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Could eosinophil chemotactic factor (CCL11) be a useful biomarker of Covid-19?

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Ethics Committee Approval
The study was approved by Tokat Gaziosmanpasa University Medical Faculty Clinical Research Ethics Committee on 25 June 2020 with the number 20-KAEK-165.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Differentiating COVID-19 positive patients from negative ones with similar symptoms and predicting the course of disease are major problems in COVID-19. For this purpose, we investigated the performance of Eosinophil Chemotactic Factor (CCL11) in COVID-19 and compared complete blood count parameters and indexes.
Methods: In this retrospective case-control study, ECF/CCL11 values, as well as the clinical, laboratory and radiological data of thirty patients who were diagnosed with Covid-19 between 15 March-15 June 2020 were compared with those of thirty healthy controls.
Results: Both patients and controls included 10 (33.30%) females and 20 (66.60%) males with a mean age of 57.2 (15.46) and 60.07 (20.59) years, respectively. Eosinophil counts of the patients on admission (EO1) were significantly lower than those of the controls and one-week later EO2 levels (P<0.001, P=0.004 respectively). EO1, NE1, NE2, PLT2/LYM2, LYM1/CRP1 and LYM2/CRP2 were the most predictive indexes. ECF values of the patients one week after admission (ECF2) were significantly lower than that of controls and admission levels (P=0.046, P=0.011 respectively). ECF2 values differentiated Covid19 negative individuals from patients with 46.70% sensitivity, 93.30% specificity at a cutoff value of ≤45.00 pg/mL. In ROC analysis of ECF2, AUC was 0.702 (P=0.045; 95% CI: 0.875-0.636).
Conclusions: Tracking ECF with CBC subsets and indexes may be helpful in the early prediction of severity, diagnosis, and follow up of critical COVID-19 patients in the course of the disease.

Keywords: Covid-19, ECF, CCL11, Diagnosis, Neutropenia, Lymphopenia

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Introduction

In early December 2019, cases of pneumonia of unknown origin appeared in Wuhan, China. A novel coronavirus was identified using metagenomic analyses from Bronchoalveolar lavage fluids at the Wuhan Virology Institute [1]. The United States Center for Disease Control and Prevention (CDC) named it 2019 novel coronavirus (2019-nCov). In infected patients, Covid-19 can cause a variety of symptoms, including fever, dry cough, shortness of breath, fatigue, lymphopenia, and eosinopenia. In more severe cases, infections that cause viral pneumonia can lead to acute respiratory syndrome (SARS) and even death [2].

Various chemokines and cytokines play roles in the proliferation of eosinophils and regulate their movement from bone marrow to tissues [3]. After allergen exposure, IL-5 is required for the migration of eosinophils from the bone marrow to the lung [4]. On allergen challenge, large amounts of IL-5 are produced by T helper 2 (Th2) lymphocytes [5]. Eosinophil migration is induced through IL-5 or CCL11 production by Type 2 native lymphoid cells (ILC2s) [6]. In recruitment of eosinophils into the tissue, chemokines CCL11 (eotaxin-1) and CCL24 (eotaxin-2) take the main part [7]. Eotaxin-1 selectively acts on the C-C motif receptor 3 (CCR3) [8]. CCL11 is involved in inflammatory conditions including allergic eosinophilia such as asthma and atopic dermatitis [9]. However, other eosinophil accumulation influencers in the lung have not yet been fully elucidated.

In recent studies, eosinophil counts in severe Covid-19 patients decreased significantly and the severity of the disease was associated with the level of eosinopenia. We also thought that this decrease in eosinophils might be related to Eosinophil Chemotactic Factor (ECF) / CCL11. Molecular (rt-PCR) or radiological diagnosis of patients with Covid-19 and those with similar symptoms takes too long, and these two groups are often confused. There is a need for simple and accessible laboratory biomarkers for the effective diagnosis of Covid-19 patients, and the prediction of disease course. For this purpose, we investigated the performance of ECF/CCL11 in Covid-19.

We aimed to find simple and accessible laboratory biomarkers to distinguish suspected COVID-19 patients from individuals exhibiting similar symptoms who are negative for the disease and predict the course. For this purpose, we investigated the diagnostic performance of ECF/CCL11, which is a major factor in the migration of eosinophils to tissues in Covid-19 patients with CBC subsets and indexes.

