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Usefulness of laboratory parameters and chest CT in the early diagnosis of COVID-19

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ABSTRACT

In the present study, the importance of laboratory parameters and CT findings in the early diagnosis of COVID-19 was investigated. To this end, 245 patients admitted between April 1st, and May 30th, 2020 with suspected COVID-19 were enrolled. The patients were divided into three groups according to chest CT findings and RT-PCR results. The non-COVID-19 group consisted of 71 patients with negative RT-PCR results and no chest CT findings. Ninety-five patients with positive RT-PCR results and negative chest CT findings were included in the COVID-19 group; 79 patients with positive RT-PCR results and chest CT findings consistent with COVID-19 manifestations were included in COVID-19 pneumonia group. Chest CT findings were positive in 45% of all COVID-19 patients. Patients with positive chest CT findings had mild (n=30), moderate (n=21) andor severe (n=28) lung involvement. In the COVID-19 group, CRP levels and the percentage of monocytes increased significantly. As disease progressed from mild to severe, CRP, LDH and ferritin levels gradually increased. In the ROC analysis, the area under the curve corresponding to the percentage value of monocytes (AUC=0.887) had a very good accuracy in predicting COVID-19 cases. The multinomial logistic regression analysis showed that CRP, LYM and % MONO were independent factors for COVID-19. Furthermore, the chest CT evaluation is a relevant tool in patients with clinical suspicion of COVID-19 pneumonia and negative RT-PCR results. In addition to decreased lymphocyte count, the increased percentage of monocytes may also guide the diagnosis.

KEYWORDS: Monocyte percentage. Chest CT. COVID-19. SARS-CoV-2. RT-PCR.

INTRODUCTION

The new coronavirus disease 2019 (COVID-19) continues to be a global pandemic and an international public health problem, with thousands of people dying every day all around the world. To prevent the spread of COVID-19, it is essential to diagnose the disease at an early stage and isolate infected people from the healthy population[1]. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), it is a highly contagious and pathogenic infection that can present with nonspecific findings such as fever, cough, dyspnea, headache, muscle pain, fatigue, anosmia and may lead to the development of severe pneumonia[2,3].

SARS-CoV-2 can bind to the host cell and enter into the cell through the interaction of the glycoprotein-spike on the viral outer surface with the host ACE2 cellular receptor, affecting many organs such as the brain, kidneys, liver and especially epithelial cells of the lungs[3]. Acute respiratory distress syndrome

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(ARDS) leading to respiratory failure, thromboembolic complications, diffuse intravascular coagulopathy, sepsis and eventually multiple organ failure are life-threatening complications of COVID-19[4,5]. Poor prognostic factors of COVID-19 such as advanced age, male gender, dyspnea, and presence of other comorbidities have been evidenced in many studies[5].

Confirmation of the infection is performed by the reverse transcription real-time polymerase chain reaction (RT-PCR) which is considered the gold standard for the laboratory diagnosis, but results of the test take 3-4 h and false negative rates of 15% to 20% should be taken into account[6]. However, the sensitivity and specificity of rapid antigen tests (serological diagnosis) are low compared to RT-PCR in the acute phase of the disease. Serological tests with anti-SARS-CoV-2 antibodies detection also rise within a week after the onset of symptoms. Combined RT-PCR and serological testing increases both, the sensitivity and the accuracy of COVID-19 diagnosis[7]. Therefore, alternative, cheaper and more accessible tests are needed to diagnose COVID-19 disease.

Some studies have shown that certain hematological/biochemical changes can aid in the diagnosis of COVID-19. Specificity, sensitivity and predictive values of biomarkers for the detection of inflammation, myocardial and vascular damage have also been investigated[2]. Lymphocytopenia, leukopenia, thrombocytopenia and high C-reactive protein (CRP) levels are commonly observed in patients with COVID-19, while increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK) and D-dimer levels are less commonly found[8-12].

Many studies have addressed the chest Computed Tomography (CT) as a useful diagnostic tool for COVID-19[13,14]. Although chest CT has a high diagnostic sensitivity in COVID-19, its specificity is relatively low owing to the possible overlapping findings with other respiratory infections[15]. COVID-19 pneumonia most commonly presents with pulmonary ground glass opacities predominantly of peripheral distribution. Consolidation and fine reticulations along with vascular thickening can be occasionally observed. Reverse halo sign, if present, also has a high diagnostic specificity. Presence of nodules, cavitation, lymph node involvement and pleural effusion are far less common[13-15].

When imaging features are evaluated together with clinical and laboratory findings, early diagnosis of COVID-19 pneumonia may be easily made. In our study, we investigated the importance of laboratory parameters to with respect to chest CT findings in the early diagnosis of COVID-19 disease.

