Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Clinical and laboratory features of COVID-19: Predictors of severe prognosis

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A B S T R A C T

Background: Coronavirus disease 2019 (COVID-19) emerged first in December 2019 in Wuhan, China and quickly spread throughout the world. Clinical and laboratory data are of importance to increase the success in the management of COVID-19 patients.

Methods: Data were obtained retrospectively from medical records of 191 hospitalized patients diagnosed with COVID-19 from a tertiary single-center hospital between March and April 2020. Prognostic effects of variables on admission among patients who received intensive care unit (ICU) support and those who didn't require ICU care were compared.

Results: Patients required ICU care (n = 46) were older (median, 71 vs. 43 years), with more underlying comorbidities (76.1% vs. 33.1%). ICU patients had lower lymphocytes, percentage of large unstained cell (%LUC), hemoglobin, total protein, and albumin, but higher leucocytes, neutrophils, neutrophil–lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocytes ratio (PLR), urea, creatinine, aspartate amino transferase (AST), lactate dehydrogenase (LDH), and D-dimer when compared with non-critically ill patients ($p < 0.001$). A logistic regression model was created to include ferritin, %LUC, NLR, and D-dimer. %LUC decrease and D-dimer increase had the highest odds ratios (0.093 vs 5.597, respectively) to predict severe prognosis. D-dimer, CRP, and NLR had the highest AUC in the ROC analysis (0.896, 0.874, 0.861, respectively).

Conclusions: The comprehensive analysis of clinical and admission laboratory parameters to identify patients with severe prognosis is important not only for the follow-up of the patients but also to identify the pathophysiology of the disease. %LUC decrease and D-dimer, NLR, and CRP increases seem to be the most powerful laboratory predictors of severe prognosis.

1. Introduction

A cluster of pneumoniae cases with unknown etiology emerged in Wuhan city of China in early December 2019. The causative agent was defined as a novel enveloped RNA beta-coronavirus, named as a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. The illness was subsequently termed as the Coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). On 30 January 2020, WHO declared COVID-19 as a Public Health Emergency of International Concern [2]. Although most of the patients have a milder clinical course, some of them have severe pneumonia with high mortality rate requiring comprehensive care in ICU [3]. Therefore, determining the predictive indicators of a severe infection is of great importance. It might help to understand the clinical course of the pneumonia, but more importantly, we still need to clarify the pathophysiology of the disease.

In the present study, we aimed to perform a comprehensive analysis of clinical, laboratory, and demographic characteristics of 191 patients with COVID-19, admitted to Ankara City Hospital, to determine the predictors of this serious illness.

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Table 1
Demographic, clinical, and radiologic characteristics of the patients with COVID-19.

	Total N = 191 (%)	Non-ICU patients N = 145 (%)	ICU patients N = 46 (%)	p value
Age, median (min - max), y	49 (18–92)	43 (18–83)	71 (28–92)	< **0.001**
Male gender	107 (56.0)	81 (55.9)	26 (56.5)	0.937
Healthcare Personnel	14 (7.32)	14(9.7)	0 (0)	**0.024**
Epidemiological Story	26 (13.6)	8(5.5)	18(39.1)	< **0.001**
Contact with a Positive Case	92 (48.2)	75(51.7)	17 (37.0)	0.081
PCR Confirmation	148 (77.5)	115 (79.3)	33 (71.7)	0.284
Abnormalities on chest CT	171 (89.5)	125 (86.2)	46 (100)	**0.04**
Early stage*	91 (47.6)	89 (71.2)	2 (4.4)	< **0.001**
Advanced stage**	80 (41.9)	36 (28.8)	44 (95.6)	
Onset of Symptom to Hospital admission, median (min - max), d	4 (0–15)	4 (0–15)	5 (1–15)	**0.025**
Length of Hospital Stay, median (min–max),	8 (1–33)	8 (1–22)	12 (1–33)	< **0.001**
Onset of Symptom to ICU admission, mean ± SD, d			7.09 ± 4.81	
Length of ICU Stay, mean ± SD			10.7 ± 8.16	
APACHE, mean ± SD			19.22 ± 12.93	
Comorbidity	83 (43.4)	48(33.1)	35 (76.1)	< **0.001**
Diabetes mellitus	27 (14.1)	12 (8.3)	15 (32.6)	< **0.001**
Hypertension	59 (30.9)	31 (21.4)	28 (60.9)	< **0.001**
Cardiovascular disease	20 (10.5)	8(5.5)	12 (26.1)	< **0.001**
Congestive heart failure	11 (5.8)	1 (0.7)	10 (21.7)	< **0.001**
Acute kidney disease***	19 (9.9)	4 (2.8)	15 (32.6)	< **0.001**
Chronic kidney disease	5 (2.6)	1 (0.7)	4 (8.7)	**0.012**
Cerebrovascular disease	7 (3.7)	0 (0)	7 (15.2)	NA
Respiratory rate, median (min–max)	22 (20–45)	20 (20–36)	28 (20–45)	< **0.001**
Signs and Symptoms				
Fever	103 (53.9)	74 (51.0)	29 (63.0)	0.155
Dry Cough	133 (69.6)	92 (63.4)	41 (89.1)	**0.001**
Dyspnea	76 (39.8)	38 (26.2)	38 (82.6)	< **0.001**
Diarrhea	8 (4.19)	7 (4.8)	1 (2.2)	0.682
Treatment				
Chloroquine	169 (88.5)	132 (91.0)	37 (80.4)	**0.05**
Favipiravir	49 (25.7)	13 (9.0)	36 (78.3)	< **0.001**
Oseltamivir	44 (23.0)	25 (17.2)	19 (41.3)	**0.001**
Steroid	10 (5.2)	0	10 (21.7)	**NA**
Antibiotic	169 (88.5)	123 (84.8)	46 (100)	**0.005**
Azithromycin	129 (67.5)	101 (69.7)	28 (60.9)	0.268
Ceftriaxone	14 (7.3)	8 (5.5)	6 (13)	0.106
Doxycycline	20 (10.5)	14 (9.7)	6 (13)	0.581
Tigecycline	6 (3.1)	0	6 (13)	**NA**
Oxygen support				
Nasal cannula	49 (25.7)	24 (16.6)	25 (54.3)	< **0.001**
High-flow Nasal cannula	2 (1)	0	2 (4.3)	NA
NIV	9 (4.7)	0	9 (19.6)	NA
IMV	10 (5.2)	0	10 (21.7)	NA
Death	20 (10.5)	0 (0)	20 (43.5)	NA