Materials and methods

After the Ministry of Health, Tokat Gaziosmanpasa University Medical Faculty Clinical Researches Ethical Committee also approved the study on 25 June 2020 with the number 20-KAEK-165. This retrospective case-control study conformed to the Helsinki Declaration principles. Due to the retrospective nature of the study, we did not obtain informed consent forms from the participants. Although the gold standard of diagnosis in Covid-19 is reverse transcriptase polymerase chain reaction (RT-PCR), we also included patients diagnosed with other methods, such as serologic tests or computerized tomography (CT). Based on power analysis, the inclusion of twenty-seven patients in the study planned in a single sample order yielded 80% power, 5% margin of error and an effect size of 0.50. Our patient group included thirty randomly chosen Covid-19 patients diagnosed with any of those diagnostic methods between 15 March and 15 June 2020, who were compared with thirty randomly chosen age and gender-matched healthy controls. All demographic and laboratory data of patients and controls were gathered by the same researchers. We did not know their eosinophil levels or ECF(CCL11) levels until all specimens were collected and assayed at one session by the same researcher. Considering all these conditions, we do not have any concerns of bias. Patients who underwent by-pass operation within the last month, those with a history of metabolic, malignant, and rheumatic diseases and pregnant women were excluded from the control group.

Data collection

All data of the patients were obtained retrospectively from archived medical file materials. The collected data includes demographic information, clinical medical history, concomitant diseases, signs and symptoms, laboratory findings and radiological imaging findings. The data of the hospitalization day of the patient was considered the admission day data. The data obtained at the end of one week after hospitalization was noted as the "first week data". Radiological images were classified as atypical, intermediate, and typical appearance according their compatibility with Covid-19.

Determination of serum ECF / CCL11 levels

The samples for measuring serum ECP levels were obtained from samples sent to the central laboratory for routine biochemical tests. No other samples were obtained from the patients for the purpose of study and no data were used except hospital and laboratory data. Serum ECF / CCL11 levels of the controls and Covid-19 patients at the time and first week of admission were measured with the Elabscience Co. 14780 commercial kit (Memorial Drive, Suite 216, Houston, Texas, USA) using the Enzyme Linked Immuno-Sorbent Assay (ELISA) method as per the kit package insert.

Statistical analysis

Descriptive analyses yield information about the features of the study groups. The data of continuous variables are presented as mean (standard deviation), and data on categorical variables are given as n (%). When comparing the means of quantitative variables between groups, the significance test of the difference between two means was used for the normally distributed variables, and the Mann Whitney U test was used for non-normally distributed variables. For intra-group comparison, the significance test of the difference between the two partners was used for the normally distributed variables, while Wilcoxon test was used for the non-normally distributed variables. Chi-square test was used to evaluate whether there was a relationship between qualitative variables. Paired t test was used to evaluate relations between quantitative variables. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of ECP in Covid-19 disease. P values of less than 0.05 were considered statistically significant. Ready-made statistics software was used for calculations (SPSS 22.0 Chicago, IL, USA).

Results

Both our patient and control groups with mean ages of 57.2 (15.46) and 60.07 (20.59) years, respectively, consisted of 10 (33.30%) females and 20 (66.60%) males. PCR tests of 20 (66.60%) patients were positive, while those of 4 (13.30%) patients was negative. Serologic tests were positive in 24 (80%) patients. While the result of 24 (92.30%) patients who underwent computed tomography (CT) imaging were compatible with the disease, 2 (6.70%) were evaluated as negative. On admission, 22 (73.30%), 22 (73.30%), 10 (33.30%) and 24 (80.00%) of the patients had fever, coughing, dyspnea, and fatigue, respectively. Twenty-six (86.70%) patients had mild-moderate and 4 (13.30%) had severe disease. Mid-treatment, 22 (73.30%) were in mild-moderate and 8 (26.70%) were in severe condition. After a week of treatment, 24 (80.00%) were in mild-moderate and 6 (20.00%) were in severe condition. Four (13.30%), 2 (6.70%), 6 (20.00%), 2 (6.70%) and 2 (6.70%) of the patients had chronic lung disease, Diabetes Mellitus, hypertension, cardiovascular disease, and malignant comorbidities, respectively. While 3 (10.00%) of the patients lost their lives during the treatment process, 27 (90.00%) patients recovered and were discharged. The qualitative variable distributions according to the groups are shown in Table 1.

