakaların anlamlı derecede daha yüksek NEU değerlerine (p=0,001) ve PCT değerlerine (p=0,024) sahip olduğu gözlenmiştir.

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LYM (p=0,007), HGB (p=0,029), PLT (p=0,023), HCT (p=0,005), MCV (p=0,039), MCH (p=0,048), MCHC (p=0,001) ve RDW (p=0,023) parametreleri şiddetli grupta anlamlı derecede düşüktür. Yaş, HCT, MCV, MCHC, üre, ürik asit, sodyum ve potasyum parametrelerinin mortalite için anlamlı risk faktörleri olmadığı belirlenmştir (p>0,05). MCHC'de azalma (OR: 0,996; p=0,007) ve sodyumda azalma (p=0,031) hastalık şiddeti üzerinde hafifletici bir etki göstermiştir. Diğer parametrelerin etkisi istatistiksel olarak anlamlı bulunmamıştır. **Sonuç:** Eozinofil düzeyinin COVID-19'un şiddeti ve mortalitesi üzerine etkisi bulunmamış olup, MCHC'de azalma ve sodyumda azalma hastalık şiddeti üzerinde hafifletici bir etki göstermiştir. Bu göstergelerin COVID-19 hastalarındaki klinik önemini araştırmak için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Hastalık Şiddeti, Eozinofiller, Mortalite

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INTRODUCTION

COVID-19 is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). As the number of individuals infected with COVID-19 continues to rise globally and its effects on healthcare systems are observed, it is evident that clinical laboratories will play a crucial role in screening, diagnosis, monitoring, and contributing to treatments.

In this pandemic, the fundamental role of clinical laboratories extends beyond the etiological diagnosis of COVID-19. Monitoring COVID-19 patients biochemically through in vitro diagnostic tests is crucial not only for assessing disease diagnosis, severity, and progression but also for monitoring therapeutic interventions. One of the most significant contributions of laboratory findings encompasses the staging, prognosis, and therapeutic monitoring of COVID-19. Many laboratory tests can be highly beneficial in determining disease severity and assessing the risk of developing acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and multiple organ failure (2).

Eosinophils are granulocytes that have strong pro-inflammatory effects and have been shown to participate in inflammation, immunoregulation, and host defense against various diseases, including viral infections. Eosinopenia is defined as a decrease in the circulating eosinophil count in peripheral blood. Eosinopenia has been observed during infection with SARS-CoV-2, the causative agent of COVID-19. Some studies have reported an association between eosinopenia and worsening respiratory symptoms (3). Recently, the role of eosinopenia as a diagnostic and prognostic indicator for COVID-19 has garnered interest. The role of eosinopenia becomes highly crucial as an early diagnostic indicator for COVID-19 infection, especially during pandemics when

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resources are limited, and early decisions about patient triage and isolation are deemed extremely beneficial until nucleic acid confirmation is performed (4,5,6).

Regarding laboratory findings, in patients with severe illness, in addition to increased levels of inflammatory markers such as C-reactive protein (CRP), D-Dimer, and procalcitonin, other typical indicators include an increase in neutrophil counts and a decrease in lymphocyte levels. The aforementioned laboratory findings are shared with SARS-CoV-2 and MERS-CoV. A distinctive feature associated with SARS-CoV-2 infection is a decrease in eosinophil levels (eosinopenia). However, the results of previous studies on the relationship between eosinopenia and disease severity have been inconsistent (7,8,9). Since COVID-19 can lead to high mortality, studies have been conducted to investigate the relationship between eosinopenia and COVID-19 mortality, as well as to identify clinical conditions that may potentially lead to mortality. Identifying laboratory tests that contribute to the diagnosis and monitoring of COVID-19 is crucial not only for the diagnosis stage but also for distinguishing between severe and non-severe cases, as well as identifying those at low or high risk of mortality (10).

During a severe infection such as COVID-19, the levels of almost all markers can change, correlating with the severity of the disease and survival. However, until a biomarker is proven to have a significant impact, it cannot be translated into clinical practice for treatment guidance. Various studies have documented the relationship between the severity of COVID-19 and circulating levels of CRP and interleukin-6, evaluating the accuracy of CRP levels in predicting treatment responses. Promising findings related to prothrombin and D-Dimer have also been reported. However, the clinical utility of these biomarkers in COVID-19 is far from being proven (11). The surge in data generation during this pandemic has led to the publication of numerous studies with many significant disadvantages, weakening the strength of the findings.

