Original Article

The Role of Laboratory Measurements on D-dimer Level in Patients with COVID-19: A Retrospective Study

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ABSTRACT

Introduction: Inflammation may raise the concentration of D-dimer level in COVID-19 patients. There is no consensus on the role of inflammation on the D-dimer level in the literature. We aimed to examine the role of inflammation in D-dimer level in COVID-19 patients.

Methods: The patients who were suspected of COVID-19 disease were referred by one of the medical doctors to a private medical lab between 1 July and 30 November 2020. The patients with COVID-19 infection were diagnosed using a combination of IgG and IgM antibodies. The confirmed laboratory patients were considered cases (n=204) and others as healthy controls (n=440) in this case-control investigation.

Results: In this study, the patients were older compared to the healthy controls; 54.5 vs. 51.5 years; P=0.0251. The patients had a significantly higher concentration of D-dimer (483.5 vs. 318 µg/ml; elevated prevalence: 48.53% vs. 22.95%; P<0.001) and significantly higher median CRP concentration compared to the healthy controls (89.0 vs. 36.63 IU/ml (P<0.001), respectively. The patients and controls had a similar median ferritin concentration. The nominal logistic regression model showed that D-dimer (P=0.00274) was the only variant factor between the COVID-19 patients and healthy controls. The CRP concentration was not shown to determine the D-dimer levels in COVID-19 patients (P=0.4713).

Conclusions: This study showed that patients with COVID-19 have elevated levels in CRP and D-dimer. The study did not confirm the role of inflammation in elevating D-dimer in COVID-19 patients. The inflammatory and thrombosis markers are required to be measured in COVID-19 patients with different severities at various follow-up periods in a prospective study.

Keywords: inflammation; thrombosis; COVID-19

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INTRODUCTION

The outbreak of novel coronavirus infection (2019-nCoV), known as COVID-19, was originated from China in late 2019 and spread to other countries; including Iraqi Kurdistan.[1] Globally, by 22 March 2021, there were 122,822,505 confirmed cases of COVID-19, including 2,709,041 deaths.[2]

A growing body of literature reports high incidence rates of venous and arterial thrombotic complications in critically ill COVID-19 patients. The cumulative incidence rate of thrombotic complications was determined to be 31% (95% CI 20-41%). Pulmonary embolism (PE) is considered the most frequently diagnosed thrombotic complication in patients with COVID-19 disease[3]. Thrombosis incidence rates are between 20% and 30% among critically ill COVID-19 patients, even with prophylaxis.[4]

Thrombosis is important to COVID-19 patients because it contributes to morbidity and mortality.[5] For example, the cumulative incidence of thrombosis of large-vessel thrombotic events was 49% in a Dutch study in COVID-19 patients. The majority of patients had pulmonary emboli on computed tomography in segmental and sub-segmental pulmonary arteries.[3] In addition, an Italian study reported a 21% cumulative incidence of thromboembolic; including 27.6% in the intensive care unit (ICU) and 6.6% in the general ward.[6]

Malas et al. reviewed the evidence for the role of thromboembolism in the COVID-19 outcomes in a meta-analysis. The overall thromboembolism was determined to be 21% (95% CI: 17-26%) and 31% (95% CI: 23-39%) in ICU. The overall pulmonary embolism rates were 13% (95% CI: 11-16%) and 19% (95% CI: 14-25%) in ICU. They reported that the pooled mortality rates in patients with and without thromboembolism were 23% (95% CI: 14-32%) and 13% (95% CI: 6-22%), respectively. The patients who developed thromboembolism had 74% higher pooled odds of mortality rate compared to those patients who did not develop thromboembolism (OR, 1.74; 95% CI, 1.01-2.98; P = 0.04).[7]

Significance of the study

It is suggested that inflammation increases the production of clotting factors in the liver. For instance, fibrinogen levels in a severe case of COVID-19 were 10-14 g/L, compared with 2-4 g/L normally and 5-6 g/L in a pregnant woman. The COVID-19 patients have sticky blood.[8]