MATERIALS AND METHODS

Patients and study design

This retrospectively study included patients who sought our hospital for the first time with suspicion of COVID-19 between April 1st, 2020 and May 30th, 2020. This study was carried out at the Izmir Tepecik Training and Research Hospital, Izmir, one of the largest and busiest State hospitals in Turkey in terms of outpatient clinics and patient beds.

Variables and data collection

The sample size for the study was calculated using the G*Power software, version 3.1.9.2 (Franz Faul, Universitat Kiel, Germany). The required number has been reached with data from the hospital information system (HIS) and the Picture Archiving and Communication System (PACS) of the hospital. We randomly selected the patients among those who sought our hospital within the first seven days of of symptoms with no prior hospital admissions or treatment. Simultaneous chest CT results, complete blood count parameters and routine biochemistry tests were evaluated in all patients. Patients younger than 18 years, pregnant women and patients with procalcitonin levels exceeding 0.5 ng/mL were excluded from the study. Patients with negative RT-PCR results and without chest CT findings constituted the non-COVID-19 group. Patients with positive RT-PCR results were divided into two groups according to the presence or absence of chest CT findings, as the group COVID-19 and the group of COVID-19 pneumonia, respectively. Patients with positive CT findings were divided into subgroups of mild, moderate and severe COVID-19 pneumonia according to the percentage of lung involvement and the severity of changes in chest CT. Two experienced radiologists with more than 10 years of experience in thoracic imaging evaluated the chest CT results and classifications were consensusal. Approval for the conduction of the study was obtained from the local ethics committee of the Tepecik Training and Research Hospital (decision Nº 2020/10–25, dated August 12, 2020).

Case definition

A suspected case was defined according to the guideline for COVID-19 released by the General Directorate of Public Health Division of the Turkish Ministry of Health[16]. The criteria are as follows:

1) Presence of at least one of the signs and symptoms of fever or acute respiratory disease (cough and respiratory distress);

Inability to explain the clinical manifestation(s) with another cause/disease AND;
The patient and /or his/her relative being abroad within 14 days before the onset of symptoms; OR

2) Presence of at least one of the signs and symptoms of fever or acute respiratory disease (cough and respiratory distress);
Close contact with a confirmed COVID-19 case within 14 days before the onset of symptoms; OR
3) Presence of at least one of the signs and symptoms of fever and severe acute respiratory infection (cough and respiratory distress);
Requirement for hospitalization due to Severe Acute Respiratory Infections AND;
Failure to explain the clinical manifestation(s) with another cause/disease; OR
4) Cough or shortness of breathe with a sudden start of fever without any nasal discharge.

Laboratory assessments

At the first admission of the patients, complete blood count parameters, serum CRP, procalcitonin (PCT), ferritin, lactate dehydrogenase (LDH), urea, creatinine, total bilirubin (T.Bil), D-dimer, ALT, AST, CK and highly sensitive troponin I (hs-TNI) were determined. Complete blood count parameters were assessed by the UniCel DxH 800 hematology analyzer (Beckman Coulter, Miami, FL, USA) was employed; serum D-dimer levels by the CS 2500 automated coagulation analyzer (Sysmex Corporation, Kobe, Japan); serum PCT and hs-TNI levels by th ADVIA Centaur XP immunoassay analyzer (Siemens Healthineers, Erlangen, Germany) and serum CRP, ferritin, ALT, AST, urea, creatinine, LDH, CK, T.Bil levels by the AU 5800 chemistry analyzer (Beckman Coulter, High Wycombe, UK).

SARS-CoV-2 nucleic acid amplification tests in throat swab specimens were performed by reverse transcription real-time polymerase chain reaction (RT-PCR) with the Bio-Speedy COVID-19 RT-qPCR kit(Bioeksen R&D Technologies Ltd., Istanbul, Turkey).

CT image acquisition

All CT examinations were performed on the same 16-slice CT scanner (Philips Brilliance CT, Philips Healtcare, Netherlands) with routine low-dose chest CT protocol (100 kVP, semi-automated mAs depending on the patient's size, rotation time: 0.5 s) in a single breath-hold cycle without contrast administration. Presence of typical chest CT findings such as ground glass opacities, crazy paving pattern, traction bronchiectasis, vascular dilatation and consolidation were evaluated and chest CT findings were graded as mild, moderate and severe depending on the extent of lung involvement and distribution pattern (unilateral/bilateral, lower lobe predominance/diffuse, limited ground glass opacities/crazy-paving with consolidation) etc. The extent of lung involvement was assessed only visually; no additional tools or methods were used.