Table 1: Distribution of qualitative variables of patient group

Variables		n(%)
Gender	Female	10(33.3)
	Male	20(66.7)
Discharge	Discharged	27(90.0)
	Passed Away	3(10.0)
Chronical Lung Disease (CLD)	None	0(86.7)
	Present	4(13.3)
Diabetes Mellitus (DM)	None	28(93.3)
	Present	2(6.7)
Hypertension (HT)	None	0(80.0)
	Present	6(20.0)
Cardio-Vascular Disease (CVD)	None	28(93.3)
	Present	2(6.7)
Malignancy	None	28(93.3)
	Present	2(6.7)
Serological Test Positivity	Negative	6(20.0)
	Positive	24(80.0)
Polymerase Chain Reaction (PCR)	Negative	4(13.3)
	positive	20(66.6)
Computed Tomography (CT)	Incompatible	2(6.7)
	Compatible	24(92.3)
Clinical Condition (Admission)	Mild-Moderate	26(86.7)
	Critical-Severe	4(13.3)
Clinical Condition (Mid-Treatment)	Mild-Moderate	22(73.3)
	Critical-Severe	8(26.7)
Clinical Condition (After a week)	Mild-Moderate	24(80)
	Critical-Severe	6(20)
Fever	None	8(26.7)
	Present	22(73.3)
Dyspnea	None	20(66.6)
	Present	10(33.3)
Coughing	None	8(26.7)
	Present	22(73.3)
Malaise	None	6(20.0)
	Present	24(80.0)

Data were expressed in numbers and percentages. Pearson's chi-square test was used.

Laboratory findings

In our study, the eosinophil counts (EO1) of the patients at the time of admission were significantly lower than that of the controls (P<0.001). There was a significant increase in eosinophil levels (EO2) one week after admission compared to the admission levels (EO1) (P=0.004). A reliable demonstrator of eosinopenia, mean ratio of neutrophil to eosinophil on admission (NEU/EO1) was significantly higher than that measured one week later (NEU/EO2) (P=0.041). White Blood Cell (WBC1) counts of Covid-19 patients on admission were significantly lower than that of controls (P=0.007). Neutrophil (NEU1) counts on admission and one week later (NEU2) were significantly lower than those of controls (P=0.009, P=0.041, respectively). Lymphocyte (LYM1) counts on admission and one week later (LYM2) were significantly lower than those of controls and admission levels were significantly lower than those obtained one week later (P=0.001, P=0.033, and P=0.022, respectively). Monocyte counts on admission (MO1) and one week later (MO2) were significantly lower than those of controls (P=0.010 and P=0.049 respectively). Basophil counts on admission (BAS1) and one week later (BAS2) were significantly lower than those of controls (P<0.001 and P<0.001 respectively). Platelet counts on admission (PLT1) were significantly lower than those of controls and one week later (P=0.006 and P=0.001, respectively). EO1% was significantly lower than EO2% (P=0.041). PLT2/LYM2 ratios were significantly higher than controls and admission PLT1/LYM1 ratios (P=0.026 and P=0.020, respectively). Ferritin levels on admission were significantly higher than controls and lower than one week later (P=0.033 and P=0.011, respectively). Hs-CRP levels on admission were significantly higher than that of controls (P=0.048). The AUCs of EO1, NE1, NE2, PLT2/LYM2, LYM1/CRP1 and LYM2/CRP2 were 0.856, 0.778, 0.719, 0.738, 0.747 and 0.702 respectively, with cut-off values of 0.04, 3.32, 3.21, 144.59, 1.99 and 7.84, respectively. The sensitivity and specificity of EO1, NE1, NE2, PLT2/LYM2, LYM1/CRP1 and LYM2/CRP2 were 66.70% and 93.30%, 53.30% and 93.30%, 46.70% and 93.30%, 80.10% and 80.50%, 100.00% and 66.70, and 100.00% and 53.30%, respectively. The distribution of quantitative variables according to groups is shown in Table 2.