The aim of this study is to determine the relationship between blood eosinophil levels and COVID-19 mortality.

MATERIAL AND METHODS

Patients

The data for the study were retrospectively collected by researchers between March 2020 and December 2021 from Izmir Menemen State Hospital. The study includes demographic information, clinical symptoms, comorbidities, laboratory data, and radiological materials of 678 confirmed COVID-19 patients who presented to the hospital. This is a descriptive study, and no specific sampling method was employed.

Clinical Classifications

Cases with a confirmed diagnosis of COVID-19 were included, consisting of individuals with SARS-CoV-2 infection confirmed through molecular methods, as well as patients with typical COVID-19 findings on CT scans. Patients currently hospitalized, those

discharged without medical advice, individuals undergoing steroid treatment, and patients presenting with eosinophilia were excluded from the study.

Data collection

According to the guidelines of the World Health Organization, patients with a positive result in the nucleic acid test for SARS-CoV-2 using real-time reverse transcription polymerase chain reaction (RT-PCR) were considered confirmed COVID-19 cases. Patients classified as moderate, severe, and critical cases during the assessment at the time of admission were included in the study. The collected data were evaluated based on these three groups of patients. Disease severity levels were classified according to the guidelines of the World Health Organization and the United States: Moderate disease: Presence of symptoms and signs of respiratory infection, but oxygen saturation is 94% or higher. Severe disease: Respiratory rate exceeding 30/minute, oxygen saturation below 94%, PaO2/FiO2 value less than 300 mmHg, or infiltration affecting more than 50% of the lungs. Critical disease: Defined by respiratory failure, septic shock, and/or multiple organ failure (12). In our hospital, an eosinophil count below 0.8% in mm^3 is defined as eosinopenia (reference range: 0.8-6). Eosinophil values within the first 24 hours following admission were collected for the patients included in the study. Patient information was kept confidential, consisting of demographic details, laboratory findings, accompanying illnesses, medical histories, clinical symptoms, chest CT images, and clinical details. The inclusion of other laboratory parameters may provide a better predictive model for disease outcomes in COVID-19 patients.

Statistical analysis

The data was analysed through IBM SPSS Statistics (20.0) software. Categoric variables were presented by number and percentages and continuous variables were given via descriptive statistics. Parametric tests were used for the statistical evaluations when the normality assumptions were met. Mann-Whitney U for was used for two independent groups, and multivariate logistic regression analysis were used to identify the relations. p value less than 0.05 was considered statistically significant.

Study approval

This protocol was approved by the Ethics Committee of Katip Çelebi University Non Interventional Clinic Studies (no. 57; date of approval: February 24, 2022), and was performed in accordance with the Declaration of Helsinki. Informed consent was not obtained as this is a retrospective study.

RESULTS

In our study, there were 307 (45.3%) female and 371 (54.7%) male patients. Patients under the age of 40 constituted 85 (12.5%), those between the ages of 40-64 accounted for 287 (42.3%), and patients aged 74 and above were 149 (22.0%). Disease severity was categorized into 67 (9.9%) severe cases and

118 (17.4%) critical cases, combined to form a total of 185 (27.3%) severe/critical cases, which were compared with 493 (72.7%) moderate cases. The fatality rate in our study was 14.6%, and the rate of severe/critical disease progression was 27.3%.

The severity of the disease did not show a significant difference according to gender (p=0.398). The rate of critical cases was significantly lower in individuals under 40 years old, and significantly higher in individuals over 74 years old (p<0.001). There is a significant relationship between the severity of the disease and age groups (p<0.001). In individuals under 40 and those between 40-64 years old, the rate of severe/critical cases was lower compared to other age groups. The rate of severe/critical cases was higher in individuals hospitalized (p<0.001), and the majority of death cases were observed in severe/critical cases (p<0.001). The presence of typical COVID-19 symptoms was associated with a higher incidence of severe/critical cases (p<0.001). Severe/critical cases were more prevalent in patients with severe findings on COVID-19 CT and positive PCR results (p<0.001). The majority of cases discharged with recovery were moderate cases, while the majority of referred cases were severe/critical (p<0.001). The rate of hospital discharge in severe cases was significantly higher (p<0.001) (Table 1).

