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Thorax CT Involvement can be Predicted by Evaluating the Laboratory Parameters of Patients Admitted to the Emergency Department During the COVID-19 Pandemic Period.

Hasan Basri Çetinkaya[1], Hikmet Çoban[2]
[1]Department of Emergency Medicine, Balıkesir University, Balıkesir, Turkey
[2]Department of Chest Diseases, Balıkesir University, Balıkesir, Turkey

Aims: In this study, we evaluated the predictability of lung parenchymal involvement on computed tomography (CT) with laboratory parameters in patients with confirmed coronavirus disease 2019 (COVID-19) with and without lung parenchymal involvement at the first admission to the emergency department.

Methods: 109 patients diagnosed with COVID-19 in the emergency COVID department between April and September 2020 were included in the study. Laboratory parameters and thorax CT images were evaluated to evaluate the severity of the disease in all patients. The relationship between laboratory parameters was analysed in the patient groups with and without CT involvement.

Results: CT involvement was detected in 58 of 109 patients included in the study. There was a significant difference in lymphocyte, monocyte, eosinophil, ferritin, fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet (PLT) and urea values in the group with CT involvement. ROC (Reciever Operator Characteristics) analysis was performed to evaluate the diagnostic performance of laboratory parameters in CT involvement. Significant diagnostic predictability values were determined for age, lymphocyte, monocyte, eosinophil, ferritin, fibrinogen, CRP, ESR, PLT and urea. The highest AUC (Area Under the Curve) values were obtained in CRP, ESR and eosinophil parameters.

Discussion: Lymphocyte, monocyte, eosinophil, ferritin, fibrinogen, CRP, ESR, PLT and urea parameters can be used to predict lung involvement in the emergency department in patients with COVID-19 disease. According to these values, thorax CT can be decided for the patients. CRP, ESR and eosinophil parameters provided the highest specificity and sensitivity values in predicting lung involvement.

Keywords: COVID-19, Lung, Tomography, Laboratory Parameters
Short Title in English: COVID-19

Introduction

Due to the pandemic caused by COVID-19, worldwide cases are increasing day by day and the disease is becoming a global outbreak. As the number of patients increases, it poses great challenges for the health system [1,2]. Early diagnosis and treatment continue to be key elements of COVID-19 management. Laboratory and radiological findings of patients diagnosed with COVID-19 are critical in the diagnosis and treatment of the disease [3]. A significant correlation has been shown between pulmonary inflammation and lymphocyte, monocyte, CRP, procalcitonin(PCT) values. Thorax computed tomography (CT) is often performed performed to rule out pneumonia in patients who were diagnosed with COVID-19 at emergency service admission. It was found that there was a significant correlation between pulmonary involvement and laboratory results and computed tomography played an important role in the diagnosis, and evaluation of the disease [4]. CT scan increases the cost and poses a risk of exposure to medical radiation. In addition to these disadvantages, in hospital emergency

services where trauma, and stroke admissions are intense, a large number of patients have to undergo a CT scan in a limited time. In patients diagnosed or suspected of COVID-19, 30 minutes or more is required for post-CT cleaning. This long period may cause disruptions in CT scans in routine emergency practice. This cleaning time delays access to CT for other patients in the emergency department. Depending on the prolongation of this period, other patient groups will be more likely to be exposed to COVID-19 [5,6].

In this study, it was planned to determine the predictability of COVID-19 lung involvement with routine laboratory evaluations in the emergency department. Thus, by looking at the laboratory tests, it can be estimated which patients may have a higher risk of COVID-19 lung involvement. With this estimation, computed tomography can be performed only in patients who are thought to have lung involvement. Patients who do not require thorax CT will be excluded.

Materials and Methods

A total of 109 patients with PCR positivity who applied to the emergency department of Balıkesir University Medical Faculty Hospital between April and September 2020 were included in the study. Patients with chronic disease (cirrhosis, cardiac failure, chronic renal failure) that may affect clinical and laboratory parameters and patients using drugs (such as steroids) that may affect laboratory values were excluded from the study. Children and pregnant women were excluded from the study. Laboratory data were obtained from detailed medical records. Complete blood count, kidney and liver function tests, inflammation parameters such as CRP, ESR, PCT, ferritin, D-dimer and fibrinogen were recorded at the first admission to the emergency department. NLR value was calculated. CT examinations were performed with a 16-line multi-detector CT scanner (Siemens Somatom Sensation; Siemens, Erlangen, Germany). CT images of all patients included in the study were evaluated and cases with bacterial pneumonia or pulmonary oedema were excluded from the study. This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and the local ethics committee approved this study (Decision Number: 2020/182).

