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RESEARCH ARTICLE

Evaluation of Biomarkers and Severity of COVID-19 in A Single Center

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ABSTRACT

Objectives: The clinical course of COVID-19 ranges from mild to severe. The predictability of clinical outcomes gains importance in managing the disease. In this retrospective cohort study, we aimed to investigate the relationship between biomarker levels and the clinical severity of COVID-19.

Methods: COVID-19 patients (n=618) admitted to a tertiary care hospital in Istanbul, Turkey were classified according to their clinical status using a scoring system designed by WHO. Laboratory parameters such as D-dimer, ferritin, and lymphocyte count levels were evaluated. In order to find out the relation between laboratory biomarkers and the severity of COVID-19, univariable and multivariable logistic regression analyses were used.

Results: A positive correlation was found when WHO Score was compared with D-dimer levels (r=.508, p<0.01), and ferritin levels (r=.391, p<0.01), whereas a negative correlation was observed between WHO Score and lymphocyte count levels (r=-.381, p<0.01). The cut-off values for D-dimer and ferritin were found as 0.86 ng/mL (70.9% sensitivity and 87.1% specificity) and 92.74 ng/mL (78.5% sensitivity and 52.2% specificity) respectively. According to the multivariable logistic regression model, lymphocyte count (β=- 0.305, p<0.001) and D-dimer levels (β=1.326, p<0.001) are the statistically significant regressors for hospitalization need.

Conclusion: Patients with higher D-dimer and ferritin levels were likely to have more severe disease, whereas patients with higher lymphocyte counts overcame the disease mildly. Unlike other studies, evaluating D-dimer and lymphocyte count will likely give more detailed information on COVID-19 clinical outcomes. *J Microbiol Infect Dis 2022; 12(3):89-96.*

Keywords: *COVID-19, ferritin; D-dimer, absolute lymphocyte count, multivariable logistic regression analysis*

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel viral agent that belongs to the *Coronaviridae* family that causes an ongoing global pandemic of coronavirus disease 2019 (COVID-19) [1]. From the beginning of the pandemic, national and international health authorities have been proposing various algorithms for the diagnosis, management, and treatment of the disease [2,3]. Infected patients show varying clinical outcomes as asymptomatic, mild, or critical, according to international guidelines [3]. The severity of the disease and mortality appear to be related to some risk factors, including age and numerous comorbidities like diabetes mellitus and hypertension, considering the epidemiological data [4]. On the other hand, among symptomatic patients, nearly 15%

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needed to be hospitalized, and 5% of them were classified as requiring intensive care [3].

Early diagnosis of COVID-19 has been an important issue from a public health point of view in order to isolate the ones with the suspicion of the disease to protect the people who are uninfected [5]. In addition to diagnosis, checking the clinical laboratory parameters in the follow-up of patients as early as possible is a crucial tool for evaluating the outcome of patients [6]. Laboratory parameters that are requested for COVID- 19 patients are mainly complete blood count, D-dimer, CRP, PCT (procalcitonin), and ferritin to manage the disease, which is also recommended by the Turkish Ministry of Health [2,7]. The need to interpret the biomarkers is especially reported to be important for identifying the patients with rapid progression risk from moderate to the critical stage of the infection to prevent the deterioration of the process [8].

In this study, several laboratory biomarkers, such as ferritin, D-dimer, and the clinical outcome, as well as the demographic characteristics of the COVID-19 patients, were cross-matched to investigate a possible relationship between them. It is aimed to broaden the horizon of clinicians about these diagnostic and prognostic tools to be more effectively used during SARS-CoV-2 infection.

METHODS

Data Collection

This retrospective cohort study was conducted in Göztepe Medical Park Hospital, Istanbul, Turkey. Nine hundred eighty-six patients were evaluated positively for SARS-CoV-2 from December 1, 2020, to May 1, 2021. Of the 618 patients (who were admitted to the emergency department, intensive care unit, and pandemic services of Göztepe Medical Park Hospital) the laboratory results of ferritin, D-dimer, absolute lymphocyte count (ALC), and hospital admission status were recorded. The study consisted of three groups ambulatory, service admission, and intensive care unit patients, according to their clinical status. We also classified patients from uninfected to non-survived between 0 to 8 by the WHO scoring system [9]. The local institutional ethics committee (E-22481095-020, 22.06.2021) and the Ministry of Health have approved the study protocol. Patient informed consent was taken.