The prognostic effects of hyper-inflammation in COVID-19 patients have shown that non-survivors patients have elevated inflammatory markers compared to survivors. The elevated inflammatory markers are not normalized throughout the entire hospitalization.[9] This finding suggests that maybe the elevated inflammation is related to the pathogenesis of COVID-19. In this regard, the elderly and patients with non-communicable diseases have more difficulty in overcoming COVID-19 disease. These patients have a more extreme inflammatory response when infected by COVID-19.[10] Despite confirmation of thrombosis in COVID-19 patients, the role of inflammation in the development of thrombosis in COVID-19 patients has not been sufficiently examined. In addition, there is no consensus on the role of inflammation in the development of thrombosis in patients with COVID-19. In addition, the previous large study conducted in this region did not include biomarkers.[11] A review study reported that CRP, vitamin D levels, and prolactin are attributed to COVID-19 disease.[12] In this study, we aimed to investigate the role of inflammation in elevating D-dimer level in patients with COVID-19 was examined in this case-control study.

Patients and methods

Study design, population, and data collection

The suspected patients with COVID-19 disease who were referred by one of the medical doctors to our private medical lab between 1 July and 30 November 2020 were included in this comparative case-control study. The persons who were suspected to have COVID-19 disease were referred by a medical doctor; including internists or infectionists. The referred persons had signs and symptoms of COVID-19 disease, such as fever, headache, myalgia, sore throat, or fatigue. The populations of this study were male and female with various medical, educational, and socio-economic backgrounds living in Duhok city.

The blood samples were taken from the patients for the analysis of the requested medical tests. We obtained the ethical clearance for this protocol from the local health ethics committee called Duhok Directorate General of Health. It is a joint health ethics committee of the Duhok Directorate General of Health and the University of Duhok. The protocol was registered on 13th December 2020 as reference number 13122020-6-10. The data were collected from our private lab called Jeen lab in Duhok city. The Jeen lab is located in the main area of Duhok city. Therefore, patients visit the lab for medical tests irrespective of socio-demographic and medical perspectives. In addition, we considered a broad period to include as many as patients with different medical and socio-demographic characteristics.

In this study, patients who were referred from a medical doctor to the Jeen lab in Duhok city and underwent the COVID-19 test were eligible to be included in the study. Patients with the following test results were eligible to be included in this study. The tests were LDH, D-Dimer, ferritin, CRP, 2019 nCoV IgG, and 2019 nCoV IgM.

Diagnostic and measurement criteria

In this study, the patients who were confirmed to have COVID-19 disease through medical laboratory tests

were considered cases and others as controls. The patients who were referred to the lab had signs and symptoms of COVID-19. The diagnosis of COVID-19 was performed using a combination of IgG and IgM. Zeng et al. (2020) approved that combining IgG and IgM gives the sensitivity and specificity of 99.5% and 100% over a standard RT-qPCR assay, respectively.[13] The patients who were diagnosed with COVID-19 were considered cases and the patients who had not COVID-19 were determined as healthy subjects in this study as suggested by Zeng et al. (2020). The outcomes of interest were compared between the cases and controls consequently.

We obtained the blood tests from the local electronic registry of our private lab. We analyzed the readily available laboratory tests associated with inflammation-associated markers. The biomarkers included in this analysis were ferritin, C reactive protein (CRP), LDH, and D-dimer. The plasma level of D-dimer was measured using Cobas C311 on an automated coagulation analyzer (Roch, Germany), while the serum level of all other markers in addition to COVID-19 IgG and IgM was measured using Cobas C411 on an automated analyzer (Roch, Germany).