Data are median (minimum value – maximum value) or n (%). P values comparing ICU patients and non-ICU patients.
ICU = intensive care unit. NA = not applicable. NIV; non-invasive ventilation, IMV; invasive mechanical ventilation, *Single or multiple patchy ground glass opacities predominantly in the peripheral areas of the lungs, **Bilateral multi-lobar ground glass opacities and consolidation, *** Acute kidney disease was defined as 0.3 mg/dL increases of admission creatinine level compared to basal creatinine level.

2. Materials and methods

2.1. Study design and participants

This retrospective case series was approved by the ethics board of Ankara City Hospital (No. E1-20-531). All consecutive COVID-19 patients admitted to Ankara City Hospital from March 13 to April 30 were enrolled. The diagnostic criteria of WHO interim guidance were used [3]. Demographic, clinical, laboratory data, and radiological findings were extracted from electronic medical records and case record forms. All laboratory results of the patients within the 24 h of admission were recorded. The baseline parameters were selected to predict the prognosis of the patients when they first presented to the hospital to help the clinicians identify patients who may need ICU care at some point of hospital stay and need a close follow-up.

Data on the following laboratory parameters were collected: complete blood count parameters (CBC), urea, creatinine, estimated glomerular filtration rate (eGFR), total protein, albumin, AST, ALT, LDH, creatine kinase (CK), prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen, D-dimer, and ferritin. CBC was performed using the ADVIA 2120 Hematology System (Siemens Healthcare Diagnostics, Erlangen, Germany). Biochemical parameters defined above were measured using an Atellica Solution Immunoassay & Clinical Chemistry Analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). eGFR values were calculated using the CKD-EPI formula [4]. PT, APTT, INR, fibrinogen, and D-dimer were analyzed using the Sysmex CS-5100 System (Siemens Healthcare Diagnostics, Erlangen, Germany).

2.1.1. Diagnostic criteria

Chest computed tomography (CT) and oro/nasopharyngeal swab sample for RT-PCR were obtained for all suspected patients in addition to routine blood tests. COVID-19 was diagnosed using consistent clinical manifestations, such as fever and respiratory symptoms, findings of pneumonia on CT, and/ or positive SARS-CoV-2 PCR results according to the WHO interim guidance [3]. Patients requiring treatment in an intensive care unit (ICU) on admission or at some point during hospital stay (ICU group) and those not needing ICU care (non-ICU group) were compared in terms of clinical and demographic data, radiological characteristics, and routine blood test results.