Laboratory Tests

Whole blood samples of the subjects were collected in EDTA vial tubes, and hematological parameters such as ALC were determined by Mindray BC-6200 Auto Hematology Analyzer (High-tech Industrial Park, Nanshan, Shenzhen 518057, P. R. China). Ferritin and D-dimer levels were determined by Abbott Architect ci8200 Autoanalyzer (Abbott Park, Illinois, USA). All the samples were collected at admission to the outpatient clinic, COVID-19 pandemic service, and intensive care unit.

Statistical Analysis

All statistical analyses were performed in NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA.) Software. Descriptive statistics (medians, standard deviation, frequency, minimum and maximum values) and data distribution were reported using the Shapiro-Wilk Test. To estimate associations between two independent groups Mann-Whitney U Test was used. Spearman's Correlation Analysis was performed to determine the relationship between two quantitative data groups. Kruskal Wallis test was used to compare two or more independent samples which did not show a normal distribution. The significance level was evaluated as $p<0.01$ and $p<0.05$. Biomarkers associated with the need for hospitalization were analyzed firstly in the univariable and then in a multivariable regression model.

RESULTS

The study population comprised 618 COVID-19 patients with a positive SARS-CoV-2 RT-PCR test. 579 (93.7%) patients survived the disease, while 39 (6.3%) died. The distribution of the patients according to their sex was 290 (47%) female, 328 (53%) male, and the clinical outcome was 493 (79.8%) ambulatory, 68 (11%) service, and 57 (9.2%) ICU admitted. The mean age of the study population was 43.38±15.98 ranging from 18 to 75.

Values of the laboratory parameters classified by hospital admission status and sex are represented in Table 1. Survival status within the scope of each laboratory parameter is shown in Table 2.

Spearman’s Correlation Analysis

There was a weak positive correlation between age and D-dimer levels ($r=.456$, $p<0.01$) also between age and ferritin levels ($r=.426$,

p<0.01), whereas a weak negative correlation between age and ALC (r=-.274, p<0.01) was present according to Spearman's correlation analysis. Furthermore, a positive correlation was found between WHO Score and D-dimer levels (r=.508, p<0.01) and also between WHO Score and ferritin levels (r=.391, p<0.01). However, a negative correlation was found between WHO Score and ALC (r=-.381, p<0.01).

ROC Curve Analysis

D-dimer, ferritin, and ALC were evaluated in the patients. Clinical sensitivity and specificity of ROC curves were illustrated to show the need for hospitalization and two laboratory parameters, D-dimer and ferritin, in Figure 1 and Figure 2, respectively (Table 3). Lower WHO scores were observed in patients whose ferritin levels were below the cut-off value (92.74 ng/mL) (Figure 3). Moreover, D-dimer levels higher than the cut-off value (0.86 ng/mL) were detected in patients with higher WHO scores (Figure 4).