ECF2 values of the patients one week after admission were significantly lower than that of controls (P=0.046). The ECF2 values of the patients after one week also decreased significantly compared to the ECF1 values of admission (P=0.011). The distribution of quantitative variables according to the groups is shown in Table 2. In Figure 1, ROC analysis results of ECF2, EO1, NE1 and NE2 are presented.

Figure 1: ROC curves of selected variables

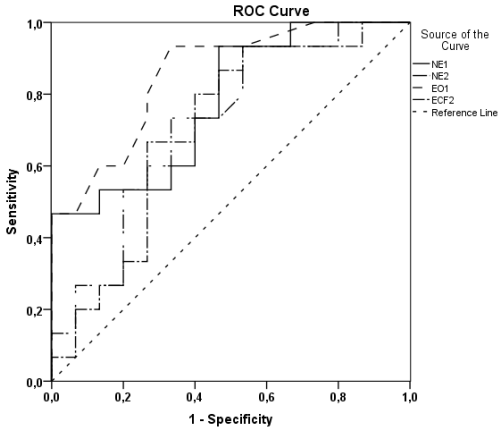

Table 2: Distribution of quantitative variables by groups

Variables	Groups				*P*-value$_1$
	Control		Patient		
	Mean (SD)	Median[Q3-Q1]	Mean (SD)	Median[Q3-Q1]	
Age	60.07 (20.59)	66[42-75]	57.2 (15.46)	59[46-69]	0.670
ECF1(pg / mL)	225.22 (205.47)	157.22[83.89-315]	145.96 (108.75)	143.89[61.67-155.56]	0.305*
ECF2(pg / mL)	225.22 (205.47)	157.22[83.89-315]	99.14 (112.01)	70.00 [18.89-126]	0.046*
P-value $_2$		0.999**		0.011**	
EO1(x10^3/µL)	0.16 (0.14)	0.09[0.06-0.24]	0.04 (0.03)	0.04[0.02-0.07]	<0.001*
EO2(x10^3/µL)	0.16 (0.14)	0.09[0.06-0.24]	0.15 (0.1)	0.12[0.06-0.21]	0.935*
P-value $_2$		0.999**		0.004**	
NE1/E01	84.98 (81.99)	69.33[22.87-104.14]	123.48 (86.10)	96[51.44-178]	0.174
NE2/EO2	84.98 (81.99)	69.33[22.87-104.14]	60.81 (70.74)	24.67[17.15-77.08]	0.285
P-value $_2$		0.999**		0.041**	
WBC1(x10^3/mL)	11.09 (7.89)	9.22[6.55-13.43]	5.05 (1.24)	5.07[4.02-6.12]	0.007
WBC2(x10^3/mL)	11.09 (7.89)	9.22[6.55-13.43]	6.81 (3.20)	5.95[4.28-7.6]	0.062
P-value $_2$	0.999		0.059		
NE1(x10^3/µL)	8.15 (7.64)	4.97[3.43-11.48]	3.55 (1.15)	3.32[2.47-4.63]	0.009*
NE2(x10^3/µL)	8.15 (7.64)	4.97[3.43-11.48]	4.84 (3.48)	3.43[2.63-4.92]	0.041*
P-value $_2$		0.999**		0.394**	
LYM1(x10^3/µL)	2.07 (0.95)	1.92[1.32-2.88]	1.08 (0.52)	0.87[0.65-1.39]	0.001
LYM2(x10^3/µL)	2.07 (0.95)	1.92[1.32-2.88]	1.39 (0.69)	1.56[0.74-1.85]	0.033
P-value $_2$	0.999		0.022		
MO1(x10^3/µL)	0.63 (0.38)	0.51[0.38-0.87]	0.35 (0.10)	0.33[0.27-0.4]	0.010
MO2(x10^3/µL)	0.63 (0.38)	0.51[0.38-0.87]	0.41 (0.16)	0.38[0.26-0.49]	0.049
P-value $_2$	0.999		0.096		
BAS1(x10^3/µL)	0.08 (0.05)	0.08[0.04-0.1]	0.03 (0.02)	0.03[0.02-0.04]	<0.001*
BAS2(x10^3/µL)	0.08 (0.05)	0.08[0.04-0.1]	0.03 (0.02)	0.03[0.02-0.04]	<0.001*
P-value $_2$	0.999			0.859**	
PLT1	233.8 (82.11)	193.8[179.9-280]	160.74 (47.34)	169.6[127.2-186.7]	0.006
PLT2	233.8 (82.11)	193.8[179.9-280]	261.51 (100.87)	253.9[210.7-332.4]	0.416
P-value $_2$	0.999		0.001		
EO1 %	1.69 (1.45)	1.04[0.67-2.62]	1.01 (0.73)	0.96[0.52-1.14]	0.113
EO2 %	1.69 (1.45)	1.04[0.67-2.62]	2.27 (1.59)	2.61[0.63-3.81]	0.307
P-value $_2$		0.999**		0.041**	
NEU1 %	66.97 (16.57)	63.94[52.08-82.71]	69.68 (10.24)	72.1[61.68-73.6]	0.594