2.2. Statistical analysis

Statistical analyses were performed using the SPSS 21.0. The Kolmogorov-Smirnov test was performed to check the normality of the variables. Descriptive analysis was presented using mean ± SD for normally distributed variables and median (minimum-maximum value) for non-normally distributed variables. Demographic and laboratory data were compared between the groups using the Student's *t* test for parametric and the Mann-Whitney *U* test for non-parametric variables. Comparisons for categorical variables were executed using the chi-square test or the Fisher's exact test. Receiver operation characteristic (ROC) curve was performed to analyze the efficiency of the disease severity diagnosis. Binary logistic regression analysis was performed to define the independent predictors of the disease severity. To include the appropriate parameters in the logistic regression model, firstly we examined the bivariate relationships among parameters, and then clinically most relevant variables were included in the model. To eliminate the effects of potential confounders, namely age, gender, and chronic disease parameters included in the model, we used enter method and parameters with p values greater than 0.200 were excluded for the final model with the Forward LR test. The Hosmer-Lemeshow goodness of fit test was used. The odds ratio (OR) was calculated for significantly associated variables. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Clinical and demographic characteristics

The study included 191 hospitalized patients with COVID-19 diagnosis according to WHO criteria [3]. In addition to consistent clinical symptoms and findings of COVID-19, all patients had PCR confirmation and/or radiologic findings. Of the patients, 148 (77.5%) had PCR confirmation and 171 (89.5%) had abnormalities on chest CT consistent with COVID-19. All SARS CoV-2 PCR negative patients (n = 43, 22.5%) had compatible signs, symptoms, and typical CT findings for COVID-19 without any alternative diagnosis, and 13 of whom were in the ICU group (Table 1). They were compatible with the probable case criteria according to the WHO interim guidance [3]. Other possible respiratory pathogens were also excluded with the respiratory PCR panel, which yielded a negative result based on the Fast Track FTD Respiratory pathogens 21 (Fast Track Diagnosis, Luxembourg) kit (Adenovirus, Bocavirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Enterovirus, Human metapneumovirus A/B, Influenza A, Influenza A (H1N1), Influenza B, Mycoplasma pneumoniae, Parainfluenza 1, 2, 3, and 4, Parechovirus, Respiratory syncytial virus A/B, Rhinovirus).

The median age was 49 years (min–max, 18–92), and 107 patients (56%) were male. The median time from onset of symptoms to admission were 4 days (min–max,1–15). The most common symptoms on admission were dry cough [133 (69.6%)], fever [103 (53.9%)], and dyspnea [76 (39.8%)]. Diarrhea was uncommon [8(4.1%)]. Eighty-three patients (43.4%) had comorbidities. Hypertension, diabetes, and cardiovascular disease were the most common pre-existing conditions (30.9%, 14.1%, and 10.5%, respectively) (Table 1).

Among these patients, 145 (75.9%) were isolated in clinical wards and 46 (24.1%) required ICU support. Compared with the non-ICU group (n = 145), critically ill patients who received ICU care (n = 46) were significantly older [median age 71 years (min–max, 28–92) vs 43 years (min–max, 18–83); $p < 0.001$]. In addition, patients in the ICU group more frequently had underlying comorbidities [35 (76.1%) vs 48 (33.1%); $p < 0.001$]. Diabetes mellitus and cardiovascular disease had been defined as predictors of severity previously [3]. We also wanted to evaluate the effect of each of hypertension and heart failure on severity. Diabetes mellitus, acute and chronic kidney disease, hypertension, congestive heart failure, and other cardiovascular diseases were all found significantly higher in the ICU group ($p < 0.05$ for each comorbidity).

There were no significant differences for PCR results between groups ($p < 0.284$). However, advanced stage radiologic abnormalities (single/multiple patchy ground glass opacities, predominantly in the peripheral areas of the lungs) were more common in the ICU group [44 (95.6%) vs 36 (28.8%); $p < 0.001$].

The mean time frame from onset of symptoms to ICU admission was 7.09 ± 4.81 days. The length of hospital stay was significantly higher in the ICU group ($p < 0.001$). The mean ICU follow up time was 10.7 ± 8.16 days for critically ill patients. The mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 19.22 ± 12.93 on the day of ICU admission (Table 1).

3.2. Main interventions and treatment

A total of 169 (88.5%) patients received antibiotic therapy [mostly azithromycin, 129 (67.5%)]. Doxycycline, ceftriaxone, and tigecycline were the other antibiotics used, respectively.