We collected the blood samples (5 ml) using a sterile syringe and put in a sterile test tube without anticoagulant for measurements of COVID-19 (IgG and IgM), CRP, Ferritin, and LDH tests. The D-Dimer test sample (3 ml) was collected in the test tube containing sodium citrate as an anticoagulant and left to clot for 30 minutes, and then centrifuged at 4500 rpm for 10 minutes. The tube was inverted several times immediately after blood collection to prevent coagulation, and then centrifuged at 3500 rpm for 10 minutes. The Cobas C311 Principle and Cobas C411 Principle was used for the analysis of the samples.

Eight ml of venous blood were collected into two tubes from the patients for the analysis of the requested medical tests. Four ml were poured into gel tubes and were allowed 10 minutes to clot and was centrifuged at 4500 rpm for 10 minutes. Then, the tube was analyzed for the following tests; LDH, CRP, Ferritin, and 2019 nCoV IgG, and 2019 nCoV IgM. Another four ml of the blood was entered into a sodium citrate tube and was mixed well and centrifuged at 3500 rpm for 10 minutes for D-Dimer test.

Serum analysis

All the laboratory kits and reagents used through this study were provided from international suppliers and companies.

Equipment

- Cobas c 311

The Roche Diagnostic analyzer is automated, software-controlled for clinical chemistry analysis. It is designed for both quantitative and qualitative in vitro determination a large variety of test for analysis. The samples were performed by this device for following tests: CRP, The samples were performed by this device for following tests; CRP, D-Dimer and LDH.

- Cobas e411

The Roche Diagnostic analyzer is fully automated. It is designed for both quantitative and qualitative in vitro assay determination for a broad range of applications including anemia; bone, cardiac and tumor markers; critical care; fertility/hormones; maternal care; and infectious diseases. The analyzer is available as a rack or disk sample handling system. The samples were performed by this device for following tests: Ferritin and 2019 nCoV IgG, and 2019 nCoV IgM.

Statistical analysis

The general information of the study was presented in mean (Sta. Deviation) or number (percentage). The differences in general, inflammation and thrombosis levels between the COVID-19 and healthy controls were examined using an independent t-test, Pearson Chi-squared, or Mann-Whitney U tests. The uncertainty in the mean difference was calculated using a 95% confidence interval. The nominal logistic regression model was used to examine the most variant factors between the COVID-19 and healthy controls. The role of inflammation in the thrombosis concentration was examined using the standard least squared analysis model. We considered the significant difference when the p-value was less than 0.05. The statistical calculations were performed using JMP Pro 14.3.

RESULTS

General and biomedical measurements

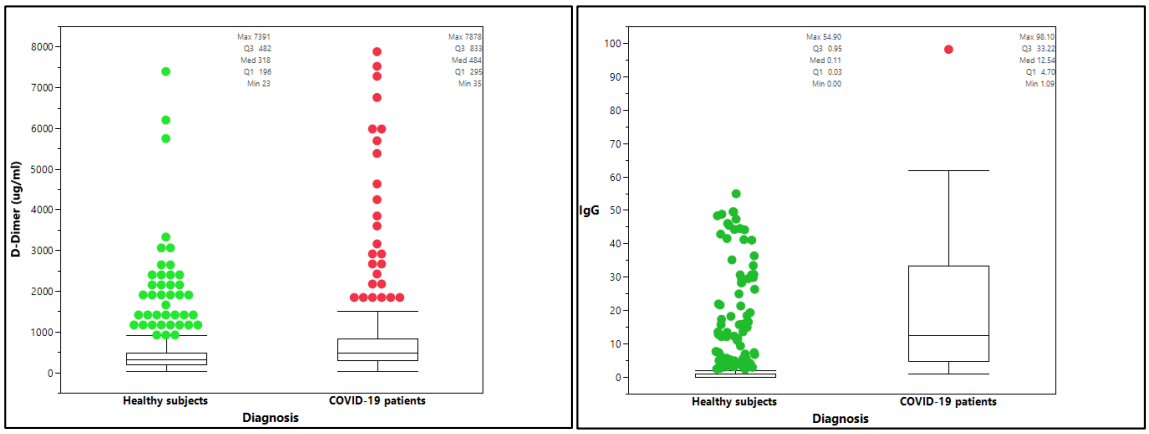
Of the total 1036 cases that were collected from the lab, the cases that had not the D-dimer and IgG and IgM

