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Original Article

Interleukin-5, Interleukin-6 and Eosinophils in COVID-19 Egyptian Patients: Potential Clues for Prognosis and Immunotherapy

Sara I. Taha*[1], Eman M. EL Sehsah [2], Shaimaa H. Fouad [3], Hieba G. Ezzelregal [4], Aya H. Moussa [5], Shaimaa A. Abdalgeleel [6], Mariam F. Abdelmaksoud [1].

[1] Department of Clinical Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
[2] Department of medical microbiology /Immunology, Faculty of Medicine, Mansoura university, Mansoura, Egypt.
[3] Department of Internal Medicine [Allergy and Clinical Immunology], Faculty of Medicine, Ain Shams University, Cairo, Egypt.
[4] Department of Pulmonary Medicine, Faculty of Medicine, Ain Shams university, Cairo, Egypt.
[5] Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
[6] Department of Biostatistics and Epidemiology, National Cancer Institute, Cairo University, Cairo, Egypt.

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*Corresponding author
Email: dr_sara_ib@med.asu.edu.eg

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ABSTRACT

Background: A decrease in eosinophil levels was found in Corona Virus Disease-19 [COVID-19] patients [eosinopenia]. However, recent research on eosinopenia and disease severity has yielded conflicting results.

Objectives: To investigate the relationship between interleukin [IL]-5 and IL-6 levels, COVID-19 severity, and eosinophil count in Egyptian patients.

Patients and Methods: Eighty-three COVID-19 patients were enrolled. At hospital admission, patients' medical records were reviewed for sociodemographic, clinical, and laboratory data. IL-5 and IL-6 levels in pretreatment serum samples were measured by enzyme linked immunosorbent assay [ELISA].

Results: Severe disease patients had significantly lower eosinophil levels than non-severe patients [0.0 $\times 10^3/\mu L$ [0.0-0.4] vs. 0.2$\times 10^3/\mu L$ [0.0-0.4]; $P \leq 0.001$]. On the other hand, levels of IL-5 [180.0 pg/ml [10.0-960.0] vs. 300.0 pg/ml [170.0-690]; P=0.013] and IL-6 [110.0 pg/ml [20.0-600.0] vs. 45.0 pg/ml [20.0-120.0]; $P \leq 0.001$] were significantly higher. Additionally, eosinophils were significantly negatively correlated with biomarkers of coagulation dysfunction [D-dimer; P=0.016], inflammation [C-reactive Protein [CRP]; P=0.037 and ferritin; P=0.049] and cytokine storm [IL-6; P=0.018], but there was no significant correlation between eosinophils and IL-5 [P=0.931]. In addition, eosinophil count showed little diagnostic significance in distinguishing between severe and non-severe COVID, with an area under the curve [AUC] of 0.174.

Conclusion: Anti-COVID-19 immunotherapy could target IL-5, IL-6, and eosinophils. IL-6 levels outperformed IL-5 levels and the peripheral eosinophil count in predicting COVID-19 development. Despite its weak predictive potential, eosinopenia has been related to severe COVID-19 infection and a higher risk of in-hospital death.

Keywords: COVID-19; Eosinophils; IL-5; IL-6; Severity; Progression.

INTRODUCTION

Inflammation, immunological dysregulation, and cytokine storms characterize the coronavirus disease 2019 [COVID-19] pandemic [1].

Many studies have been conducted on the disease, including diagnostic and prognostic biomarkers and potential treatments and prevention methods [2].

Eosinophils develop in the bone marrow in

response to cytokines such as interleukin [IL]-5 [3] to make up a minor fraction [1% to 3%] of the pool of circulating leukocytes [4].

Eosinophil levels in the blood are clinically relevant. Because of the cytotoxic proteins packed in their preformed granules, such as major basic protein and eosinophil peroxidase, eosinophils are regarded as effective proinflammatory cells [5].

They can play a role in the immunopathology of various diseases, including bronchial asthma and hyper-eosinophilic syndrome [6], and protective immunity against bacteria, viruses, and parasites [7,8].

Interestingly, in several studies, eosinopenia has been documented in patients with COVID-19 as a factor that might help in severe disease diagnosis and prognosis [9–11]. However, studies suggested that patients with eosinophil-associated conditions [e.g., asthma] are not at higher risk for severe disease and may even be protected [12].

The cytokine release syndrome [CRS] is thought to be responsible for COVID-19 severe symptoms and high mortality [13]. IL-6, a major mediator in COVID-19 infection, has been a special focus among CRS-related cytokines [14].