Chloroquine was administered to 169 (88.5%) patients and favipiravir was given to 49 (25.7%) patients (Table 1). Favipiravir was used mostly in severely/critically ill patients (78.3%). Oseltamivir was also used empirically until the influenza PCR test was concluded. It was used significantly more in ICU patients, since they were critically ill. Steroid treatment was given only in 21.7% (10/46) of the ICU patients according to clinical judgement of the ICU specialist for critical illness related corticosteroid insufficiency. Anticoagulant treatment was given to all ICU patients routinely. However, it was not given to non-ICU patients since there was no advice for its implementation in COVID-19 patients at that time of the point. Immunomodulatory therapy (IL-1 or IL-6 inhibitor) was not given to the patients since there was a knowledge gap. There is not a precise treatment agent for COVID-19 to date. Supportive treatment is still the main intervention. Oxygen inhalation therapy with nasal cannula were administered in 49 (25.7%) patients. The need of nasal cannula oxygen therapy was significantly higher in ICU patients [(54.3% (n = 25) vs 16.6% (n = 24); $p < 0.001$)]. Among the ICU patients, high flow nasal oxygen therapy was required 2 patients (4.3%), noninvasive ventilation was needed in 9 patients (19.6%), and invasive mechanical ventilation was needed in 10 patients (21.7%). Death occurred in 20 (43.5%) critically ill patients in the ICU group (Table 1). All other patients were clinically improved and discharged.

3.3. Laboratory parameters in patients with COVID-19 on admission

Blood routine parameters were recorded on admission day for all patients and then compared between groups. There were several significant differences. The ICU group showed higher white-blood cell, neutrophil counts, neutrophil–lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocytes ratio (PLR), urea, creatinine, AST, LDH, PT, INR, fibrinogen, CRP, ferritin, D-dimer levels, as well as lower lymphocytes, %LUC, hemoglobin, hematocrit, total protein, and albumin ($p < 0.001$) (Table 2).

3.4. The efficacy analysis of blood routine parameters in the prediction of critically ill patients diagnosed with COVID-19

A ROC curve analysis was used to determine the efficacy of various parameters predicting severe prognosis (Figs. 1, 2, and 3). D-dimer, CRP, and NLR had the highest AUC in the ROC analysis (0.896; 0.874; 0.861, respectively).

AUC, optimal cut-off, and sensitivity and specificity values of laboratory parameters are given in Table 3.

The binary logistic regression model included ferritin, %LUC, NLR, and D-dimer. The results of the logistic regression model are given in Table 4. It was statistically significant with $\chi 2 = 85.177$; $p < 0.001$. The model correctly classified 91.7% of the cases. Increasing ferritin, D

Table 2
Baseline blood-routine parameters of the patients with COVID-19.