Statistical Analysis

Shapiro-Wilk test was used to test the normality of variables. Continuous variables were presented as median (1st quartile - 3rd quartile) values since the data were not normally

distributed. Mann-Whitney's U-test was used for comparison of two independent groups. Categorical variables were expressed with numbers and percentages. Comparisons between the groups were performed with Pearson chi-square test for categorical variables. Risk factors were also evaluated with binary logistic regression analysis. Receiver operating characteristics (ROC) curve analysis was performed to evaluate and compare the performances of diagnostic markers. Significance level was taken as $\alpha = 0.05$. Statistical analyses were performed with IBM SPSS Statistics version 22.0 (IBM Corp., USA) and MedCalc version 12.3.0.0.

Results

The study included 109 patients, 58 (53.21%) of whom had positive chest CT findings and 51 (46.79%) of whom had negative chest CT findings. Among 109 patients, 45 (41.28%) were male, 64 (58.72%) were female, and the median age was 56 (1^{st} Q - 3^{rd} Q: 38-68) years.

There was a significant difference between chest CT positive and negative groups in terms of age, lymphocytes, monocytes, eosinophils, ferritin, fibrinogen, CRP, ESR, PLT and urea. There was no significant difference between the two groups in terms of NLR and the other variables (Table-1).

We conducted backward conditional logistic regression analysis by including the variables into the model which were found statistically significant in univariate analysis. In the last model remaining variables were eosinophils, monocytes, ferritin, ESR and urea. The last model was statistically significant ($p<0.001$ for Omnibus test; $p=0.917$ for Hosmer&Lemeshow test). Eosinophils was not statistically significant in the model. One unit decrease in the monocytes increased the risk of chest CT positivity 1.006 times ($p=0.001$), one unit increase in the ferritin increased the risk of chest CT positivity 1.014 times ($p=0.021$), one unit increase in the ESR increased the risk of chest CT positivity 1.069 times ($p=0.001$), and one unit increase in the urea increased the risk of chest CT positivity 1.090 times ($p=0.013$), compared to chest CT negative patients (Table-2).

We performed ROC curve analyses to evaluate the diagnostic performances of age, WBC, neutrophil count, lymphocyte count, NLR, monocyte count, eosinophil count, ferritin, PCT, fibrinogen, D-dimer, CRP, ESR, PLT, RDW, urea, creatinine, AST and ALT in discriminating patients with positive and negative CT imaging findings. Optimal cut-off values were obtained according to Youden J index, corresponding sensitivity and specificity values are given. Significant diagnostic performances were obtained for age, lymphocyte count, monocyte count,

eosinophil count, ferritin, fibrinogen, CRP, ESR, PLT and urea. Three largest AUCs were obtained for CRP, ESR and eosinophil count. (Table-3, Figure-1).

Discussion

In our study, there was a significant difference in age, lymphocyte count, monocyte count, eosinophil count, platelet count, ferritin, fibrinogen, CRP, ESR, and urea parameters between patients with and without lung involvement in thoracic CT. Sensitivity of COVID-19 pneumonia in CT was found to be 75% or more in patients with lymphocyte count ≤1610(µL), age>44, eosinophil count≤37(µL), CRP>6.26(mg/L)., and urea>26(mg/dl) . In CT, the specificity of COVID-19 pneumonia was found to be 90% or more in patients with fibrinogen>383(mg/dl), sedim>43(mm/h) and platelet ≤170(10^3/mm^3). In the retrospective conditional logistic regression analysis, eosinophil count, monocyte count, ferritin, ESR and urea parameters were determined in the last model by including the variables found to be statistically significant in the univariate analysis. Although eosinophil count was not statistically significant in the model, a one-unit decrease in monocyte count value significantly increased the risk of thoracic CT positivity by 1.006 times, a one-unit increase in ferritin increased the risk of thoracic CT positivity by 1.014 times, a one-unit increase in ESH increased the risk of thoracic CT positivity by 1.069 times and a one-unit increase in the urea value increased the risk of thoracic CT positivity by 1.090 times.

Lymphopenia is a laboratory finding of COVID-19 infection and was detected in 63% of cases [7]. It has been suggested that the degree of lymphopenia may predict the severity, progression and prognosis of COVID-19 [8,9]. In our study, a significant difference was found between lymphocyte count between patients with and without involvement in thoracic CT. In patients with lymphocyte count ≤1610(µL), the sensitivity and specificity was found 75.44%, and52%, respectively in predicting involvement in thoracic CT.