THE AIM OF THE WORK

This study aimed to investigate the link between eosinophil count as well as serum levels of IL-5 and IL-6 and COVID-19 severity, using a cohort of Egyptian COVID-19 patients.

MATERIALS AND METHODS

Study design and patient selection:

This comparative cross-sectional study was conducted on a sample of COVID-19 adult patients [n = 83]. All patients in the severe group were recruited from the intensive care units, while the non-severe patients were recruited from general wards of isolation Hospitals of Ain-Shams University [ASU], Cairo, Egypt, from January to February 2021. Positive laboratory test results for SARS-CoV2 from respiratory specimens using the real-time reverse transcription-polymerase chain reaction [RT-PCR] assay using the Abbott m2000 Real Time System [Abbott, Germany] confirmed COVID-19 infection in all patients. Patients who were chronically immunosuppressed, known to be pregnant, receiving long-term oral corticosteroids or antivirals, or had active neoplasia, gastrointestinal nematode infections or allergies were excluded.

All participants were subjected to complete medical history taking, focusing on age, sex, and clinical symptoms. They also had a chest CT at Ain Shams University [Siemens 16-channel scope, Erlangen, Germany]. All patients were followed until discharge from hospital or in-hospital death.

The Ain Shams University Hospitals Central Laboratories performed baseline laboratory tests such as CBC by Sysmex XT-1800i autoanalyzer [Sysmex, Japan], CRP [reference range [RR] < 5mg/L] and ferritin [RR: male: 30-400 ng/ml; female: 15-400 ng/ml] by COBAS autoanalyzers [Roche Diagnostics GmbH, Mannheim, Germany], and D-dimer [RR: <0.5 mg/L] by VIDAS PC autoanalyzer [BioMerieux, France]. As determined at the time of admission, disease severity was classified as mild, moderate, severe, and critical [15].

Severe cases met all the following conditions: Respiratory rate ≥ 30 breath/min; Oxygen saturation ≤ 93 % at rest; arterial blood oxygen partial pressure [PaO_2]/fraction of inspired oxygen [FiO_2] ≤ 300 mmHg.

In addition, they demonstrated a larger than 50% advancement of pulmonary lesions in chest imaging within 24–48 hours. Critical cases satisfied one of the following criteria: respiratory failure and mechanical ventilation, shock, and organ failures needing ICU monitoring and treatment.

Intensive Care Unit [ICU] management of COVID-19 patients:

Symptomatic treatment with intravenous para-cetamol for fever and myalgia, proton pump inhibitors, and motility regulators were incorporated in Ain Shams University [ASU] isolation hospitals procedures. Sub-cutaneous Enoxaparin 0.5 mg/kg/ day was given as prophylactic anticoagulation. Lopinavir-Ritonavir [200/50mg] 2 pills bid for 5-10 days.

Tocilizumab was used in the following circumstances: COVID-19 compatible chest imaging; the need for >4- 6 L/min oxygen; inflammatory markers elevation [ferritin >600 ug/mL, D-dimer >1 mg/L]; ≤ 48-hour mechanical ventilation [in Critical cases].

Tocilizumab was infused slowly intravenous [IV]. The initial dose was 8 mg/kg, and if the patient needed a second dose, it was estimated at 4 mg/kg after 12 hours.

In the absence of Tocilizumab, 1 mg/kg/day IV

methylprednisolone was given for 5 days, then 0.5 mg/kg/day IV for 2 days. Prone positioning was recommended [30 minutes/2 hours] unless contra-indicated. Supplemental oxygen therapy was initiated immediately with a target SpO_2 of 94%.

Sample collection and cytokine measurement:

From all participants, 3 mL of venous blood was collected by venipuncture under complete aseptic conditions on a serum separation tube for IL-5 and IL-6 analysis. The blood samples were allowed to clot then were centrifuged at 1000 × g for 20 minutes. Sera were collected and stored at -80^{o} C until analysis.

Serum levels of IL-5 and IL-6 were assessed using human ELISA kits supplied by Bioassay Technology Laboratory, Shanghai, China [Catalog Numbers: E0091Hu and E0090Hu, respectively] following the manufacturer's instructions. The results were expressed in pg/ml.

Data analysis:

The results were generated using Statistical Package for Social Sciences [SPSS] [version 26]. Single-sample Kolmogorov-Smirnov tested data normality. Variables were compared using the Mann–Whitney U test for continuous ones and the Chi-square test for categorical variables.