		Median (min, max)			
	Normal Range	Total (N = 191)	Non-ICU group (n = 145)	ICU group (n = 46)	P Value*
Leucocytes ($\times 10^9$ per L)	4.2–10.8	5.96 (1.95–24.5)	5.51 (1.95–15.0)	8.7 (3.52–24.5)	< **0.001**
Neutrophils ($\times 10^9$ per L)	1.7–7.9	3.92 (1.03–21.1)	3.35 (1.03–12.0)	7.28 (2.34–21.1)	< **0.001**
Lymphocytes ($\times 10^9$ per L)	1.5–4.5	1.23 (0.23–3.54)	1.31 (0.37–3.54)	0.9 (0.23–2.43)	< **0.001**
Monocytes ($\times 10^9$ per L)	0.1–0.9	0.39 (0.04–1.38)	0.4 (0.04–1.38)	0.38 (0.11–1.36)	0.986
Eosinophil ($\times 10^9$ per L)	0.02–0.55	0.04 (0–0.56)	0.04 (0–0.56)	0.05 (0–0.31)	0.955
Red blood cell ($\times 10^{12}$per L)	4.2–5.65	4.79 (1.84–5.89)	4.87 (3.87–5.89)	4.23 (1.84–5.52)	< **0.001**
Hemoglobin (g/dL)	13–16.6	13.8 (5.8–17.9)	14.2 (9.6–17.9)	11.3 (5.8–17.2)	< **0.001**
Hematocrit (%)	38–49	40.3 (18.5–53.5)	41.3 (30.2–53.5)	34.3 (18.5–46.8)	< **0.001**
Platelet ($\times 10^9$ per L)	160–385	219.5 (58–736)	217 (75–736)	230 (58–727)	0.623
Ferritin (μg/L)	10–291	110 (5–1372)	87 (5–1007)	361 (15–1372)	< **0.001**
%LUC	0–4	1.6 (0.2–5)	1.7 (0.5–5)	1.2 (0.2–4.6)	< **0.001**
D-dimer (Quantitative) (mg/L)	< 0.55	0.44 (0.19–28.4)	0.42 (0.19–28.49)	1.37 (0.22–11.5)	< **0.001**
C-reactive protein (g/L)	0–0.005	0.0124 (0–0.34)	0.0081 (0–0.24)	0.123 (0–0.34)	< **0.001**
NLR**		35.1 (0.47–34.5)	2.41 (0.47–19.5)	9.04 (1.99–34.5)	< **0.001**
MLR***		0.3 (0.05–3.75)	0.27 (0.05–1.51)	0.39 (0.15–3.75)	< **0.001**
PLR****		175.785 (60.6–1248)	166.48 (60.62–617.7)	256.67 (87.2–1248)	< **0.001**
aPTT (sec)	21–32	24.6 (19.1–37.5)	24.6 (19.1–37.5)	25.0 (19.8–30)	0.324
Prothrombin Time (sec)	9.8–1.4	12.3 (10.7–16.9)	12.3 (11.1–16.8)	13.4 (10.7–16.9)	< **0.001**
INR (INR)	0.8–1.2	1.05 (0.91–1.46)	1.04 (0.94–1.46)	1.14 (0.91–1.46)	< **0.001**
Fibrinogen (g/L)	1.7–4.2	3.53 (1.98–8.35)	3.43 (2.05–7.71)	4.37 (1.98–8.35)	**0.001**
Urea[a](mg/dL)	20–49	30 (10–186)	28 (10–49)	47 (19–186)	< **0.001**
Creatinine[a] (mg/dL)	0.7–1.3	0.81 (0.4–2.52)	0.78 (0.4–1.47)	0.98 (0.4–2.52)	< **0.001**
eGFR (ml/dk/1.73 m^2)	greater than 90	96 (19–213)	101 (47–213)	78 (19–131)	< **0.001**
Total Protein (g/L)	57–82	68 (0.68–79)	70 (0.68–79)	60 (52–73)	< **0.001**
Albumin (g/L)	32–48	44 (20–63)	45.5 (36–63)	36 (20–51)	< **0.001**
Aspartate amino transferase (U/L)	< 35	26 (7–218)	25.5 (7–218)	31.5 (15–167)	**0.001**
Alanine amino transferase (U/L)	< 50	26 (8–145)	25 (8–145)	32 (10–81)	0.204
Lactate dehydrogenase (U/L)	120–246	240 (145–622)	219 (145–535)	312 (186–622)	< **0.001**
Creatine kinase (U/L)	32–294	112 (18–1098)	107,5 (30–1098)	122 (18–794)	0.833

ICU: intensive care unit, IQR: interquartile range, BUN; Blood urea nitrogen. P < 0.05 was considered statistically significant. *P values indicate differences between ICU and non-ICU patients. **NLR; Neutrophil Lymphocyte Ratio, *** MLR; Monocyte Lymphocyte Ratio, ****Platelet Lymphocyte Ratio. [a]BUN and creatinine levels were compared after patients with chronic kidney disease (n = 5) were excluded.

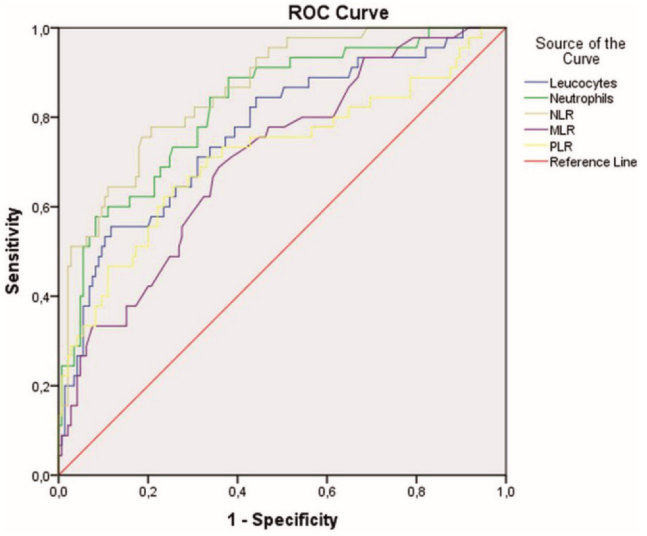

Fig. 1. The ROC curves of various parameters of blood routine in predicting severe SARS-CoV-2 infection, on admission. NLR: Neutrophils-to-lymphocytes ratio; MLR: Monocyte-to- lymphocytes ratio; PLR: Platelet-to-lymphocyte ratio.