NEU2 %	66.97 (16.57)	63.94[52.08-82.71]	66.12 (14.61)	66.09[54.79-68.93]	0.882
P-value $_2$	0.999		0.226		
LYM1 %	24.3 (14.31)	23.46[9.5-37.27]	21.59 (9.03)	20[17.47-30.88]	0.540
LYM2 %	24.3 (14.31)	23.46[9.5-37.27]	24.51 (12.57)	26.27[17.4-34.18]	0.967
P-value $_2$	0.999		0.273		
MPV1	8.8 (0.63)	8.7[8.3-9.4]	8.88 (0.62)	9[8.4-9.3]	0.727
MPV2	8.8 (0.63)	8.7[8.3-9.4]	8.95 (0.97)	8.8[8.3-9.4]	0.626
P-value $_2$	0.999		0.822		
NE/LYM1	5.89 (6.85)	2.74[1.4-8.7]	4.18 (2.85)	3.45[1.87-4.23]	0.653*
NE/LYM2	5.89 (6.85)	2.74[1.4-8.7]	7.27 (11.26)	2.53[1.6-4]	0.999*
P-value $_2$		0.999**		0.570**	
NMR1	14.70 (14.16)	12.43[6.43-16.06]	10.17 (3.52)	9.87[7.2-12.7]	0.443*
NMR2	14.94 (14.95)	11.3[6.76-15.75]	12.48 (8.07)	9.8[7-13.67]	0.787*
P-value $_2$		0.510**		0.281**	
LMR1	4.16 (2.78)	3.58[1.79-5.9]	3.01 (1.32)	2.9[2.05-3.48]	0.389*
LMR2	4.14 (2.68)	3.51[1.81-5.36]	3.88 (2.17)	3.64[1.74-6.05]	0.983*
P-value $_2$		0.778**		0.211**	
LYM/CRP1	17.25 (33.75)	9.21[0.39-16.63]	0.80 (0.65)	0.69[0.13-1.53]	0.021*
LYM/CRP2	17.25 (33.75)	9.21[0.39-16.63]	1.78 (2.22)	1.02[0.6-2.2]	0.061*
P-value $_2$		0.999**		0.031**	
PLT/LYM1	153.81 (141.41)	111.48[76.65-142.88]	183.75 (112.61)	149.3[97.85-213.45]	0.106*
PLT/LYM2	153.81(141.41)	111.48[76.65-142.88]	253.68 (186.74	205.14[144.59-312.19]	0.026*
P-value $_2$		0.999**		0.020*	
Glucose1(g/dl)	157.81 (93.05)	121.3[101.9-133.3]	168.33 (170.62)	122.35[103.4-156.7]	0.864
Glucose2(g/dl)	135.22 (51.06)	119.2[99.4-133.3]	130.35 (38.89)	116.5[99.75-156.7]	0.773
P-value $_2$	0.303		0.342		
Creattinine1(mg/dl)	0.84 (0.19)	0.85[0.75-0.93]	6.73 (25.72)	0.98[0.9-1.11]	0.479
Creattinine2(mg/dl)	0.82 (0.18)	0.85[0.75-0.93]	5.13 (18.33)	0.95[0.84-1.06]	0.467
P-value $_2$	0.043		0.827		
Troponin-I1	11.52 (6.20)	9.9[8.09-10.22]	105.67 (337.62)	15[4.86-23.95]	0.510
Troponin-I2	12.7 (6.46)	10.13[8.09-19.77]	18.55 (16.24)	13.69[4.29-29.05]	0.379
P-value $_2$			0.355		
D-dimer1(µg/L)	0.38 (0.39)	0.21[0.08-0.77]	0.47 (0.34)	0.33[0.2-0.79]	0.614
D-dimer2(µg/L)	0.38 (0.39)	0.21[0.08-0.77]	1.04 (1.09)	0.66[0.2-1.56]	0.176
P-value $_2$		0.999**		0.407**	
Ferritine1(ng/mL)	95.44 (92.93)	72.41[35.83-155.05]	596.75 (411.68)	491.25[303.1-876.9]	0.033
Ferritine2(ng/mL)	95.44 (92.93)	72.41[35.83-155.05]	624.5 (490.91)	508.5[286.95-838.35]	0.055
P-value $_2$		0.999**		0.011**	
Fibringn1(mg/dL)	274.5 (47.38)	274.5[241-308]	348.2 (124.87)	326.5[274-500]	0.444
Fibringn2(mg/dL)	274.5 (47.38)	274.5[241-308]	392.9 (121.36)	395[332-500]	0.217
P-value $_2$	0.999		0.169		
hs-CRP1(mg/L)	24.24 (43.00)	3.06[1.89-41.8]	65.81 (64.99)	43.15[15.64-96.6]	0.048
hs-CRP2(mg/L)	24.24 (43.00)	3.06[1.89-41.8]	57.77 (96.02)	29.06[11.96-51.45]	0.227
P-value $_2$		0.999**		0.078**	