The Spearman correlation coefficient was used to correlate non-normal variables [*r*]. The best cut-off values were determined using the Receiver Operation Curve [ROC] analysis. A *P*-value of 0.05 was considered significant.

RESULTS

Out of a total of 83 participants, 42 patients were assigned to the non-severe group, and 41 to the severe group. The male to female ratio did not differ significantly between the two groups.

The median age of all included participants was 55 years [IQR: 23-82] and was significantly higher in the severe group [56 years [IQR: 32-82] vs. 45 years [23-78]; *P*=0.005] than in the non-severe group. Fever [48.2%] and dyspnea [47.2%] were the most prevalent initial symptoms.

The most common comorbidities were hypertension [41%] and diabetes [36.1%]. However, chronic kidney disease [26.5%] was the only comorbidity significantly associated with severe disease [*P*=0.004]. Oxygen saturation was significantly lower in the severe group than in the non-severe group [81% [60.0-98.0] vs. 95.5% [93.0-97.0]; $P \leq 0.001$].

Of all included patients, 62.0 [74.7 %] were discharged alive, while 21[25.3%] died during their hospital stay.

The in-hospital death rate was significantly higher in the severe group than in the non-severe group [20 [95.2%] vs. 1 [4.8%]; $P \leq 0.001$].

Baseline demographic, clinical, and laboratory data, as well as the fate of the included subjects, are shown in Table 1.

Serum levels of IL-5 and IL-6, as well as eosinophil counts, varied scientifically between non-severe and severe groups. Hence, levels of IL-5 [180.0 pg/ml [10.0-960.0] vs. 300.0 pg/ml [170.0-690]; *P*=0.013] and IL-6 [110.0 pg/ml [20.0-600.0] vs. 45.0 pg/ml [20.0-120.0]; $P \leq 0.001$] were significantly higher in the severe group, while absolute eosinophil counts were significantly lower [0.0 $\times 10^3/\mu L$ [0.0-0.4] vs. 0.2$\times 10^3/\mu L$ [0.0-0.4]; $P \leq 0.001$] [Table 1].

Only the platelet count revealed a significant positive association with eosinophil count [*P*=0.029], but IL-6 showed significant positive correlations with CRP [*P*=0.037] and D-dimer [*P*=0.001] and a significant negative correlation with absolute eosinophil count [P=0.020].

Additionally, eosinophils were found to have significant negative correlations with biomarkers of coagulation dysfunction [D-dimer; *P*=0.016] inflammation [CRP; *P*=0.037 and ferritin; *P*=0.049] and cytokine storm [IL-6; *P*=0.018], but there was no significant correlation between eosinophils and IL-5 [*P*=0.931] [Table 2].

The IL-6 AUC was 0.737 [95%CI: 0.628-0.842] in the ROC curve analysis, demonstrating a good diagnostic value for COVID-19 severity with a diagnostic sensitivity of 87.8% and specificity of 52.4%.

IL-5 and eosinophils, on the other hand, had little diagnostic significance in distinguishing between severe and non-severe illness, with an AUC of 0.343 and 0.174, respectively [Table 3].

Table [1]: Baseline data and fate of all studied patients and according to COVID-19 severity