Previous studies have shown that two-thirds of patients infected with COVID-19 have elevated CRP. In the early stage of the disease, CRP was correlated with lung lesions, severity of pneumonia, and overall disease severity [9-13]. In our study, a significant difference was found between CRP values between patients with and without involvement in thoracic CT. Predicting of involvement of thoracic CT in patients with CRP>6.26(mg/L) sensitivity and specificity were 75.86%, and 76.47%, respectively.

A meta-analysis evaluating severe and non-severe confirmed COVID-19 cases showed significant reductions in monocyte, eosinophil and platelet levels in patients with severe disease [13]. In our study, a significant difference was found between monocyte, eosinophil and platelet values between patients with and without involvement in thoracic CT. The sensitivity and specificity in predicting thoracic CT involvement were 64.91% and 64%, respectively, in patients with monocytes ≤466(µL), and a one-unit decrease in monocytes increased the risk of thoracic CT positivity 1.006 times. The sensitivity and specificity in predicting thoracic CT involvement were 77.19% and 70%, respectively, in patients with eosinophils ≤37(µL). The sensitivity and specificity in predicting thoracic CT involvement were 29.31% and 96.08%, respectively, in patients with platelets ≤170(10^3/mm^3).

Ferritin levels have been shown to increase significantly compared to those without severe COVID-19 disease and patients with mortality have higher ferritin levels [9,12,14]. In our study, a significant difference was found between ferritin values between patients with and without involvement in thoracic CT. The sensitivity and specificity in predicting thoracic CT involvement were 61.40% and 75%, respectively, in patients with ferritin >65(ng/mL), and a one-unit increase in ferritin value showed that it increased the risk of thoracic CT positivity 1.014 times.

Fibrinogen levels have been shown to be higher in COVID-19 patients compared to healthy controls, as well as higher in critical COVID-19 patients compared to mild or moderate cases [12,13,15]. However, fibrinogen level may not have a predictive value for mortality in COVID-19 patients [16]. It is recommended that fibrinogen be evaluated together with D-dimer levels to have more appropriate prognostic assumptions [17]. A significant correlation has been reported between the severity of COVID-19 disease and D-dimer serum level [9,12,13,18,19]. However, in a cohort, it was shown that there was no difference between the severity of the disease and D-dimer level in COVID-19 patients [20]. D-dimer has been emphasized to have a promising value for guiding anticoagulation strategies in the treatment of COVID-19 [17]. In our study, a significant difference was found in fibrinogen values between patients with and without involvement in thoracic CT. In patients with a fibrinogen value >383 mg/dl, sensitivity and specificity was 53.57% and 91.67%, respectively, in predicting thorax CT involvement. In our study, D-Dimer levels were found to be similar between patients with and without involvement in thoracic CT. This may be due to the small number of severe patients in our study.

Among the laboratory tests used for the evaluation of the acute phase reaction reflecting the inflammatory condition, ESR is considered the least specific. It is known to be affected by a large number of other physiological and pathophysiological conditions and its use is limited to a few specific clinical conditions [21]. Nevertheless, ESR is still persistently used in routine laboratory patient examinations regardless of the clinical problem [22]. It has been shown that there is a significant difference in ESR values between severe and non-severe COVID-19 cases [9,13,23]. In our study, a significant difference was found between ESR value among patients with and without involvement in thoracic CT. The sensitivity and specificity in predicting thoracic CT involvement were 53.57% and 91.67%, respectively, in patients with ESR >43 mm/h, and a one-unit increase in ESR increased the risk of thoracic CT positivity by 1.069 times.

When severe COVID-19 cases and mild cases were compared, statistically significantly higher AST, ALT, creatinine, and urea levels were found [9,13]. In our study, a significant difference was found between blood urea values among patients with and without involvement in thoracic CT, and the sensitivity and specificity in predicting thoracic CT involvement were 74.14% and 60.78%, respectively, in patients with urea values >26 mg/dl. A one-unit increase in urea value increased the risk of thoracic CT positivity 1.090 times. In our study, creatinine, AST and ALT levels were found to be similar between patients with and without involvement in thoracic CT.