Table 1: Comparison of Clinical Findings in Case Groups

	Disease Severity		
	Moderate Case (n=493) n(%)	**Severe/Critical Case (n=185) n(%)**	**p**
Gender			
Female	225 (73.3)	82 (26.7)	0.759
Male	268 (72.2)	103 (27.8)	
Age			
Below 40 years	69 (81.2)	16 (18.8)	**<0.001**
40-64 years	220 (76.7)	67 (23.3)	
65-74 years	112 (71.3)	45 (28.7)	
74 years and older	92 (61.7)	57 (38.3)	
Presence of chronic illness			
Yes	338 (73.3)	123 (26.7)	0.606
No	155 (71.4)	62 (28.6)	
Hospitalization status			
Yes	461 (75.9)	146 (24.1)	**<0.001**
No	32 (45.1)	39 (54.9)	
Total death			
Yes	41 (41.4)	58 (58.6)	**<0.001**
No	452 (78.1)	127 (21.9)	

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CT Findings			
No Ct finding /incompatible with COVID-19	162 (85.7)	27 (14.3)	**<0.001**
Typical COVID-19 finding	331 (67.7)	158 (32.3)	
COVID-CT			
Mild	69 (71.9)	27 (28.1)	
Moderate	212 (73.4)	77 (26.6)	**<0.001**
Severe	49 (47.6)	54 (52.4)	
PCR			
Negative	2 (18.2)	9 (81.8)	**<0.001**
Positive	223 (85.1)	39 (14.9)	
Discharge Status			
Transfer(same or more comprehensive)	93 (38.1)	151 (61.9)	
Discharge with recovery	388 (92.4)	32 (7.6)	**<0.001**
Death	10 (90.9)	1 (9.1)	
Other	2 (66.7)	1 (33.3)	
Outpatient Treatment Death			
None	462 (78.3)	128 (21.7)	**<0.001**
Exist	31 (35.2)	57 (64.8)	

Eosinophil levels were found not to be effective in disease severity (p=0.941). When examining other hemogram parameters, NEU (neutrophil) values (p=0.001) and PCT (procalcitonin) values (p=0.024) were significantly higher in critical cases. LYM (lymphocyte) (p=0.007), HGB (hemoglobin) (p=0.029), PLT (platelet) (p=0.023), HCT (hematocrit) (p=0.005), MCV (mean corpuscular volume) (p=0.039), MCH (p=0.048), MCHC (mean corpuscular hemoglobin concentration) (p=0.001) and RDW (red cell distribution width) (p=0.023) parameters were observed to be significantly lower in the severe group (Table 2).

Table 2: Comparison of Hemogram Parameters According to the Severity of the Disease

	Disease Severity		**p**
	Moderate Case (n=493) mean±SD	**Severe/Critical Case (n=185) mean±SD**	
NEU(×103/µl)	8.29±6.57	10.95±5.15	**0.001**†
WBC (×103/µl)	4.93±7.48	7.05±17.17	0.135†
RBC (×103/µl)	9.59±20.02	14.00±26.64	0.505†
LYM(×103/µl)	1.26±2.46	0.96±1.20	**0.007**†

Monocyte (×103/µl)	2.60±25.89	3.56±15.15	0.282†
Eosinophil(×103/µl)	0.16±0.11	0.14±0.05	0.941†
Basophil	0.37±1.32	3.04±4.03	0.244†
HGB	7.75±8.22	6.89±12.35	**0.029**†
PLT	310.02±134.77	257.68±115.36	**0.023**†
HCT	30.50±15.43	21.28±18.82	**0.005**†
MCV	73.26±23.38	67.27±27.91	**0.039**†
MCH	22.13±11.76	20.04±13.87	**0.048**†
MCHC	20.43±15.87	13.44±15.58	**0.001**†
RDW	11.57±6.53	10.42±6.59	**0.023**†
MPV	8.75±37.06	3.92±5.05	0.070†
PDW	16.38±2.56	16.23±3.51	0.544†
PCT	9.21±12.89	14.58±14.44	**0.024**†

†Mann-Whitney U, p<0.05

Eosinophil levels were found not to be effective in disease severity (p=0.632). When examining other hemogram parameters, the NEU values of critical cases were found to be significantly elevated (p=0.046). Furthermore, in the severe group, the parameters of HGB (p=0.007), HCT (p=0.017), MCV (p<0.001), MCHC (p=0.002), and RDW (p=0.038) were significantly lower (Table 3).