were excluded from the analysis. Accordingly, 644 cases were included in the first step of the analysis. Of these cases, 204 (31.7%) were diagnosed to have COVID-19 and the remaining were considered healthy subjects (440, 68.3%). The patients and controls were comparable in gender (male/female; 46.14%/53.86% vs. 54.41%/45.59%, P=0.0519, respectively). The patients were significantly older compared to the healthy controls; 54.5 vs. 51.5 years; P=0.0251. The patients had a significantly higher median concentration of D-dimer compared to the healthy controls; 483.5 vs. 318 µg/ml; elevated: 48.53% vs. 22.95%; P<0.001. Similarly, the patients had significantly higher median CRP concentration; 89.0 vs. 36.63 IU/ml (P<0.001), respectively. The patients and controls had a similar median ferritin concentration. There was no statistically significant difference in the median of ferritin between the cases and controls, 250 vs. 458.5 ng/ml, respectively (Table 1 and Figure 1).

Table 1: Comparison of general and biomedical measurements between the lab-confirmed cases of COVID-19 and healthy subjects

	Study groups		
Subjects' characteristics (n=644)	**Healthy subjects (n=440)**	**COVID-19 patients (n=204)**	**P-Value**
Age (years)			
Mean (Sta. Deviation)	51.5 (15.5)	54.4 (15.2)	0.0251[a]
95% CI	50.0-52.9	52.3-56.5	
Gender			
Male	203 (46.14)	111 (54.41)	0.0519[b]
Female	237 (53.86)	93 (45.59)	
D-dimer (µg/ml)			
Median (Interquartile Range)	318 (286.25)	483.5 (537.25)	<0.001[c]
95% CI	425.6-554.0	741.5-1116.4	
D-dimer category			
Normal	339 (77.05)	105 (51.47)	<0.001[b]
Elevated	101 (22.95)	99 (48.53)	
CRP (IU/ml)			
Median (Interquartile Range)	12.5 (36.63)	44 (89.0)	<0.001[c]
95% CI	28.6-39.8	49.5-69.6	
Ferritin ng/ml			
Median (Interquartile Range)	250 (522)	458.5 (829.75)	0.169[c]
95% CI	315.51-533.99	346.60-825.89	

[a]An independent t-test, [b]Pearson Chi-squared, and [c]Mann-Whitney tests were performed for statistical analyses.