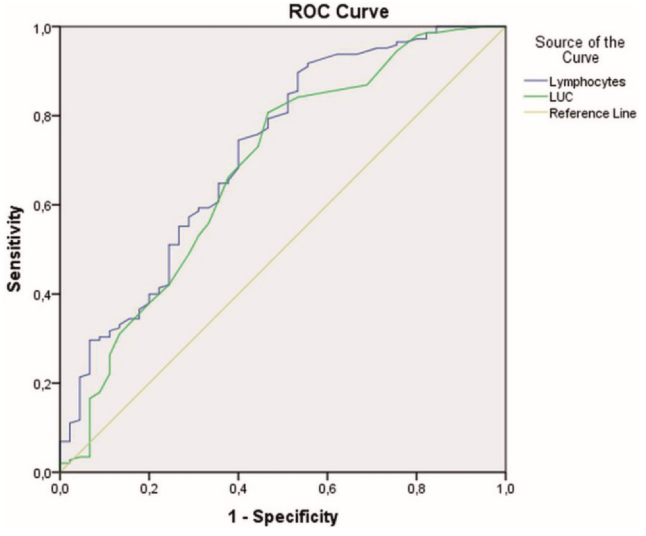

Fig. 2. The ROC curves of lymphocytes and %LUC in predicting severe SARS-CoV-2 infection, on admission. LUC: Large unstained cells.

dimer, and NLR, and decreasing %LUC were independent predictors of the disease severity with the likelihood ratios shown in Table 4.

4. Discussion

SARS-CoV-2 infection may lead to a wide clinical spectrum ranging from subclinical disease to severe pneumonia. Our initial findings showed that, laboratory parameters including %LUC, NLR, D-dimer, and CRP made the highest contribution to the prediction of the disease severity besides age, comorbidity presence, and symptoms on the admission.

Of the patients enrolled in the study, 24.1% were critically ill. In line with Wang et al, the patients in the ICU group were older and showed more comorbidities compared to those in the non-ICU group. In addition, gender was not found as a determinative factor for critical illness [5]. On admission, prominent symptoms that occurred significantly more frequently in the ICU group were dry cough and

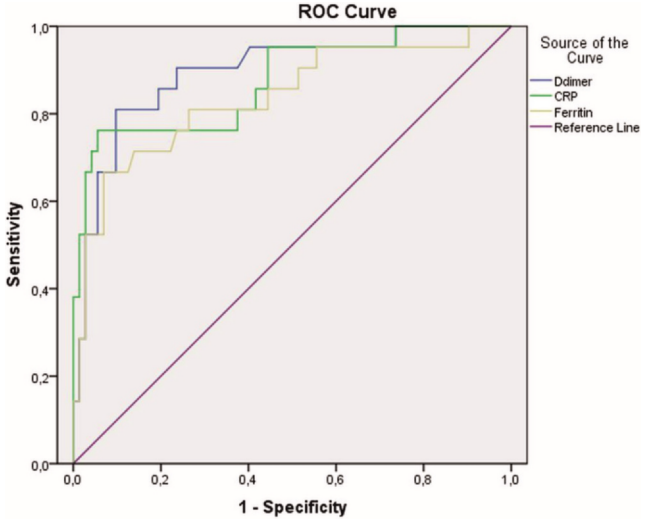

Fig. 3. The ROC curves of D-Dimer, Ferritin, and CRP in predicting severe SARS-CoV-2 infection, on admission. CRP: C reactive protein.

dyspnea. The mean duration from the onset of symptoms to ICU requirement was 7.09 ± 4.81 days, which had been reported as 10 days median previously [5]. The evaluation of severe prognostic factors in that time course is important to prioritize patients, who may be in greater need of ICU.

In our cohort, all ICU patients had pneumonia. As previously reported, the hallmark abnormalities on CT were bilateral multi-lobar ground glass opacities [5], which were detected in the present study in 95.6% of the ICU patients.

Patients in need of ICU care are the most vulnerable targets for death in COVID-19. Yang et al. reported 61.5% (32/52) mortality in critically ill patients [6]. In the present study, mortality rate was 43.5% (20/46) in the ICU group, whereas no death occurred in the non-ICU patients (0/145). Therefore, determining the prognostic severity criteria is fundamental to provide early intervention to patients who may require ICU support.

In regard to the laboratory evaluation, SARS-CoV-2 causes alterations in some routine blood parameters. As for admission laboratory parameters, decreased hemoglobin, lymphocyte, %LUC, and albumin, and upregulated leucocytes, neutrophils, NLR, ferritin, D-dimer, creatinine, LDH, and CK levels are distinguishing features of the critically ill patients. Higher levels of leucocytes were prominent characteristics of the critically ill patients in the present study, in consistent with the *meta*-analysis, which reported higher white blood cell counts in patients with severe COVID-19 [7]. In contrast to this study, there was no significant differences between our groups regarding thrombocytes levels. Wang et al. reported no significant differences between ICU and non-ICU patients, regarding thrombocytes and monocytes, which is consistent with our findings [5]. SARS-CoV-2 causes increases in

Table 4
Logistic regression analysis.