Table 3: Comparison of Hemogram Parameters According to the Mortality

	Mortality		p
	Survived (n=579) mean±SD	**Deceased (n=99) mean±SD**	
NEU(×103/µl)	8.77±6.54	10.06±4.46	**0.046**†
WBC (×103/µl)	5.33±9.52	6.23±16.78	0.200†
RBC (×103/µl)	9.70±20.17	16.25±29.48	0.174†
LYM(×103/µl)	1.22±2.36	0.97±0.79	0.251†
Monocyte (×103/µl	2.89±25.27	0.72±0.70	0.739†
Eosinophil(×103/µl)	0.16±0.11	0.13±0.05	0.632†
Basophil	0.80±2.15	0.10±0.00	0.394†
HGB	7.89±9.63	5.31±7.53	**0.007**†
PLT	306.20±135.12	244.89±89.74	0.066†
HCT	29.52±16.11	19.35±18.65	**0.017**†

MCV	73.36±23.65	61.52±28.74	**0.000**†
MCH	21.44±11.49	22.74±16.87	0.848†
MCHC	20.06±15.92	10.84±14.70	**0.002**†
RDW	11.46±6.56	10.18±6.48	**0.038**†
MPV	8.23±34.68	3.18±4.01	0.075†
PDW	16.46±2.54	15.22±4.39	0.284†
PCT	10.08±13.43	13.73±13.19	0.365†

†Mann-Whitney U, p<0.05

In this study; when biochemical tests were evaluated according to mortality, D-Dimer (p=0.049), HDL (p=0.022), albumin (p=0.031), fasting glucose level (p=0.040), urea (p=0.014), uric acid (p=0.002), creatinine (p<0.001), and potassium (p=0.016) levels were found to be significantly higher in the deceased group. Sodium (p<0.001) was significantly lower in the deceased group.

When biochemical tests were evaluated among case groups, in the Critical Case group, D-Dimer (p=0.003), albumin (p=0.004), fasting glucose (p=0.005), urea (p<0.001), uric acid (p<0.001), creatinine (p<0.001), sodium (p=0.025), and potassium (p<0.001) parameters were observed to be significantly elevated, while ALT (p=0.042), AST (p=0.020), and fibrinogen (p=0.016) parameters were significantly lower (Table 4).

Tablo 4: Comparison of Biochemical Parameters According to Disease Severity

	Disease Severity		**p**
	Moderate Case (n=493) mean±SD	**Severe/Critical Case (n=185) mean±SD**	
CRP (mg/L)	35.00±23.03	41.86±28.98	0.156†
LDH (mg/dL)	103.17±133.24	73.80±81.44	0.196†
D-Dimer (mg/L)	4.14±18.26	7.80±21.79	**0.003**†
HDL	137.28±5.87	136.72±5.67	0.376†
Ferritin	286.42±239.36	325.93±262.15	0.339†
Albumin	8.92±8.15	14.45±9.71	**0.004**†
Troponin	51.22±309.57	7.64±22.46	0.472†
Prothrombin Time	13.25±18.29	13.62±19.93	0.497†
Fasting Glucose	135.52±63.83	178.69±75.80	**0.005**†
Urea	46.30±29.61	78.83±49.13	**<0.001**†
Uric Acid	11.80±27.52	35.43±69.08	**<0.001**†
Creatinine	10.15±29.08	20.63±41.33	**<0.001**†

ALT	45.03±40.99	37.96±33.52	**0.042**†
AST	38.14±27.24	31.32±19.73	**0.020**†
Na	135.99±5.34	125.11±30.82	**0.025**†
K	18.81±14.11	24.74±12.54	**<0.001**†
Respiratory Rate	17.47±9.01	19.13±8.88	0.560†
Saturation	91.59±7.06	88.49±9.12	0.061†
Alkaline Phosphate	90.75±46.55	86.19±43.67	0.633†
CK_MB_Mass	59.76±45.83	56.56±37.27	0.875†
Initial Hem	5.99±3.80	6.34±4.29	0.647†
Fibrinogen	205.70±163.30	153.59±131.53	**0.016**†

†Mann-Whitney U, p<0.05

In this study; the mortality status did not show significant gender differences (p=0.635). Mortality rate was significantly lower in individuals under 40 years old and significantly higher in those aged 74 and above (p<0.001). Hospitalized individuals had a higher mortality rate (p<0.001). The presence of typical COVID-19 symptoms indicated an increased mortality rate (p=0.001). Mortality rate was higher in severe COVID-19 CT cases (p<0.001) and in cases with positive PCR results (p=0.009).

Age, HCT, MCV, MCHC, urea, uric acid, sodium and potassium parameters were not identified as significant risk factors for mortality (p>0.05) (Table 5).

In this study a decrease in MCHC (OR: 0.996; p=0.007) and a decrease in sodium (p=0.031) were observed to have a mitigating effect on disease severity. The predictive effect of other parameters is not statistically significant.