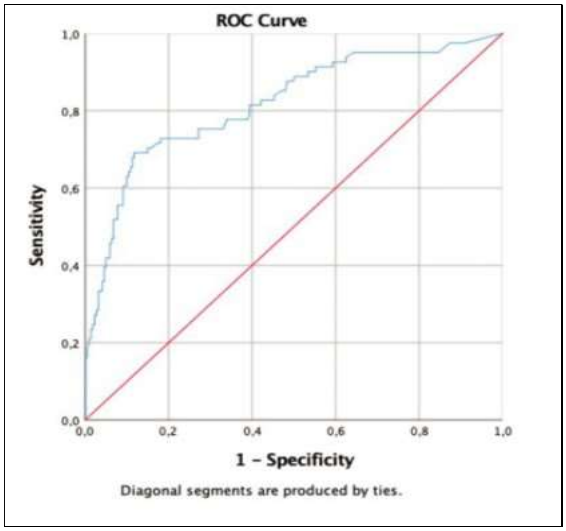

Figure 1. ROC curve of D-dimer and hospitalization Need

Multivariable Logistic Regression Model

A multivariable logistic regression model was used to ascertain the effect of ferritin, D-dimer, and ALC levels on hospitalization needs. The multivariable regression model was fitted with a stepwise method to the dataset with a dependent variable such as hospitalization need and independent variables such as ferritin, D-dimer, and ALC levels. The logistic regression model was statistically significant (X^2=102.25, p<0.001). When multivariable regression coefficients were evaluated, it was found that the D-dimer level significantly positively affected hospitalization need (β=1.326, p<0.001). In contrast, ALC has a significant negative impact on hospitalization needs (β=-0.305, p<0.001) (Table 4). According to the analysis, ALC and D-dimer levels were statistically substantial regressors for hospitalization needs in ambulatory or hospitalized patients.

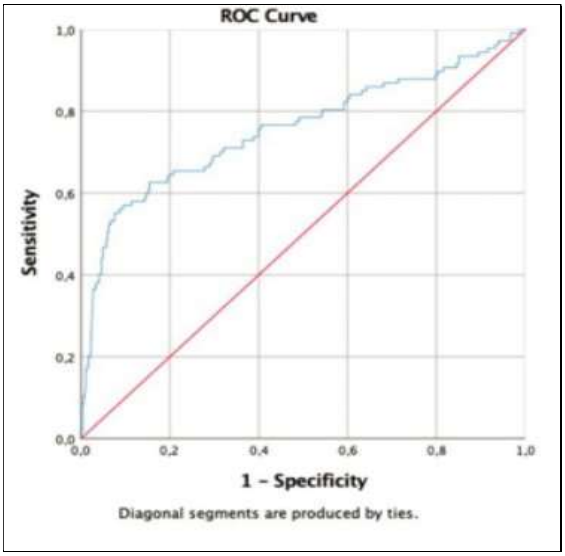

Figure 2. ROC curve of ferritin and hospitalization need.

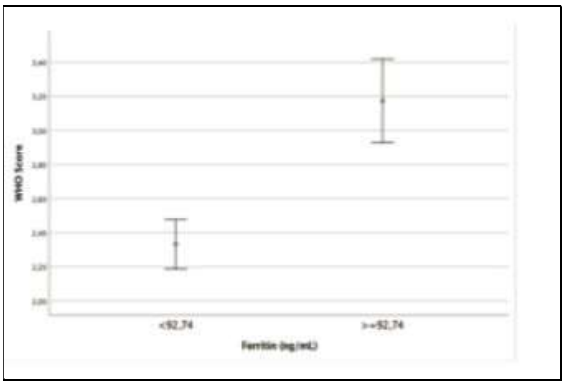

Figure 3. Ferritin values grouped by cut-off value (92.74 ng/mL) versus WHO score.

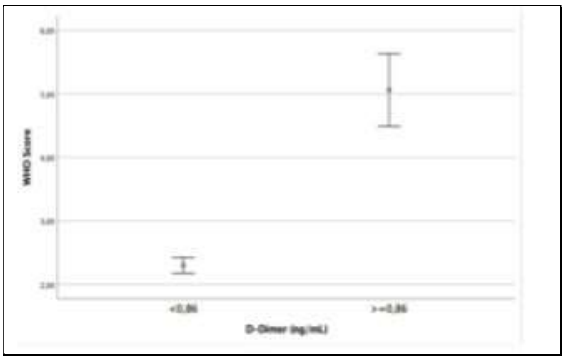

Figure 4. D-dimer values grouped by cut-off value (0.86 ng/mL) versus WHO Score.

Table 1. Selected parameters classified by hospital admission and sex.