Parameter		All cases	SEVERITY		
			Non-severe	Severe	P-value
		n=83	n=42	n=41	
Age (years)	Median (IQR)	55.0 (23.0-82.0)	45.0 (23.0-78.0)	56.0 (32.0-82.0)	**0.005**
Sex n., %	Male	38.0 (45.8%)	16.0 (42.1%)	22.0 (57.9%)	0.155
	Female	45.0 (54.2%)	26.0 (57.8%)	19.0 (42.2%)	
Co-morbidities n., %	Diabetes	30.0 (36.1%)	12.0 (40.0%)	18.0 (60.0%)	0.198
	HTN	34.0 (41.0%)	16.0 (47.1%)	18.0 (52.9%)	0.723
	CKD	22 (26.5%)	17.0 (77.3%)	5.0 (22.7%)	**0.004**
	CLD	1.0 (1.2%)	0.0 (0.0%)	1.0 (100.0%)	-----
	IHD	9.0 (10.8%)	6.0 (66.7%)	3.0 (33.3%)	-----
	COPD	8.0 (9.6%)	3.0 (37.5%)	5.0 (62.5%)	-----
Symptoms n., %	Diarrhea	1.0 (1.2%)	1.0 (100%)	0.0 (0%)	------
	Cough	8.0 (9.6%)	8.0 (100%)	0.0 (0%)	------
	Fever	40.0 (48.2%)	20.0 (50.0%)	20.0 (50.0%)	0.916
	Dyspnea	39.0 (47.2%)	18.0 (46.2%)	21.0 (53.8%)	0.455
O_2 saturation (%)	Median (IQR)	94.0 (60-98)	95.5 (93.0-97.0)	81 (60.0-98.0)	**≤ 0.001**
Laboratory data median (IQR)	TLC (×10³/µL)	8.0 (2.7-31.7)	8.1 (3.6-9.4)	8.0 (2.7-31.7)	0.131
	Neutrophils (×10³/µL)	6.3 (2.1-30.1)	5.9 (2.8-8.2)	7.1 (2.1-30.1)	**0.021**
	Lymphocytes (×10³/µL)	0.7 (0.2-3.3)	1.0 (0.2-3.3)	0.6 (0.2-2.8)	0.255
	Monocytes (×10³/µL)	0.3 (0.06-3.9)	0.6 (0.1-0.9)	0.3 (0.0-3.9)	0.065
	Eosinophils (×10³/µL)	0.1 (0.0-0.4)	0.2 (0.0-0.4)	0.0 (0.0-0.4)	**≤ 0.001**
	Hemoglobin (gm/dL)	12.1 (6.6-15.4)	11.7 (9.0-15.1)	12.3 (6.6-15.4)	0.376
	Platelets (×10³/µL)	198.0 (31.0-533.0)	209.5 (98-501)	198.0 (31.0-533.0)	0.862
	CRP (mg/L)	49.5 (0.2-392.0)	40.0 (0.2-95.0)	61.3 (0.4 -392)	**0.027**
	D-dimer (mg/L)	0.84 (0.28-9.8)	0.75 (0.28-1.0)	0.9 (0.3-9.8)	**0.001**
	Ferritin (ng/mL)	655.0 (40.0-4841.0)	441.5 (52.0-1200)	735.0 (40.0-4841.0)	0.223
	IL-5 (pg/mL)	240.0 (10.0-960.0)	300.0 (170.0-690)	180.0 (10.0-960.0)	**0.013**
	IL-6 (pg/mL)	80.0 (20.0-600.0)	45.0 (20.0-120.0)	110.0 (20.0-600.0)	**≤ 0.001**
Fate	Discharged	62.0 (74.7%)	42.0 (67.7%)	20.0 (32.3%)	**≤ 0.001**
	Died	21.0 (25.3%)	1.00 (4.8%)	20.0 (95.2%)	

----- no p-value due to small number; CKD: chronic kidney disease; CLD, chronic liver disease; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; HTN, hypertension; IHD: ischemic heart disease; IL: Interleukin;IQR: interquartile range;O2: Oxygen; TLC: Total leucocytic count. Significance (P-value) was set at ≤0.05.

Table [2]: Correlation of interleukin-6, interleukin-5 and eosinophils with other parameters in all studied COVID-19 patients

Parameter	Interleukin-6		Interleukin-5		Eosinophils	
	(r)	P-value	(r)	P-value	(r)	P-value
TLC	0.022	0.846	-0.105	0.343	0.015	0.819
Neutrophils	0.182	1.000	-0.173	0.117	0.018	0.872
Lymphocytes	-0.154	0.164	0.175	0.115	-0.150	0.175
Monocytes	-0.163	0.141	0.073	0.514	0.137	0.217
Eosinophils	-0.256	**0.020**	-0.010	0.931	---------	-------
Haemoglobin	0.095	0.391	0.187	0.091	-0.085	0.444
Platelets	-0.014	0.899	-0.162	0.143	0.240	**0.029**
CRP	0.230	**0.037**	0.018	0.873	-0.230	**0.037**
D-dimer	0.465	**≤ 0.001**	0.153	0.168	-0.264	**0.016**
Ferritin	0.002	0.987	-0.153	0.166	0.049	**0.049**
IL-5	-0.035	0.752	-------	--------	-0.010	0.931
IL-6	------	-------	0.132	0.235	-0.259	**0.018**

CRP: C-reactive protein; IL: Interleukin;(r): Spearman rank correlation coefficient; TLC: Total leucocytic count. Significance (P-value) was set at ≤0.05.