Statistical analysis

The SPSS statistical software, version 25.0 (SPSS Inc., Chicago, IL, USA) was used for all the calculations. The normality of variables distribution was evaluated by the one sample Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was used for the comparison between groups of normal distributed data, and Kruskal-Wallis test was used for non-normal distributed data. The Mann-Whitney U test was used in paired groups for parameters found to be significant. The significance level adjusted by the Bonferroni correction was 0.05/3 = 0.017. The chi-square or the Fisher's exact test was used for comparison between groups. Results of normally distributed parameters are given as mean ± standard deviation, and results of the parameters that did not show normal distribution are expressed as the median value (25-75th percentile). The Spearman's correlation test was used for correlation between variables.

To predict the diagnosis of COVID-19 the Receiver Operating Characteristics (ROC) analysis was performed between the groups with negative and positive RT-PCR results without CT findings. The non-COVID-19 group was used as the reference group and the risk analysis was evaluated for the groups using the multinomial logistic regression analysis. The mild COVID-19 pneumonia group was used as the reference group and the risk analysis was evaluated for the subgroups by the multinomial logistic regression analysis.

RESULTS

The non-COVID-19 group consisted of 71 patients with negative RT-PCR results and negative chest CT findings. Ninety-five patients with positive RT-PCR results and negative chest CT findings were included in the group COVID-19 and 79 patients with positive RT-PCR results and chest CT findings were included in group COVID-19 pneumonia. The COVID-19 pneumonia group consisted of three subgroups of COVID-19 pneumonia patients with mild (n=30), moderate (n=21) and severe (n=28) lung involvement (Figure 1). Therefore, CT findings were

positive in 45% of all COVID-19 patients confirmed by RT-PCR.

The mean age of the whole group of patients was 40.5±13.8 years. The mean age of the COVID-19 pneumonia group was statistically significantly higher (46.5±15.6 years) (p=0.001). No significant difference was found in gender distribution among the groups. The main symptoms were dry cough (53%), fever (26%), shortness of breathe (21%), fatigue (30%), headache (22%) and anosmia (9.1%) (Table 1).

A significant difference was found between the COVID-19 group and the COVID-19 pneumonia group, and also between the non-COVID-19 group and the COVID-19 pneumonia group regarding the time between the onset of symptoms and hospital admission. Considering all groups, a significant difference was found in hemoglobin (HGB), white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), monocyte count (MONO), platelet count (PLT), monocytes percentage (MONO%), plateletcrit (PCT), monocyte : lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet : lymphocyte ratio (PLR), and in serum CRP, procalcitonin (PCT), ferritin, D-dimer, T.Bil and LDH (Table 2).

In patients of the COVID-19 pneumonia group, among the complete blood count parameters only the platelet count was significantly different between the subgroups.

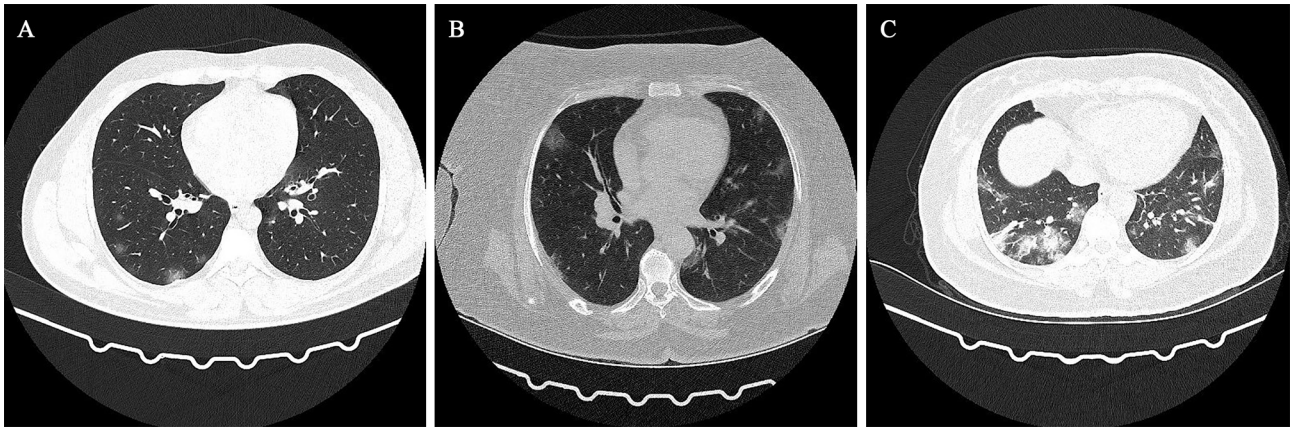

Figure 1 - A) Mild pneumonia: peripherally located ground-glass opacities in the right lower lobe; B) Moderate pneumonia: peripherally located ground-glass opacities, bilateral lung involvement; C) Severe pneumonia: diffuse bilateral lung involvement, predominantly in the lower lobes with a mixed pattern of ground glass opacities, crazy-paving pattern and consolidation.