Table 5: Multivariate Logistic Regression Analysis for Mortality Risk Factors

	OR	%95 GA	p
Age	1.053	(0.970-1.142)	0.218
HCT	1.028	(0.855-1.237)	0.768
MCV	0.974	(0.815-1.165)	0.773
MCHC	0.699	(0.222-2.202)	0.540
Urea	1.002	(0.964-1.041)	0.932
Uric acid	1.428	(0.911-2.237)	0.120
Na	0.868	(0.646-1.166)	0.347
K	0.594	(0.109-3.227)	0.547

DISCUSSION

In our study, which examined 678 patients diagnosed with COVID-19, we initially investigated factors influencing both the severity of the disease and mortality, particularly focusing on eosinophils. The fatality rate in our study was 14.6%, and the rate of severe/critical disease progression was 27.3%. An article evaluating fatality rates in hospitalized patients from different regions worldwide reported a fatality rate of 18.8% (13). Age has consistently been identified as one of the most important demographic factors affecting the severity of the disease course and fatality (14). A large-scale meta-analysis showed that the fatality rate was 2,32 times higher in individuals aged 70 and older (15). In Italy, one of the countries with the highest reported fatality rates in Europe, where a quarter of the population is aged 65 and over, an analysis found a crude fatality rate of 7.2%, with the fatality rate rising to approximately 20% in cases over 80 years old (16). In our study, a significant relationship was found between disease severity and age groups, with a notably higher rate of critical cases in individuals aged 74 and above. Elderly patients have numerous risk factors that predispose them to infection, and weakened immune function is one of them (17). Most of the cases hospitalized, referred, and deceased in our study were in this age group. However, referred patients are those referred from our hospital due to the need for intensive care, which may explain the higher rates of death and severe/critical cases in this group. Cases discharged with recovery mostly belonged to the moderate clinical cases. The out-of-hospital mortality rate is also high in severe cases, which is related to the advanced age group of patients admitted to the intensive care unit. Aging poses a significant risk in both getting sick and the severe progression of the disease. Especially in the elderly, the accurate identification of patients who need intensive care monitoring is crucial, and defining risk factors decisive for severe progression and intensive care follow-up is crucial, especially during periods of increased patient load. Identifying high-risk patients is essential for the effective use of healthcare resources in the face of an increasing patient burden.

In our study, when hematological parameters were examined according to disease severity, eosinophils were not identified as a parameter indicating disease severity. NEU and PCT values of critical cases are significantly higher. LYM, HGB, PLT, HCT, MCV, MCH, MCHC, and RDW parameters are significantly lower in the severe group. In a study by Yan et al., a progressive decrease in eosinophil levels, after controlling for confounding factors, was associated with the mortality rate in COVID-19 patients (18). Lymphopenia has been reported as a widespread anomaly in COVID-19 patients. They stated that coronaviruses, especially, affect T lymphocytes by reducing their numbers. This result is consistent with our study (19, 20). In the study by Li et al., the HGB level was found to be low, similar to our

results. This may be due to chronic disease anemia in elderly patients (21). Although low Hb levels are considered one of the poor prognosis criteria, more comprehensive studies are needed to explain this. Gu et al. mentioned an association between an increase in RDW and the severity of COVID-19, but our study did not show such a result (22). An increase in RDW may occur in systemic inflammations, but we may not have been able to demonstrate this increase due to the intensification of the patients' need for intensive care and their referral.

In our study, when hematological parameters were examined based on mortality, NEU values of critical cases were significantly higher. HGB, HCT, MCV, MCHC, and RDW parameters were significantly lower in the severe group. Hematological parameters were found in a similar way according to the severity of the disease. While lymphocytes were significantly lower in disease severity, they were not found to be effective in mortality. Lymphopenia is a prominent feature in critical patients with SARS-CoV-2 infection. Targeted invasion of SARS-CoV-2 viral particles damages the cytoplasmic component of lymphocytes, leading to their destruction (22). In patients who died from COVID-19, a significantly low lymphocyte count was determined compared to survivors (23). In a study, it was shown that the eosinophil counts of non-survivors were significantly lower compared to survivors (18). This result could not be supported by our study. However, eosinopenia may serve as a prognostic indicator for more severe COVID-19. COVID-19-associated eosinopenia is likely a secondary outcome and does not directly contribute to the course of the disease (24). The complete blood count (CBC) test, which is easily accessible in outpatient settings, is practical and cost-effective (25).