Table 3: Receiver operating characteristic (ROC) analysis for interleukin-6, interleukin-5 and eosinophils between non-severe and severe COVID-19 groups

Parameter	Cut off point	AUC (95% CI)	Sensitivity (%)	Specificity (%)
Eosinophils (×10³/µL)	0.04	0.174 (0.076-0.272)	43.9	4.8
IL-5 (pg/mL)	175	0.343 (0.218-0.468)	58.5	21.4
IL-6 (pg/mL)	47.5	0.737 (0.628-0.842)	87.8	52.4

CI: Confidence interval; CRP: C-reactive protein; IL: Interleukin

DISCUSSION

In our study, we analyzed laboratory data examined to evaluate the role of peripheral eosinophil count and levels of IL-5 and IL-6 as predictive tools in the clinical course of COVID-19 and as the potential target for wise, timely administered use of immunotherapy. In COVID-19 patients, anti-inflammatory medications that modulate the cytokine pathway are being examined as a potential treatment option [16-18].

Our results revealed that serum levels IL-5 and IL-6 varied significantly between non-severe and severe groups and were significantly higher in the severe group. Our findings are consistent with those of Lucas *et al*. [19], who found increased IL-5 levels in severe COVID-19 patients than moderate disease patients and healthy controls. They also reported that IL-5 could predict mortality, with a predictive value of roughly 0.73. In addition, they found that IL-5 levels increased within 6–11 days from symptom onset, to which a subsequent increase of eosinophils followed on days 11–15, then the last phase of COVID-19 was associated by a further rise of IL-5 on days 16–20 with a relative slowdown of blood eosinophil count. A possible explanation for these findings is the eosinophil's antiviral enzyme activity, which can help eliminate SARS-CoV-2 in the early phase of infection. Eosinophil's antiviral effects are not required later in COVID-19 when the immune system slows viral replication. Hence IL-5 synthesis is moderately reduced [19,20]. Nonetheless, tissue damage and disease progression in severe disease, the immune system enters on a pathologic route marked by an uncontrolled cytokine storm, with a new pathological surge of IL-5 [19-21].

Similarly, in a study of a fatal COVID-19 case by Bouadma *et al*. [20], they reported that IL-5 levels were elevated between 1- and 2-fold on the 14th day after infection but decreased between days 16 and 22 before increasing again on day 24. On the contrary, Ghazavi *et al*. [22] showed that IL-5 levels did not significantly change according to COVID-19 severity nor between the diseased and the control groups.

Our results demonstrated a good diagnostic value of IL-6 for COVID-19 severity with a diagnostic sensitivity of 87.8% and specificity of 52.4%. Our results of increased serum levels of IL-6 agree with a study by Chen *et al*. [23]. They found that serum IL-6 concentrations in COVID-19 patients were elevated than the reference concentration [7 pg/mL] in 13.4% of moderate patients, 27.1% of severe patients, and 86.2% of critical patients, suggesting a correlation between IL-6 and COVID-19 severity with the critical patients having significantly higher IL-6 values compared with the moderate and severe patients [$P < 0.001$]. Also, Han *et al*. [24] examined the predictive value of various cytokines and concluded that IL-6 was the best predictor of severe COVID-19. Many other studies concluded that IL- 6 concentrations correlated to the severity and the unfavorable outcome of COVID-19 [25-29].

Our findings revealed that eosinopenia was more severe in the severe group than in the non-severe group. Eosinophil levels were also found to negatively correlate with coagulation, inflammation, and cytokine storm markers but a positive correlation with platelet counts. ROC curve analysis revealed that the absolute eosinophil count had poor predictive power for COVID-19 severity with an AUC of 0.174.

The pathogenesis of eosinopenia during COVID-19 is still being researched. Some scientists have speculated that eosinophils may migrate in response to SARS-CoV-2 infection because of their antiviral characteristics represented in the chemicals produced by their degranulation [4,30]. The drop in eosinophil count in peripheral blood could be due to increased recruitment into the infected airways and other epithelial viral portals [31], which explains why the severe group in our study did not develop eosinophilia despite the elevated IL-5 levels in their blood.

Our results showed that the peripheral blood eosinophil levels in patients with severe COVID-19 were considerably lower than those non-severe. Huang *et al*. [32] discovered similar results, reporting that the eosinopenia group had a significantly higher ICU transfer rate than the non-eosinopenia group.

In a study on 190 COVID-19 patients, Yan *et al*.[33] reported that patients with critical disease had much lower eosinophil counts than those with moderate and severe conditions. They also reported that patients with bilateral pneumonia in chest CT imaging had considerably lower eosinophil counts than those with unilateral pneumonia. Furthermore, compared to individuals with no ground-glass opacity in chest CT scans, patients with ground-glass opacity had lower eosinophil counts; however, these differences were not statistically significant.