Laboratory Parameters	Hospital Admission	Mean ± SD	Min-Max (Median)	p-value
D-Dimer (n=618) (ng/ml)	Ambulatory	0.56 ± 1.24	0.001-8.26 (0.18)	0.001**
	Service Admission	1.63 ± 2.28	0.001-11.13 (0.92)	
	Intensive Care Unit	5.31 ± 4.83	0.01-17.86 (4.06)	
Sex	Male	1.51 ± 2.86	0.01-17.74 (0.28)	0,810
	Female	1.3 ± 2.82	0.01-17.86 (0.28)	
Ferritin (n=618) (ng/ml)	Ambulatory	367.45 ± 1955.7	1.26-34219.78 (97,5)	0.001**
	Service Admission	1732.05 ± 5934.81	4.07-35512 (248.1)	
	Intensive Care Unit	4505.31 ± 7531.02	7.33-38312 (2000)	
Sex	Male	1287.88 ± 4609.42	2.53-38312 (209.85)	0.001**
	Female	652.87 ± 2788.51	1.26-29786.86 (59.53)	
Lymphocyte (n=618) (x10^9 cells/L)	Ambulatory	1.53 ± 0.72	0.01-4.85 (1.44)	0.001**
	Service Admission	1.08 ± 0.83	0.01-3.59 (0.92)	
	Intensive Care Unit	0.61 ± 0.68	0.01-3.08 (0.37)	
Sex	Male	1.4 ± 0.83	0.01-4.85 (1.33)	0.856
	Female	1.39 ± 0.72	0.01-4.29 (1.31)	

Sex: Mann Whitney U Test, *p<0.05, **p<0.01
Hospital Admission: Kruskal Wallis Test, *p<0.05, **p<0.01

Table 2. Mean, median, and minimum/maximum values of the parameters classified by survival.

Laboratory Parameters	Survival	Mean ± Sd	Min-Max (Median)	p-value
D-Dimer (n=618) (ng/ml)	Survived	0.8 ± 1.66	0.001-11.13 (0.23)	0.001**
	Non-Survived	6.38 ± 4.91	1.16-17.86 (4.95)	
Ferritin (n=618) (ng/ml)	Survived	559.61 ± 2791.7	1.26-37964 (104.31)	0.001**
	Non-Survived	5857.89 ± 8478.98	28.02-38312 (2000)	
Lymphocyte (n=618) (x10^9 cells/L)	Survived	1.46 ± 0.75	0.01±4.85 (1.37)	0.001**
	Non-Survived	0.45 ± 0.59	0.01±2.9 (0.28)	

Mann Whitney U Test, *p<0.05, **p<0.01

Table 3. Results of ROC Analysis to Assess Hospital Admission (Ambulatory or Hospitalized)

Laboratory Parameters	Sensitivity (%)	Specificity (%)	Cut-off Value	Area Under the Curve (AUC)
D-Dimer (ng/ml)	70.9	87.1	0.86	81.9
Ferritin (ng/ml)	78.5	52.2	92.74	75.6

Table 4. Logistic regression model of independent variables and hospitalization need.

		Univariable					Multivariable				
Model	Variables	B	S.D.	Exp (B)	Wald	p	B	S.D	Exp (B)	Wald	p
1	Ferritin	1.549	0.128	0.212	146.462	0.001**					
	D-Dimer	0.530	0.086	0.171	37.857	0.001**	0.282	0.095	1.326	8.900	0.001**
	Lym	-1.470	0.186	1.400	62.414	0.001**	-1.187	0.287	-0.305	17.112	0.001**

**p<0.01 *p<0.05

DISCUSSION

In this study, a positive correlation was found when WHO Score was compared with D-dimer levels, and ferritin levels, whereas a negative correlation was observed between WHO Score and lymphocyte count levels. When multivariable logistic regression is examined, lymphocyte count and D-dimer levels are found to be statistically significant regressors for hospitalization. Zhou et al. were able to show a relationship between serum ferritin levels and the prediction of SARS-CoV-2 infection severity using logistic regression analysis [10]. In a meta-analysis conducted by Taneri et al., it was indicated that pathologically high serum ferritin levels could be caused by several reasons, such as older age, anemia, and hypertension [11]. The reason behind the rise of ferritin levels could originate from a pre-existing condition, so clinicians should be alert to the baseline value of ferritin levels to choose a patient-specific treatment strategy. Since ferritin is both an acute phase reactant and shows the storage of iron, it may show basal differences and, therefore, cannot be a reliable prognostic indicator for COVID-19 alone. Evaluation of D-dimer and the ALC together could be more directly connected with COVID-19 and could have an important role in estimating the prognosis, as seen in the result of the multivariable regression model. Moreover, D-dimer originates from the degradation of a cross-linked fibrin network and is considered a valuable biomarker for the activation of fibrinolysis and coagulation [12]. D-dimer cut-off value of our study for hospitalization need was found as 0.86 ng/mL. Gungor et al. conducted a meta-analysis for the discrimination of severe and non-severe COVID-19 patients, which showed similar results to our study in terms of D-dimer level [13]. Huang et al. proposed that D-dimer level for ICU. admitted COVID 19 patients was 0.6-14.4 ng/mL whereas 0.3-0.8 ng/mL for non-ICU care patients [14]. In terms of evaluating mortality, the D-dimer cut-off value of 2.025 ng/mL was found in a retrospective study that included 1114 COVID-19 patients [15]. Unlike those studies, which are generally based on differentiation of severe and non-severe patients, we aimed to predict the hospitalization need of COVID-19 patients by determining the cut-off value of D-dimer.