Data were presented as mean (standard deviation) or median. quartile 1-quartile 3. *P*-value 1: *: Mann Whitney U test was used. For others. the significance test of the difference between the two means was used. *P*-value 2: **: Wilcoxon test for others the difference between two spouses. ECF: Eosinophil Chemotactic Factor, EO: Eosinophil, NE: Neutrophil, LYM: Lymphocyte, MO: Monocyte, BAS: Basophil, WBC: White Blood Cell, PLT: Platelet. Annex '1' at the end of parameters refers to 'value at admission' while '2' refers to 'one week after'.

Discussion

In the present study, the mean ages of both groups were 57.20 (15.46) and 60.07 (20.59) years, respectively, showing that hospitalized Covid-19 patients were over 40 years of age. With aging, the body's defenses decrease due to deterioration of immune and physiological functions. They had fever (73.30%), dyspnea (33.30%), cough (91.70%) and fatigue (80.00%). Patients who have these symptoms should take isolation measures and begin medical treatment to protect themselves and those around. Our patients had various comorbidities such as chronic lung disease, Diabetes Mellitus, hypertension, cardiovascular disease, and malignant diseases (13.30%, 6.70%, 20.00%, 6.60%, and 6.60%, respectively). Elderly patients had more underlying diseases, all of which increase the severity of the disease and hospitalization rates.

In line with the existing literature, in our study, patients had eosinopenia at the time of presentation, which improved significantly after one week. Three (20.00%) patients who died had eosinopenia both at the time of admission and one week later. Since the absolute eosinophil counts may vary between different laboratories, we preferred to calculate the NE/EO ratio instead of the absolute eosinophil count to achieve standardization. In the patient group, the NE2/EO2 ratios were significantly lower than those of NE1/EO1.

Since the beginning of the Covid-19 pandemic, eosinopenia or low eosinophil levels (<0.01x109 /L) were observed in most hospitalized patients in all patient series, which was associated with the severity of the disease. Eosinopenia was seen in 79% of PCR-confirmed SARS-Cov2 positive patients (n=52) and 36.00% of SARS-Cov2 negative patients [10].

Liu et al. [11] reported that eosinopenia at admission of patients mostly improved upon discharge, and this indicated improved clinical condition. Li et al. [12] conducted a retrospective case control study on 989 patients who applied to the fever clinic in Wuhan, China. Eosinopenia alone distinguished Covid-19 patients and controls with similar symptoms with 74.70% sensitivity and 68.70% specificity, and an Area Under Curve of 0.717 in ROC analysis. In our study, EO, NE1 and NE2 were highly capable of distinguishing Covid-19 negative patients with Covid-19 like symptoms.