In our study, we found a significant negative correlation between eosinophils and biomarkers of coagulation dysfunction [D-dimer] inflammation [CRP and ferritin] and cytokine storm [IL-6]. Similar results were obtained by Huang *et al*. [32], who demonstrated a negative correlation between eosinophils and inflammation biomarkers, including CRP, ferritin, and IL-6. The same study reported that the absolute eosinophil count was zero in 61% of

ICU admitted COVID-19 patients, a phenomenon described by Shaaban *et al.* [34] as "the almost zero eosinophil effect," caused by the infection-induced cytokine storm. Similarly, Nair *et al.* [35] discovered that the eosinophil count was linked negatively with the duration of ICU admission, mechanical ventilatory and oxygen support, and CRP levels in their included COVID-19 patients. Yan *et al.* [33] also found a significant negative correlation between eosinophil counts and inflammation biomarkers, including CRP, procalcitonin, and ferritin. They also found that eosinophil counts were significantly positively correlated with D-dimer levels.

Our study revealed a significantly positive correlation between eosinophil and platelet counts despite the drop in platelet count in the severe group was not statistically significant.

Previous research has found that eosinophils and platelets interact [36] and that eosinophil counts are inversely associated with stroke severity [37], a complication that has been seen in COVID-19 patients [38].

Yan *et al.* [33] produced somewhat comparable results. Furthermore, Jiang *et al.* [39] found in their meta-analysis of 7,613 COVID-19 patients that the severe cases and the non-survivors had a lower platelet count than those with non-severe disease and survivors. Many other studies supported the same findings [40,41].

Our data showed that non-survivors, when compared to survivors, had significantly lower levels of eosinophil counts. Similar results were obtained by Yan *et al.* [33] and Roca *et al.* [42] in their cohort study of 294 patients.

In our study, ROC curve analysis revealed that the absolute eosinophil count had poor predictive power for COVID-19 severity. Similarly, Le Borgne *et al.* [43] concluded that eosinopenia could not be used alone to predict COVID-19 severity. It should be coupled with other markers in a combined severity prediction score or multi-marker strategy to increase its predictive value. Mu *et al.* [44] reported that persistently low eosinophil counts predicted an unfavorable outcome in their included COVID-19 patients. While Huang *et al.* [32] suggested that the predictive power of the absolute eosinophil count for severe COVID-19 was nearly equivalent to that of the CRP and ferritin, having the advantage of being a cost-effective marker. Xiao *et al.* [45] developed the [COVID-19-REAL] risk stratification score to identify COVID-19 patients based on many clinical and hematologic variables, including eosinophil count of < 5/µl. Similarly, Tordjman *et al.* [46] developed the PARIS score, which uses eosinophil counts of < 60/µl as one of several hematologic criteria that predicted the likelihood of a SARS-CoV-2 diagnosis. Outh *et al.* [47] proposed that eosinopenia was more sensitive and specific than lymphocytes and could be utilized as an adjuvant index for patients with suspected COVID-19. Tan *et al.* [48] also came to the same result.

Our study had some limitations, including a limited sample size and different age groups that could have affected the cytokine production. Also, the fact that our study was conducted in a single facility. In our research, we identified IL-5, IL-6, and eosinophil as potential targets for anti-COVID-19 immunotherapy that should be monitored as they cast the light on potentially critical patients. In terms of predicting COVID-19 progression, IL-6 levels exceeded IL-5 levels and the peripheral eosinophil count. Eosinopenia has been linked to severe COVID-19 infection and a higher risk of in-hospital death, despite its low predictive capacity.

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Authors' contribution: All authors contributed significantly to this work, whether it was in the conception, study design, data acquisition, analysis, and interpretation, or in the drafting, revising, or reviewing of the article, and they all provided final approval of the version to be published.

Data availability statement:

On reasonable request, the corresponding author will provide the datasets used and/or analyzed during the current work.

Conflicts of interest disclosure:

The author[s] declared no potential conflicts of interest.

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Ethics:

The study was carried out in conformity with the Declaration of Helsinki's ethical research principles. Ethical approval for the current study protocol was obtained from Ain Shams University Faculty of Medicine Research Ethics Committee [REC] FWA 00017585. All patient data were kept private and confidential. Solely utilized them for research purposes.

Statement of informed consent:

All procedures were explained to all participants or their first-degree relatives, with informed consent obtained from them.

Consent for publication: Not applicable**.**

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