Parameters	B	Exp(B)	95% CI for Exp(B)	p
Ferritin µg/L	0.007	1.007	1.002–1.013	**0.006**
NLR	0.138	1.148	1.017–1.296	**0.025**
%LUC	−2.752	0.064	0.020–0.205	**< 0.001**
D-dimer mg/L	1.966	7.139	1.542–33.047	**0.012**

Hosmer Lemeshow GFT: p = 0.467; Model: χ^2 = 85.177; p < 0.001; Percentage Correct = 91.7%.

inflammatory factors, which results in anemia due to the destruction of red blood cell (RBC) and decreased erythrogenesis [8]. Red blood cell counts were significantly lower in critically ill patients in our cohort. The decreased hemoglobin levels were reported in severe COVID-19 patients in compatible with our results [8].

Lymphopenia and higher NLR have been reported as predictors for severe prognosis [6,9–11]. Although lymphocytosis is an expected finding for viral infections, one of the possible reasons for depletion of lymphocytes in SARS-CoV-2 infection is that lymphocytes are the target for virus since the angiotensin converting enzyme 2 (ACE 2) receptor of the virus is expressed on lymphocytes [7,12]. The other possible reasons for lymphopenia are as follows: the migration of lymphocytes from peripheral bloods to the lung, defective hematopoiesis, and the apoptosis of lymphocytes as a response to hyperinflammation [8,13]. Lymphopenia was a more distinctive feature of the critically ill patients in our cohort as reported previously [10]. The presence of prominent lymphopenia may predict disease severity. The ROC analysis revealed the optimal cut-off value for lymphocytes as $0.980x10^9$ per L (AUC;0.718), with 74.5% sensitivity and 60% specificity.

Fan et al. reported that the lymphopenic patients had a few reactive lymphocytes as lymphoplasmacytoid [10]. Large unstained cells are reported to include activated lymphocytes and peroxidase-negative cells. Lower %LUC levels were a prominent feature of the ICU patients in our cohort. The optimal cut-off value predicting the severe illness was determined as 1.450% (AUC;0.681) with 66.2% sensitivity and 62.2% specificity by the ROC analysis. Logistic regression analysis revealed that %LUC was negatively correlated with the independent predictor of disease severity with an odds ratio of 0.063. According to the statistical model including NLR, ferritin, %LUC, and D-dimer, %LUC had the highest independent contribution to the model to predict severe diagnosis. The results of our study might be an indicator of the lack of the immune response to increase the activated lymphocytes, which we observed in non-ICU patients. The lack of the defined immune response might be an important factor for the patients to experience a more severe disease.

Neutrophilia may result from the cytokine storm triggered by SARS-CoV-2. Although, the exact role of neutrophils is not known in viral infections, pro-inflammatory mediators produced by activated neutrophils have a detrimental role for the host [14]. In the *meta*-analysis of Zeng et al., higher neutrophil levels were correlated with the severity of COVID-19[7]. Consistently, our findings also suggest that higher level of

Table 3
The value of blood routine parameters in diagnosis of critically ill patients with COVID-19 on admission.

Parameters	Cut-off value	AUC (95%CI)	Sensitivity (%)	Specificity (%)	95%CI	*p* value
Leucocytes $\times 10^9$ per L	≥6.005	0.769	77.8	60.7	0.68–0.85	< 0.001
Neutrophils $\times 10^9$ per L	≥4.110	0.825	84.4	66.2	0.75–0.89	< 0.001
Lymphocytes $\times 10^9$ per L	≤0.980	0.718	74.5	60.0	0.62–0.80	< 0.001
%LUC	≤1.450	0.681	66.2	62.2	0.58–0.77	< 0.001
NLR	≥3.210	0.861	84.4	62.8	0.80–0.91	< 0.001
MLR	≥0.315	0.708	71.1	61.4	0.62–0.79	< 0.001
PLR	≥175.785	0.715	75.6	57.2	0.61–0.81	< 0.001
Ferritin µg/L	≥163.5	0.837	81	73.6	0.72–0.94	< 0.001
D dimer mg/L	≥0.565	0.896	85.7	80.6	0.81–0.97	< 0.001
CRP g/L	≥0.0087	0. 874	81	62.5	0.77–0.97	< 0.001

neutrophils may be used to predict severe cases.