Lymphopenia is also common in Covid-19, and blood eosinophil counts are positively correlated with lymphocyte levels in severe and mild coronavirus cases [13]. In our study, after one week of admission, lymphocyte levels recovered with treatment and LYM2 levels were significantly higher than LYM1. EO2 was positively and moderately correlated with LYM2, showing that eosinopenia and lymphopenia are comparable.

NE1, NE2, PLR2, LCRPR1 and LCRPR2 were the most predictive CBC subsets and indexes showing Covid-19 is an inflammatory condition. Ferritin levels on admission were significantly higher than that of controls and lower than one week later, showing recovery of inflammatory condition after one week of treatment.

In our study, patients had significantly higher Hs-CRP levels than controls on admission, in line with the laboratory findings of most inflammatory conditions.

Recently, researchers attempted to explain the role of eosinophils in inflammatory reactions and the mechanisms regulating their increased production and accumulation in various tissues. Until now, several factors with eosinophil chemotactic properties have been shown using different in vitro methods. However, sufficient comparative data on their strength, specificity, and ability to attract leukocytes are not available. Eosinophils are invoked into the lungs in response to infection with pneumo-pathogens and are associated with both pathophysiological sequelae of infection and accelerated virus clearance.

In the eosinophilic airway guinea pig hypersensitivity model, the main eosinophil chemotactic factor released into the lung was eotaxin [14]. Eotaxin plays a prominent role in eosinophil recruitment in various inflammatory diseases. Eotaxins are the C-C subfamily of eosinophil chemotactic proteins. CCL11 (eotaxin-1), CCL24 (eotaxin-2), and CCL26 (eotaxin-3) are three family members of eotaxins in humans [15].

Although most Covid-19 patients show very mild, self-limiting respiratory tract infection, severe patients show clinical symptoms such as severe eosinopenia, lymphopenia, generalized pneumonia, cytokine storm and multi-organ failure [16].

Although eosinopenia's pathophysiology in Covid-19 is not yet clear, it is multifactorial. Eosinophil outflow inhibition, eosinopoiesis blockage in the bone marrow, low production of chemokines, and stimulation of eosinophil apoptosis in acute infection are some of the causes of eosinopenia [17, 18]. Considering all these data in Covid-19 disease, there appears to be a disorder in immune response.

In the evaluation of the suspected patient with Covid-19 like symptoms, simple, fast, and accessible biochemical markers are needed to quickly distinguish the patients from negative ones and initiate empirical treatment, or to prioritize PCR or CT.

Due to high rates of eosinopenia seen in Covid-19, it is necessary to investigate the effect and diagnostic performance of CCL11, which contributes to eosinophil chemotaxis in Covid-19 patients. However, our study is the first one in this regard. We came upon studies investigating the CCL11, which is specific for eosinophils in Covid-19 disease, during the disease process.

We found that ECF2 values differentiated Covid19 negative individuals with Covid-19 like symptoms from positive patients. Tracking ECF with CBC subsets and CBC indexes may be helpful in the early prediction of severity of the disease, and the follow up of critical COVID-19 patients.

Limitations

Its retrospective, single center design and small number of hospitalized patients constitute the major limitations of our study, which needs validation with larger population-based cohorts.

Conclusions

Neutropenia, lymphopenia, and eosinopenia are seen in Covid-19. Lymphopenia and eosinopenia were positively correlated. Eosinopenia at admission is more severe compared to one week later, which is associated with good outcome. Elderly individuals with chronic diseases are more susceptible to COVID-19 and have a high likelihood of developing severe and critically severe infection. Levels of WBC, lymphocytes, neutrophils, CRP, NLR, PLR, troponin-I, and creatinine are

important indicators for severity grading in COVID-19. We can concur that EO, NE, CRP, LYM/CRP and PLT/LYM can be used as biomarkers to distinguish COVID-19 patients from healthy individuals and predict the severity of the disease. In addition, ECF / CCL11, a specific chemokine for eosinophils, may be an accessible and rapid biomarker with CBC subsets and indexes in the screening of Covid-19 patients, differentiating Covid-19 positive patients from negative ones and tracking the severity of the disease.

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