Table 1 - Baseline characteristics of COVID-19 patients.

	Total n=245	Non-COVID-19 n=71	COVID-19 group n=95	COVID-19 pneumonia group n=79	*P*
Age in years (mean±SD)	40.5±13.8	39.8±11.5	36.0±11.9	46.5±15.6	**0.001**
Female gender n (%)	124 (50.6)	35 (28.2)	47 (37.9)	42 (33.9)	0.859
Comorbidity (%)	46 (20.9)	11 (23.9)	13 (28.3)	22 (47.8)	**0.039**
Diabetes Mellitus, n (%)	25 (10.4)	6 (24.0)	3 (12.0)	16 (64.0)	**0.010**
Hypertension, n (%)	21 (8.7)	2 (9.5)	5 (23.8)	14 (66.7)	**0.020**
Coronary artery disease, n (%)	11 (4.6)	4 (36.4)	2 (18.2)	5 (45.5)	0.325
Asthma, n (%)	9 (4.1)	4 (44.4)	4 (44.4)	1 (11.1)	0.173
Clinical Symptoms					
Cough, n (%)	119 (53.1)	39 (31.7)	41 (33.3)	43 (35.5)	0.149
Fever, n (%)	63 (26.0)	8 (12.7)	26 (41.3)	29 (46.0)	**0.003**
Dyspnea, n (%)	50 (20.7)	16 (32.0)	14 (28.0)	20 (40.0)	0.181
Headache, n (%)	54 (22.3)	16 (29.6)	24 (44.4)	14(25.9)	0.473
Fatigue, n (%)	72 (29.8)	16 (22.2)	26 (36.1)	30 (41.7)	0.130
Anosmia, n (%)	22 (9.1)	4 (18.2)	13 (59.1)	5(22.7)	0.135

Statistically significant P values are shown in bold.

Table 2 - Laboratory results of the COVID-19 group.

	Non-COVID-19 n=71	COVID-19 group n=95	COVID-19 pneumonia group n=79	*P*			
				All Groups	*P**	*P***	*P****
HGB (g/dL)	14.3±1.7	14.1±1.6	13.6±1.7	0.017	-	**0.030**	**0.008**
WBC (x 10^9/L)	7.6 (6.5-8.9)	5.7 (4.8-6.9)	5.1 (4.2-6.6)	**<0.001**	**<0.001**	**0.014**	**<0.001**
NEU (x 10^9/L)	4.4 (3.6-5.3)	3.4 (2.5-4.4)	3.2 (2.2-4.2)	**<0.001**	**<0.001**	**-**	**<0.001**
LYM (x 10^9/L)	2.2 (1.8-2.7)	1.6 (1.2-1.9)	1.4 (1.1-1.8)	**<0.001**	**<0.001**	**-**	**<0.001**
MONO (x 10^9/L)	0.7 (0.5-1.6)	0.7 (0.6-0.9)	0.5 (0.4-0.7)	**<0.001**	**-**	**<0.001**	**<0.001**
PLT (x 10^9/L)	250 (212-292)	219 (192-255)	207 (168-245)	**<0.001**	**0.001**	**-**	**<0.001**
MONO %	7.4 (6.2-8.7)	12.7 (9.9-16-4)	10.0 (7.9-12-7)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
LYM %	30.2±6.1	27.8±9.7	28.3±10.0	0.225			
NEU %	59.1±6.8	56.8±10.2	59.7±10.8	0.117			
PCT	0.23 (0.19-0.26)	0.19 (0.17-0.23)	0.19 (0.16-.22)	**<0.001**	**<0.001**	**-**	**<0.001**
NLR	2.1 (1.5-2.5)	2.0 (1.5-3.0)	2.2 (1.5-3.2)	0.370			**<0.001**
MLR	0.3 (0.2-1.0)	0.4 (0.3-0.7)	0.4 (0.3-0.5)	**0.016**	**0.014**	**0.018**	**-**
PLR	113 (91-143)	137 (108-181)	139 (111-181)	**<0.001**	**<0.001**	**-**	**<0.001**
Procalcitonin (ng/mL)	0.01 (0.01-0.01)	0.01 (0.01-0.04)	0.02 (0.01-.06)	**<0.001**	**<0.001**	**-**	**<0.001**
Urea (mg/dL)	25 (21-29)	26 (22-31)	29 (22-37)	0.06			
Creatinine (mg/dL)	0.87 (0.8-0.9)	0.86 (0.8-0.9)	0.9 (0.8-1.1)	0.06			
AST (U/L)	21 (18-27)	24 (18-28)	24 (19-28)	0.108			
ALT (U/L)	21 (14-32)	19 (15-32)	22 (15-29)	0.952			
LDH (U/L)	203 (177-231)	188 (173-215)	211 (180-262)	0.022	-	0.008	0.080
T.Bil (mg/dL)	0.67 (0.5-0.8)	0.5 (0.4-0.6)	0.47 (0.4-0.7)	**<0.001**	**0.001**	**<0.001**	**<0.001**
CRP (mg/L)	1.6 (0.9-3.1)	3.7 (1.4-7.8)	9.3 (4-35)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
D-Dimer (µg/L FEU)	210 (190-300)	235 (190-347)	340 (212-707)	**<0.001**	**-**	**-**	**<0.001**
CK (U/L)	100 (67-118)	106 (81-152)	96 (58-139)	0.264			
hs-TNI (ng/L)	2.5 (2.5-2.5)	2.5 (2.5-2.5)	2.7 (2.5-5.6)	**<0.001**	**-**	**0.001**	**<0.001**
Ferritin (µg/L)	37 (21-90)	52 (20-124)	87 (42-188)	**0.001**	**-**	**0.008**	**<0.001**
Duration from symptoms onset to admission (day)	2 (1-2)	2(1-3)	3(2-5)	**<0.001**	**-**	**0.001**	**<0.001**