RDW has been shown to be a prognostic predictor for severe COVID-19 patients [24]. When severe COVID-19 cases and mild cases were compared, it was reported that PCT value was higher and was a poor prognostic marker [9,12,13]. The meta-analysis evaluating severe and non-severe confirmed COVID-19 cases showed increased neutrophil and NLR rates and no difference was found between leukocyte values [13]. In our study, no significant relationship was found between leukocyte, neutrophil, NLR and RDW values between patients with and without pulmonary involvement in thoracic CT.

Our study has its limitations; firstly, the number of patients included in the study was small. Secondly, this study was a single center study, and it is not capable of evaluating various ethnic differences, thus preventing the generalized use of the study results.

Conclusion

As a conclusion, in the first evaluation in the emergency department, a significant difference was found in lymphocytes, monocytes, eosinophil, ferritin, fibrinogen, CRP, ESR, PLT and

urea values between patients with and without pulmonary involvement in thoracic CT, and eosinophil count, ESR,and CRP values provided the highest AUC values in predicting thoracic CT involvement. It can be predicted that patients with ESR>43 mm/h and CRP>6.26 mg/L and eosinophil count≤37μL will have a high probability of lung involvement. The need for thoracic CT during the pandemic can be planned according to these criteria.

DECLARATIONS

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Conflicts of Interest/Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics Approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Balikesir University Clinical Studies Ethics Committee approved this study (Decision Number: 2020/182).

Consent to Participate

Not applicable because the study is a retrospective chart review study.

Consent for Publication

Not applicable because the study is a retrospective chart review study.

Availability of Data and Material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability

IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA [Released in 2013]) -formally registered to Bursa Uludag University School of Medicine Biostatistics Department, Bursa, Turkey- was used for the statistical analyses.

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Table-1: Comparison of demographic and laboratory characteristics between patients with positive and negative thorax CT findings.

Variable		BT positive	BT negative	p-value
Gender	male	24 (41.38)	21 (41.18)	1.000
	female	34 (58.63)	30 (58.82)	
Age (years)		60 (48-69)	44 (31-67)	0.016
WBC (µL)		5350 (4500-6600)	6100 (4800-7600)	0.125
Neutrophils (µL)		3366 (2711-4541)	3692 (2462-4680)	0.762
Lymphocytes (µL)		1244 (694-1611)	1624 (1044-1996)	0.006
NLR		2.87 (1.89-4.49)	2.26 (1.53-3.95)	0.109
Monocytes (µL)		413 (337-555)	490 (411-755)	0.004
Eosinophils (µL)		12 (4-36)	61.00 (25-112)	<0.001
Ferritin (ng/mL)		77 (39-179)	38 (18-73)	0.001
PCT (ng/mL)		0.09 (0.04-0.13)	0.07 (0.04-0.10)	0.430
Fibrinogen (mg/dl)		399 (288-516)	300 (260-336)	<0.001
D-dimer (ng/mL)		213 (142-270)	153 (130-234)	0.051

CRP (mg/L)	22 (6-48)	3 (2-6)	<0.001
ESR (mm/h)	44 (24-67)	22 (13-33)	<0.001
PLT (10^3/mm^3)	203 (166-246)	227 (197-273)	0.013
RDW (%)	14.2 (13.4-15.2)	14.0 (13.2-15.2)	0.447
Urea (mg/dl)	31 (26-40)	24 (19-34)	0.004
Creatinine (mg/dl)	0.94 (0.81-1.07)	0.89 (0.78-1.02)	0.214
AST (IU/L)	26 (22-33)	24 (21-37)	0.309
ALT (IU/L)	22 (15-28)	21 (14-38)	0.995

Data given as median (1^{st} Q - 3^{rd} Q) or n (%)

NLR: neutrophil lymphocyte ratio, PCT: procalcitonin, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PLT: platelet, RDW: red cell distribution width, AST: aspartat aminotransferaz, ALT: Alanin aminotransferaz

Table-2: Results of logistic regression analysis

Independent variables	p-value	OR	95% CI for OR	
			Lower	Upper
Eosinophils	0.071	1.008	0.999	1.016
Monocytes	0.001	1.006	1.002	1.009
Ferritin	0.021	1.014	1.002	1.025
ESR	0.001	1.069	1.027	1.113
Urea	0.013	1.090	1.018	1.168