According to the "Anti-Cytokine Anti-Inflammatory Therapies and Coagulopathy Management during COVID-19 Pandemic", which is published by the Ministry of Health, there is no precise cut-off value for D-dimer; however, two/threefold and more increase in D-dimer level is accepted as an indication for hospitalization [16]. If the D-dimer level has a twofold and more increase, anticoagulant prophylaxis should be prolonged for up to 45 days to prevent any thromboembolic situation [16]. In Turkey, as soon as the patient is hospitalized with the diagnosis of COVID-19, anticoagulant prophylaxis is given due to the risk of VTE [16]. Additionally, a decrease in thrombocyte count and in fibrinogen level, prolonged PT, and aPTT are the other factors that may affect the hospitalization need [16].

Patients with lower WHO scores had lower D-dimer levels compared to patients with higher WHO scores (Figure 4). In this study, D-dimer levels were found to be statistically significant in terms of hospitalization need ($p=0.001$, $p<0.01$) (Table 1). Additionally, Zhang et al. indicated that patients with significantly higher D-dimer levels (cut-off level of 2.0 ng/mL) should be admitted to the hospital under close monitoring even if they do not show any symptoms [17].

Increased levels of D-dimer were also found as significant ($p=0.001$, $p < 0.01$) in terms of mortality. In a systematic review conducted by Rostami et al. among 2118 patients, 1521 survivors, and 597 non-survivors, the mean values of D-dimer levels were 0.79 and 3.79 ng/mL, respectively [18].

When COVID-19 patients' D-dimer levels were examined according to sex, there was not a significant difference. Similar to our result, Tang et al. did not find any statistically significant difference in survival status among the male and female populations [19]. However, weak positive correlations between age and D-dimer levels ($r=.456$, $p<0.01$) were found in this study, as supported by Rostami et al. by indicating that age is a risk factor for coagulation disorders [18].

Furthermore, in addition to D-dimer, ferritin is also used as a biomarker to predict the clinical course. In this study, the cut-off value for ferritin within the context of hospitalization needs among COVID-19 patients was 92.73

ng/mL, with 78.5% sensitivity and 52.2% specificity. There are some studies about the determination of ferritin cut-off value to evaluate the severity of disease, especially in the ICU. Bozkurt et al. showed a cut-off value of ferritin for the prediction of the severity of COVID-19 as 264.5 ng/mL with 73.9% sensitivity and 94.2% specificity [20]. Qaeda et al. demonstrated that the ferritin cut-off value for mechanical ventilation need as 502 ng/mL [21]. A study conducted by Lino et al. indicated a cut-off value of 1873 ng/mL (sensitivity of 68.4% and specificity of 79.3%) to predict in-hospital mortality [22].

Higher ferritin levels were observed among hospitalized patients in this study group. Similar to this study, Qin et al. revealed that severe COVID-19 patients were more likely to have higher levels of ferritin values than non-severe patients [23].

In terms of mortality, non-survivor patients had significantly higher values of ferritin, with a median value of 2000 ng/mL. As reported by Qeadan et al., COVID-19 patients whose ferritin values were more than 714.3 ng/ml showed a higher risk of mortality [22]. Laguna-Goya et al. demonstrated median values among survivor and non-survivor COVID-19 patients were 984 ng/mL and 2345 ng/mL, respectively [24].