HGB = hemoglobin; WBC = white blood cell count; NEU = neutrophil count; LYM = lymphocyte count; MONO = monocyte count; PLT = platelet count; MONO% = monocytes percentage; LYM% = lymphocyte percentage; NEU% = neutrophil percentage; PCT = plateletcrit; NLR = neutrophil-to-lymphocyte ratio; MLR = monocyte-to- lymphocyte ratio; PLR = platelet to lymphocyte ratio; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; T.Bil = total bilirubin; CRP = C-reactive protein; CK = creatine kinase; hs-TNI = highly sensitive troponin I. Statistically significant P values are shown in bold. P* = comparison between non-COVID-19 and COVID-19group; P** = comparison between COVID-19 group and COVID-19 pneumonia group; P*** = comparison between non-COVID-19 and COVID-19 pneumonia group.

In addition, serum CRP, PCT, urea, creatinine, ALT, AST, LDH and ferritin levels were significantly different between the subgroups (Table 3).

The correlation analysis performed with chest CT scores in COVID-19 patients with lung involvement found CRP (p=0.001, r=0.363), LDH (p=0.001, r=0.448), ferritin (p=0.039, r=0.247), D-dimer (p=0.043, r=0.232), ALT (p=0.043, r=0.241), % NEU (p=0.023, r=0.258), NLR (p=0.047, r=0.225) showing positive correlations, and PLT (p=0.004), r=-0.325), LYM (p=0.040, r=-0.233) and plateletcrit (p=0.006, r=-0.306) showing negative correlations.

In the ROC analysis performed between the non-COVID-19 and the COVID-19 groups, the percentage value of monocytes revealed the largest area under the curve (AUC: 0.887) with the highest diagnostic specificity (98%) and a moderate sensitivity (68%), together with 98.5% positive predictive value (PPV), and 69.4% negative predictive value (NPV) predictive values (Table 4A). In the ROC analysis performed between the non-COVID and the COVID-19

Table 3 - Laboratory parameters of the COVID-19 pneumonia subgroups.

Parameter	Mild group (n=30)	Moderate group (n=21)	Severe group (n=28)	*P*			
				All groups	*P**	*P***	*P****
Age in years	40 (25-54)	47 (40-58)	50 (39-58)	0.054			
Urea (mg/dL)	27 (20-40)	26 (19-32)	33 (25-47)	**0.026**	-	-	**0.021**
Creatinine (mg/dL)	0.9 (0.7-1.0)	0.9±0.2	1.0 (0.8-1.1)	0.051	-	0.050	-
ALT (U/L)	19 (13-23)	23 (16-32)	26 (17-38)	**0.027**	-	**0.007**	-
AST (U/L)	22 (18-25)	26 (20-30)	27 (20-40)	**0.042**	0.077	**0.018**	-
LDH (U/L)	191 (172-210)	211 (188-278)	244 (214-308)	**0.009**	-	**0.001**	-
CRP (mg/L)	5.3 (2.0-10)	12.6 (5.8-46)	17 (8-41)	**0.003**	**0.009**	**0.002**	-
Procalcitonin (ng/mL)	0.01 (0.01-0.03)	0.02 (0.01-0.06)	0.04 (0.015-0.07)	0.112			
D-Dimer (µg/L FEU)	295 (190-585)	440 (310-770)	420 (305-620)	0.096			
Ferritin (µg/L)	62 (24-112)	92 (59-197)	151 (85-245)	**0.014**	0.093	**0.004**	-
HGB (gr/dL)	13.5 (12.6-15.0)	13.5 (12.8-14)	13.9 (12.7-15)	0.867			
WBC (x 10^9/L)	5.2 (4.3-6.6)	5.2 (4.6-6.2)	4.9 (4.0-6.9)	0.728			
NEU (x 10^9/L)	2.9 (2.3-4.0)	3.4 (2.6-3.8)	3.2 (2.0-4.6)	0.674			
LYM (x 10^9/L)	1.5 (1.3-1.8)	1.4 (0.9-1.6)	1.45 (1.0-1.8)	0.278			
PLT (x 10^9/L)	229 (206-278)	207 (179-231)	168 (140-213)	**<0.001**	0.072	**<0.001**	**0.029**
MONO (x 10^9/L)	0.5 (0.4-0.7)	0.5 (0.4-0.6)	0.5 (0.35-0.7)	0.805			
NEU %	58 (50-63)	59 (56-72)	62 (49-69)	0.127			
LYM %	28 (23-35)	26 (17-31)	25 (21-35)	0.247			
MONO %	10.4 (8-13)	10.0 (8-12)	9.9 (8-12)	0.604			
PCT	0.21 (0.18-0.23)	0.19 (0.16-0.22)	0.16 (0.12-0.19)	**<0.001**	**-**	**<0.001**	**0.013**
CK (U/L)	89 (50-120)	102 (58-129)	100 (70-159)	0.507			
hs-TNI (ng/L)	2.5 (2.4-4.2)	2.5 (2.5-4.1)	2.9 (2.5-10.6)	0.552			