OR: Odds ratio, CI: Confidence interval

Table-3: ROC curve analysis results for torax CT results

	AUC	p-value	cut-off value	Youden J index	Sensitivity (95% CI)	Specificity (95% CI)
Age (years)	0.634	0.015	>44	0.305	77.59 (64.7 - 87.5)	52.94 (38.5 - 67.1)
Lymphocytes (µL)	0.654	0.004	≤1610	0.274	75.44 (62.2 - 85. 9)	52.00 (37.4 - 66.3)
Monocytes (µL)	0.664	0.002	≤466	0.289	64.91 (51.1 - 77.1)	64.00 (49.2 - 77.1)
Eosinophils (µL)	0.750	<0.001	≤37	0.472	77.19 (64.2 - 87.3)	70.00 (55.4 - 82.1)
Ferritin(ng/mL)	0.683	<0.001	>65	0.364	61.40 (47.6 - 74.0)	75.00 (60.4 - 86.4)
Fibrinogen(mg/dl)	0.711	<0.001	>383	0.452	53.57 (39.7 - 67.0)	91.67 (80.0 - 97.7)
CRP(mg/L)	0.783	<0.001	>6.26	0.523	75.86 (62.8 - 86.1)	76.47 (62.5 - 87.2)
ESR(mm/h)	0.762	<0.001	>43	0.452	53.57 (39.7 - 67.0)	91.67 (80.0 - 97.7)
PLT (10^3/mm^3)	0.638	<0.001	≤170	0.254	29.31 (18.1 - 42.7)	96.08 (86.5 - 99.5)
Urea(mg/dl)	0.660	0.003	>26	0.349	74.14 (61.0 - 84.7)	60.78 (46.1 - 74.2)

AUC: Area under the curve, CI: Confidence interval
CRP: C-reactive protein, ESR: erythrocyte sedımentatıon rate, PLT: platelet,

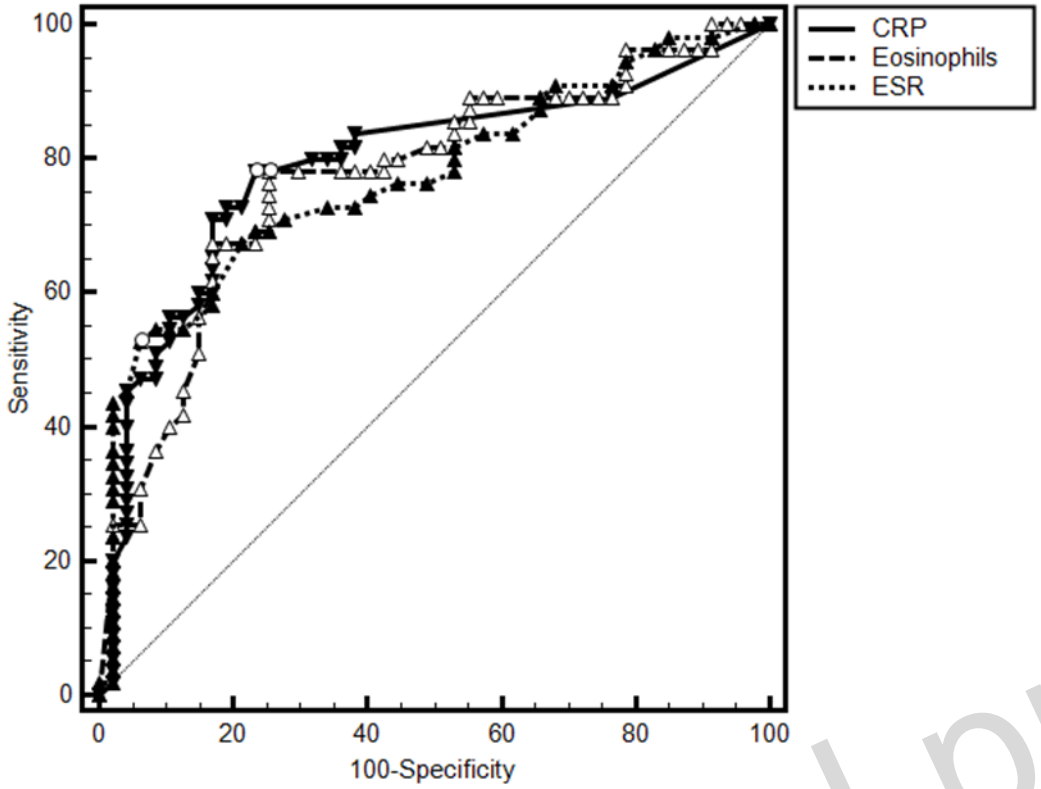

Figure-1: ROC curve for CRP, ESR and eosinophils