SARS-CoV-2-triggered hyper inflammation seems to increase NLR, which promotes severe prognosis. A possible reason for this may be the reactive oxygen radicals released from neutrophils causing the cell's DNA damage [11]. Several studies have highlighted the predictive value of NLR for illness severity [7,11,15]. Our analysis also revealed that, NLR, MLR, and PLR might be used as a predictive diagnostic tool for determining patients needing ICU support. Previous studies have mentioned that the validation of PLR value is needed [7]. In our cohort, the optimal cut-off value for PLR was determined as 175 with the highest AUC, sensitivity, and specificity (0.715, 75.6% and 57.2%, respectively). The AUC of NLR reached the highest value (0.861) at the optimal cut-off value of 3.2 to predict the severe prognosis, independently. Our findings are consistent with previous reports suggesting higher NLR as a predictive nomogram for severe COVID-19 infection [11].

Hyper coagulation and disseminated intravascular coagulopathy (DIC) are other prominent features of viral infections, which may cause various complications [16]. Hypercoagulation may be due to the hyper inflammatory response. A markedly increased levels of fibrinogen and D-dimer were reported as predictive factors for severe prognosis, in consistent with our findings [5,17]. Monitoring the fibrinogen activity may be helpful for clinicians to identify the patients with high risk for severe COVID-19, since it is not usually altered in other viral infections on admission. The optimum cut-off value for D-dimer for predicting a severe disease was determined as 0.565 mg/L using the ROC curve (Fig. 3) (85.7% sensitivity; 80.6% specificity). Binary logistic regression analysis showed that the higher level of D-dimer compared to the cut-off value (0.565 mg/L) was also significant ($p = 0.012$, OR:7.139; 95% CI: 1.542–33.047) after the adjustment of ferritin, %LUC, and NLR. Ferritin was also determined as an independent predictive factor for severe infection ($p = 0.006$).

D-dimer and PT were reported to be positively correlated with mortality [18]. Anticoagulant therapy with low molecular weight heparin to decrease the risk of venous thromboembolism and DIC was reported to be associated with better prognosis in patients with COVID-19 [18].

Although lungs are the main target organ for SARS-CoV-2, end organ damage is not limited to lungs. Lymphocytes are known to inhibit hyper immune responses occurring due to viral infection. For this reason, the lack of efficient lymphocyte levels occurring via SARS-CoV-2 infection results in increased cytokines and exacerbated inflammatory responses, which leads to damages in liver and kidney in addition to lungs [19,20]. Lymphopenia and CRP were reported as independent predictors for hepatic injury in patients with COVID-19 [21]. In the present study, elevated CRP, AST, and LDH, and decreased total protein and albumin were found as significant laboratory parameters in the ICU group on hospital admission.

Kidney is another target organ for the virus since the ACE2 receptors of SARS-CoV-2 is highly expressed on kidney tubule cells [22]. The increased creatinine and decreased eGFR levels were significantly different in the ICU group.

Compared with non-critically ill patients, the ICU patients had several laboratory abnormalities as discussed above with the literature findings. However, to the best of our knowledge, there exists no study defining the importance of decreasing %LUC levels in predicting poor prognosis. In this study, our aim was to identify a useful marker which may be helpful in making an accurate prediction of severe prognosis, and we observed that %LUC value is an independent predictor that negatively correlated with poor prognosis with an odds ratio of 0.063. Therefore, it may be an addition to the list of severe prognosis predictors that can easily be obtained since it is a parameter reported in routine complete blood cell (CBC) tests. All findings of our study may be the result of cellular immune deficiency, hyper coagulation, kidney, and hepatic injury.

In conclusion, our findings indicate that the %LUC decrease and the D-dimer, NLR, and CRP increases appear to be the most powerful laboratory predictors of severe prognosis for COVID-19. Monitoring the predictors of severity may assist clinicians to identify and follow-up patients with higher risk for progression.

5. Author's contributions

AB, HB, SK, BOO, DG, BDK, IOT, and CCG are clinicians and provided clinical details. SE and GY conducted statistical analysis and composed the figure. AB, FMY, and HB wrote and edited the manuscript. All authors were involved in the gathering of the manuscript and approved the final version.

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CRediT authorship contribution statement

Aliye Bastug: Conceptualization, Writing - original draft, Writing - review & editing. **Hurrem Bodur:** Conceptualization, Writing - review & editing. **Serpil Erdogan:** Methodology, Formal analysis. **Derya Gokcinar:** Investigation. **Sumeyye Kazancioglu:** Investigation. **Behiye Deniz Kosovali:** Investigation. **Bahadır Orkun Ozbay:** Investigation. **Gamze Gok:** Investigation. **Isil Ozkocak Turan:** Investigation. **Gulsen Yilmaz:** Methodology, Formal analysis. **Canan Cam Gonen:** Investigation. **Fatma Meric Yilmaz:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.106950.

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