Data were expressed as median values (P25, P75). ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein; HGB = hemoglobin; WBC = white blood cell count; NEU = neutrophil count; LYM = lymphocyte count; PLT = platelet count; MONO = monocyte count; NEU% = neutrophil percentage; LYM% = lymphocyte percentage; MONO% = monocytes percentage; PCT = plateletcrit; CK = creatine kinase; hs-TNI = highly sensitive troponin I; P* = comparison between mild and moderate groups; P** = comparison between mild and severe groups; P*** = comparison between moderate and severe groups.

pneumonia groups, serum CRP levels revealed the largest area under the curve (AUC: 0.884) with a moderate diagnostic specificity (67%) and a highest sensitivity (96%) together with 94.4 % PPV, and 72.3% NPV (Table 4B).

In the multinomial logistic regression analysis performed between the non-COVID-19 and the COVID-19 groups, serum CRP levels (OR=1.143, 95% CI: 1.008-1.295, p=0.037), lymphocyte count (OR=0.347, 95% CI: 0.171-0.706, p=0.003) and percentage values of monocytes (OR=1.803, 95% CI: 1.474-2.204, p <0.001) were found to be independent risk factors for RT-PCR positivity (Table 5A). Between the non-COVID-19 and the COVID-19 pneumonia groups, serum CRP levels (OR=1.225, 95% CI: 1.008-1.295, p<0.001), lymphocyte count (OR=0.166 95% CI: 0.073-0.374, p<0.001) and percentage values of monocytes (OR=1.395, 95% CI: 1.142-1.704, p=0.001) were also independent risk factors for COVID-19 pneumonia (Table 5B). The platelet count (OR=0.978, 95% CI: 0.978-0.997, p<0.001) was found as an independent risk factor for distinguishing between severe and mild COVID-19 pneumonia (Table 5C).

DISCUSSION

Although two years have passed since the beginning of the COVID-19 pandemic and vaccines have started to be applied, the early diagnosis of COVID-19 is still crucial. Prompt and urgent diagnosis of COVID-19 is essential to isolate and treat the patients, therefore preventing the transmission of the virus.

In this study, patients who sought our hospital with suspicion of COVID-19 were examined and the importance of radiological and biochemical parameters in the diagnosis of COVID-19 was investigated by evaluating laboratory

Table 4 - The receiver operating characteristic curve (ROC) for selected variables

A) between non-COVID-19 and COVID-19 groups						
Parameter	AUC (95% CI)	Cut-off	sensivity (%)	Specifity (%)	PPV (%)	NPV (%)
MONO %	**0.887 (0.828-0.932)**	**>10.9**	**68.0**	**98.0**	**98.5**	**69.4**
LYM (x10^9/L)	0.785 (0.714-0.846)	≤2	81.7	65.2	76.0	72.6
WBC (x10^9/L)	0.786 (0.715-0.846)	<6.5	71.3	75.4	79.8	65.8
NEU (x10^9/L)	0.747 (0.673-0.812)	≤0.36	42.5	95.6	93.0	55.0
PLT (x10^9/L)	0.650 (0.571-0.723)	<220	52.1	72.5	72.1	52.6
B) between non-COVID-19 and COVID-19 pneumonia groups						
Parameter	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LYM (x 10^9/L)	0.834 (0.756-0.896)	≤1.9	84.8	68.1	75.0	79.7
CRP (mg/L)	**0.884 (0.813- 0.935)**	**>6.0**	**66.7**	**95.7**	**94.4**	**72.3**
D-Dimer (µg/L FEU)	0.768 (0.683- 0.840)	>330	58.4	85.9	81.5	65.6
MONO %	0.741 (0.653- 0.816)	>9.09	63.3	84.1	81.7	66.7
Procalcitonin (ng/mL)	0.773 (0.688- 0.844)	>0.01	61.1	88.4	87.8	62.2
PLT (x10^9/L)	0.710(0.630-0.782)	≤209	55.1	78.3	74.1	60.7
Ferritin (µg/L)	0.672 (0.607-0.766)	>59.8	68.6	69.0	68.6	69.0