There was a weak positive correlation between age and ferritin levels (r=.426, p<0.01) in this study, elderly patients were more likely to be in a severe condition of the disease with higher ferritin levels. Male COVID-19 patients had higher levels of ferritin than women; however, men are more likely to have higher values, and the difference cannot be associated with COVID-19. Qaeda et al. demonstrated cut-off values for women and men in terms of in-hospital mortality as 433.3 ng/mL and 740 ng/mL, respectively [21]. In addition, a study composed of 275 SARS Cov-2 infected patients showed that increased ferritin levels are positively correlated with mortality [25]. Önal et al. showed that the mean of ferritin levels was 1844.4 ± 860.7 ug/L in patients with 30-day mortality, whereas it was 540.5 ± 96.1 ug/L in patients with 30-day no mortality [25].

As an indicator of clinical outcome, ALC has also been considered. A lymphocyte count of less than 1 x 10^9 cells/L is defined as lymphocytopenia [14]. Like in many viral diseases, lymphocytopenia is an observed clinical manifestation seen in COVID-19, and it is further related to the severity of the illness. As the condition prolongs, it may result in a more severe outcome [26]. A relationship was noticed in patients with severe infection by means of WHO scores. ALC was lower in patients with higher WHO scores (r=-.381, p<0.01).

The results of this study showed the mean counts of lymphocytes for the ambulatory, hospital, and ICU admitted patients were 1.53 ± 0.72, 1.08 ± 0.83, and 0.61 ± 0.68, respectively. Furthermore, in a small-sized cohort, the mean values of ALC (x10^9/L) were found as 1.92, 1.42, and 1.58 for mild, moderate, and severe COVID-19 patients, respectively [27].

The difference between the results could be caused by the size and the demographic characteristics of the patients. According to a meta-analysis compiled from twelve articles, the presence of lymphocytopenia can change the direction of the disease to a more severe path with a nearly three-fold increased risk [28]. It was found statistically significant that the ALC of the non-survivor patients was lower than the survivors (p=0.001; p<0.01), which is compatible with previous research [29].

In a multicentered cohort study, the presence of several risk factors and various clinical presentations of COVID-19 with high percentages of lymphocytopenia were reported among the male population [30]. In addition, investigated data showed a negatively weak correlation between the age and the ALC of the patients (r=-.274, p<0.01). However, Illg et al. reported no significant relationship between ALC and age in a recent study [29]. Present data did not signify a relationship between sex and ALC (p>0.05), similar to the research done by Waris et al. [27].

This study has also some limitations. Serial determination of D-dimer, ferritin, and ALC was not performed. The biomarker levels of patients during the post-infection period were not evaluated in the concept of this research. A comprehensive prospective cohort study can be conducted to evaluate better the change of laboratory biomarkers, including infection and post-infection period of COVID-19 patients.

CONCLUSION

Laboratory biomarkers may lead clinicians to predict the clinical outcome in terms of diagnosis, management, and complications of COVID-19. ALC, D-dimer, and ferritin, as well as age, sex, and mortality, were evaluated regarding the need for hospitalization. Cut-off values for those whose clinical status shifted from ambulatory to hospitalized were found as 0.86 ng/mL for D-dimer and 92.74 ng/mL for ferritin. Apart from this, severe lymphocytopenia is observed in more severe cases compared to mild and moderate cases. These levels may give more reliable information to clinicians concerning the hospitalization need. Therefore, according to the multivariable regression analysis, a combined evaluation of D-dimer and ALC is likely to give more detailed information to predict the hospitalization need in COVID-19.

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Authors' Contributions

Organization and Coordination, Ö.U.D., DY and SI, The Conception and Design of the Study, Ö.U.D., DY and SI, Methodology, Ö.U.D., DY and SI, Resources Ö.U.D, DY and SI, Data Curation Ö.U.D., DY, SI, IEU, MMS and O.Ç., Writing-Original Draft Preparation, Ö.U.D., DY, SI, IEU, MMS and O.Ç., Writing-Review and Editing, Ö.U.D., DY and SI, Visualization, Ö.U.D., DY, SI, IEU, MMS and O.Ç., Supervision, Ö.U.D., DY, and SI.. All authors contributed to the final approval of the version to be submitted.

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