In our investigation, scrutiny of biochemical parameters in relation to the severity of the disease revealed that in the critical/severe case group, D-Dimer, albumin, fasting glucose, urea, uric acid, creatinine, and potassium parameters were elevated. Conversely, ALT, AST, and fibrinogen showed a significant decrease according to the severity of the disease. In the early studies, it was reported that AST and ALT values were elevated in more than one-third of patients, and this was associated with prolonged hospital stays (26). Gao et al. found that D-Dimer levels were statistically significantly higher in severe cases, establishing it as the most studied and robust prognostic marker (21). There are studies indicating that COVID-19 could exacerbate existing cardiovascular diseases or lead to cardiovascular complications by increasing risk factors (27). Particularly, elevated levels of acute cardiac injury and coagulation biomarkers are known to be associated with a worse prognosis (28). Among these markers, D-Dimer is frequently employed in predicting the prognosis of COVID-19, while serum potassium levels are negatively correlated with the severity of COVID-19 (29). According to a study, hypokalemia was predominant in COVID-19 patients, and the correction of hypokalemia was challenging due to continuous renal K+

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loss caused by ACE2 disruption. In a prospective cohort study involving COVID-19 patients, the incidence of acute kidney injury and death during hospitalization was found to be significantly higher in patients with initially high serum creatinine levels compared to those with normal initial values (29). In a study, it was observed that the levels of serum aspartate aminotransferase significantly increased in patients with severe disease compared to those with moderate disease, indicating liver damage. Additionally, in critical cases, serum aspartate aminotransferase levels were further increased, suggesting worsening liver damage in critical cases (18). In advanced analyses in our study, a decrease in mean corpuscular hemoglobin concentration (MCHC) and a decrease in sodium were observed to have a mitigating effect on the severity of the disease. The predictive effect of other parameters was not statistically significant.

In our study, when biochemical parameters were examined based on mortality, it was observed that D-Dimer, HDL, albumin, fasting glucose level, urea, uric acid, creatinine, and potassium levels were significantly higher in the deceased group. In advanced analyses in our study, age, HCT, MCV, MCHC, urea, uric acid, sodium, and potassium parameters were not identified as significant risk factors for mortality. Some of these results did not align with other studies (27). The practical clinical utility of a specific biomarker is not proven until it assists clinicians in managing patients and making treatment decisions. A biomarker pipeline often involves many steps that can result in failure; therefore, the evaluation and validation of a specific molecule require rigorous studies with flawless methods and homogeneous characteristics. From this perspective, studies on the utility of biomarkers in COVID-19 have not proven an impact on treatment decisions, and they have been affected by various limitations, including differences in methods used and weaknesses in study design.

Some limitations in our study have influenced the results. It is a retrospective study, providing a lower level of evidence compared to prospective and interventional studies. Therefore, there is insufficient data to prove the usefulness of a biomarker in guiding treatment and appropriate patient management. The selected assay methods, cutoff points, and measurement times vary in our study. The collection of study subjects in a single center can affect the repeatability and robustness of the results and may lead to selection bias. The influence of unmeasured confounding factors should not be overlooked. Particularly noteworthy is the significant data gap in eosinophil counts, a parameter commonly used in current clinical practice.

CONCLUSIONS

It was found that eosinophil levels do not have an effect on the severity of the disease. Parameters such as age, HCT, MCV, MCHC, urea, uric acid, sodium, and potassium were not identified as significant risk factors for mortality. A reduction in MCHC and sodium was observed to have a mitigating effect on the severity of the disease. The

predictive effects of other parameters were statistically insignificant. Despite the identification of significant relationships, further research is needed to explore the clinical significance of these indicators in patients with COVID-19. Predicting risk, particularly in countries with limited financial resources, will aid in reducing mortality rates through monitoring and early, appropriate treatment, and will contribute to the optimal use of resources.

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Conflicts of interest: The authors have no conflicts of interest to declare.

Ethics approval: This protocol was approved by the Ethics Committee of Katip Çelebi University Non-Interventional Clinic Studies (no. 54; date of approval: February 24, 2022) and was performed in accordance with the Declaration of Helsinki. Informed consent was not obtained as this is a retrospective study.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

Author contributions: Conceptualization - GY, GŞ; Data Collection - GY, GŞ; Study Design - GY, GŞ; Supervision - GY, ET; Data Collection, Analysis, Interpretation - GY, GŞ; Literature Review - GY; Writing - GY; Critical Review - ET. All authors provided comments on the drafts and have read and approved the final manuscript.

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