AUC = area under the curve; MONO % = monocytes percentage; LYM = lymphocyte count; WBC = white blood cell; NEU = neutrophil count; CRP = C- reactive protein; PLT = platelet count; PPV = positive predictive value; NPV = negative predictive value.

Table 5 - Regression analysis of risk factors

A) between non-COVID-19 and COVID-19 groups.					
Parameter	B	SE	Wald	*P*	OR (95% CI)
CRP	0.133	0.064	4.352	0.037	1.143 (1.008-1.295)
LYM	-1.057	0.362	8.551	0.003	0.347 (0.171-0.706)
MONO %	0.589	0.103	33.021	<0.001	1.803 (1.474-2.204)
B) between non-COVID-19 and COVID-19 pneumonia groups.					
Parameter	B	SE	Wald	*P*	OR (95% CI)
CRP	0.227	0.063	13.097	<0.001	1.255 (1.110-1.420)
LYM	-1.798	0.416	18.668	<0.001	0.166 (0.073-0.374)
MONO %	0.333	0.102	10.620	0.001	1.395 (1.142-1.704)
C) between mild and severe pneumonia in the COVID-19 pneumonia group.					
Parameter	B	SE	Wald	P	OR (95%CI)
PLT	-0.023	0.007	10.716	0.001	0.978 (0.956-0.997)

OR = Odds ratio; CI = confidence interval; CRP = C-reactive protein; LYM = lymphocyte count; MONO% = monocytes percentage; PLT = platelet count.

and chest CT parameters that were controlled by RT-PCR results.

When compared to the non-COVID-19 group, in the COVID-19 group, among the complete blood count parameters WBC, LYM, NEU and PLT counts were lower, and HGB, WBC, LYM, NEU, MONO, PLT count, PCT, %MONO and MLR, PLR ratios were found to be significantly different. In previous studies evaluating complete blood count parameters in COVID-19 patients, NEU, LYM, PLT counts were also found to be lower in comparison with the control group[17]. Similar to our results, another study evaluated hemoglobin, the percentage of neutrophils, lymphocytes and especially monocytes and found higher parameters in COVID-19 patients[18,19]. Although neutropenia and lymphopenia were frequently found in studies investigating complete blood count parameters in COVID-19 patients, monocytosis was only occasionally detected[20].

Circulating monocytes and lymphocytes play an important role in maintaining immune homeostasis and

inflammatory response. These circulating mononuclear cells are among the first to respond to invasive intracellular pathogenic organisms such as SARS-CoV-2[18]. In this study, while the number of lymphocytes decreased in all groups, the percentage of monocytes was found to be higher in COVID-19 patients compared to those with COVID-19 pneumonia and to the non-COVID-19 group. In addition, in the ROC analysis between the non-COVID-19 and the COVID-19 groups regarding the ability to predict the diagnosis of COVID-19, we found that the percentage of monocytes had the highest diagnostic specificity and a moderate sensitivity in addition to the largest AUC area. This result shows that an increased percentage of monocytes and a decreased lymphocyte count are important diagnostic parameters in the early-stage of COVID-19 without chest CT findings.

Chen *et al*.[21] found significant differences between COVID-19 and influenza patients in terms of WBC, NEU, PLT, MONO counts, and percentages of neutrophils, lymphocytes, monocytes, eosinophils and basophils. They hypothesized that activated eosinophils and platelets could provide protection against respiratory viruses infections and are consumed early during coronaviruses infections with a resultant decrease in their counts[10,22]. In this study, we observed that platelet counts and plateletcrits decreased in the COVID-19 pneumonia group. Although the role of inflammatory markers in monitoring the severity of COVID-19 is controversial, they can help clinicians to evaluate the severity and prognosis of COVID-19[23].

In a study carried out with severe cases of COVID-19, serum CRP levels may increase without changes on chest CT and can be used to detect serious cases at an early-stage[24]. In this study, there was a significant difference between all groups in terms of biochemical parameters such as CRP, PCT, D-dimer and total bilirubin. Similar to ours, in a study conducted by Ferrari *et al*.[6] statistically significant differences between RT-PCR negative and positive groups were shown in serum CRP, AST, ALT and LDH levels. In a study in which clinical chest CT findings and laboratory data were evaluated, it has been shown RT-PCR misidentifications of COVID-19 cases were reduced by almost 4-fold and AST and LDH showed predictive values up to 90%[25].

In patients with clinically severe COVID-19 disease; Chen *et al*.[26] found relatively higher neutrophil ratios, CRP and PCT levels, and lower lymphocyte ratios and counts in these patients. In the multicenter retrospective study by Gao *et al*.[27] in which early-stage COVID-19 patients were examined, serum CRP andALT levels as well as the presence of comorbidities were found to be predictors of disease progression to severe pneumonia.

Among parameters of the complete blood count, the number of WBC, LYM, NEU and PLT were significantly lower in the COVID-19 pneumonia group when compared with the non-COVID-19 group. Furthermore, biochemical parameters levels including serum CRP, PCT, D-Dimer, troponin I and ferritin significantly increased in the COVID-19 pneumonia group. Serum CRP levels were found to be the most specific and sensitive diagnostic parameter according to the ROC analysis performed between both groups.

A meta-analysis examining laboratory parameters demonstrated that the PLT count was important both, in diagnosis and prognosis of COVID-19, while low leukocyte and neutrophil counts might be diagnostic markers of COVID-19, while LYM, D-dimer, and CRP levels indicated severity of COVID-19 disease[28].

In this study, in the multinomial logistic regression analysis made with respect to the non-COVID-19 group, CRP, lymphocyte count and percentage values of monocytes were independent variables in both, the COVID-19 group and the COVID-19 pneumonia group. In addition, decreased PLT counts were an independent risk factor for severity of COVID-19 pneumonia. Among the subgroups of patients with COVID-19 pneumonia, we found a significant difference between PLT counts, serum CRP, urea, creatinine, ALT, AST, LDH and ferritin levels. We found no change in complete blood count parameters other than platelets in our study, and they may be related to the identification of COVID-19 pneumonia at an early-stage at the time of the first hospital admission.

There was a positive correlation between chest CT scores and serum CRP, LDH, ferritin, D-dimer, ALT, % NEU, NLR and a negative correlation between PLT, LYM and plateletcrit. Zhang *et al*.[14] showed that early-stage chest CT scores were associated with neutrophil counts, as much as the stage of progressive disease was associated with neutrophil and WBC counts, CRP, PCT and LDH levels. In the study by Ai *et al*.[1], RT-PCR results were considered as reference in 1,014 patients, and the diagnostic sensitivity of chest CT for COVID-19 was 97%. In addition, it was observed that approximately 60% of patients had typical chest CT features, compatible with COVID-19 before the first positive RT-PCR results were obtained. Therefore, it was inferred that chest CT could be very useful in the early detection of suspicious cases. In another study evaluating the relationship between chest CT scores and serum CRP level, similar to our findings, serum CRP level were positively correlated with disease severity,without any significant difference in lymphocyte counts[29]. In another study, a significant correlation was found between chest CT scores, serum CRP and D-dimer levels[30].

Waller *et al.*[31] emphasized that the diagnostic sensitivity of chest CT for COVID-19 is higher than that reported for the RT-PCR, and that the sensitivity of chest CT may be overestimated. In addition, given the high specificity and sensitivity of RT-PCR for COVID-19, it has been suggested that it should be used as a primary diagnostic tool. In addition, even if chest CT may have methodological errors in numerous studies, it has a good sensitivity for COVID-19. Therefore, the chest CT findings should not be considered as a replacement or an alternative for RT-PCR to confirm the diagnosis of COVID-19[32].

Chest CT evaluation is important in patients with clinical suspicion of COVID-19 pneumonia and negative RT-PCR results. In addition to decreased lymphocyte count, which is one of the parameters of the complete blood count, an increased percentage of monocytes may also guide the diagnosis.

Limitations

Our study has some limitations. Firstly, it was a single-center study with a retrospective design. We did not consider false negative, false positive RT-PCR results, and an inadequate number of patients with chest CT findings. Moreover, data on treatment with steroids, dipyrone, antibiotics, anticoagulants as well as complications and outcomes were not available.

CONCLUSION

The sooner the COVID-19 detection, the sooner a close monitoring can be initiated, as well as the isolation and treatment processes. In this study, in addition to decreased lymphocytes, the increased percentage of monocytes might have aided in the diagnosis of early-stage COVID-19 infections without chest CT findings. Evaluating chest CT images together with clinical signs and symptoms and laboratory parameters may facilitate the early diagnosis of COVID-19 pneumonia, and treatment of the patients, possibly reducing associated complications.

CONFLICT OF INTERESTS

No potential conflict of interests was reported by the authors.

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