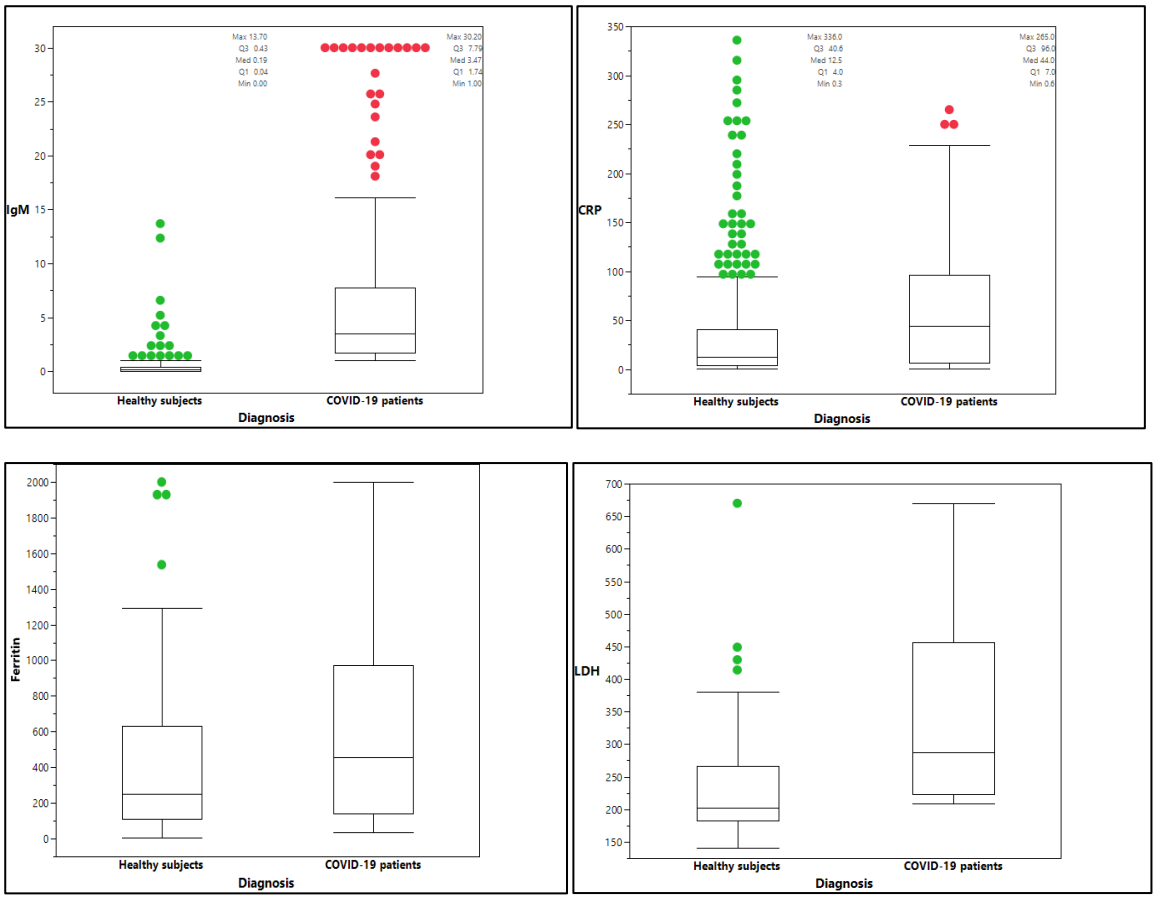


Figure 1: Analysis of SARS-Cov-2 RBD-specific IgM, IgG, ferritin, CRP, D-dimer, and LDH

Differences between COVID-19 patients and healthy controls

The nominal logistic regression model showed that D-dimer (P=0.00274) is the only variant factor between the COVID-19 patients and controls. Other factors; including ferritin, CRP, gender, and age were not found to be predictors for the difference between patients and controls (Table 2).

Role of inflammation in the concentration of D-dimer in patients with COVID-19

D-dimer was considered a dependent variable in the standard least squared analysis model and other factors considered the independent factors. The study did show that inflammation has a no role in increasing or decreasing the D-dimer level in patients with COVID-19. In addition, age, gender, IgG, IgM, and ferritin were not associated with the elevated level of concentration of D-dime in patients with COVID-19 (Table 3 and Figure 2).

Table 2: Model of examination of factors differences to diagnosis COVID-19 disease

Factors	Dependent variable: Diagnosis of COVID-19			
	OR (95% CI)	Log Worth		P-Value
Log(D-Dimer)	347.47 (4.26-28320.03	2.562		0.00274
Log(Ferritin)	112.99 (0.56-22707.88	1.235		0.05818
Log(CRP)	0.15 (0.01-2.96	0.682		0.20795
Gender		0.275		0.53079
Age	0.41 (0.01-11.58	0.221		0.60166

Table 3: Role of inflammation in the concentration of D-dimer in patients with COVID-19

Controlling factors (n=204)	Dependent variable: D-dimer	
	Log Worth	P-Value
Age	0.928	0.11807
Log(IgG)	0.742	0.18116
Log(IgM)	0.536	0.29110
Log(CRP)	0.327	0.47136
Log(Ferritin)	0.046	0.89972
Gender	0.022	0.95046

The standard least squared analysis model was performed for the statistical analysis.

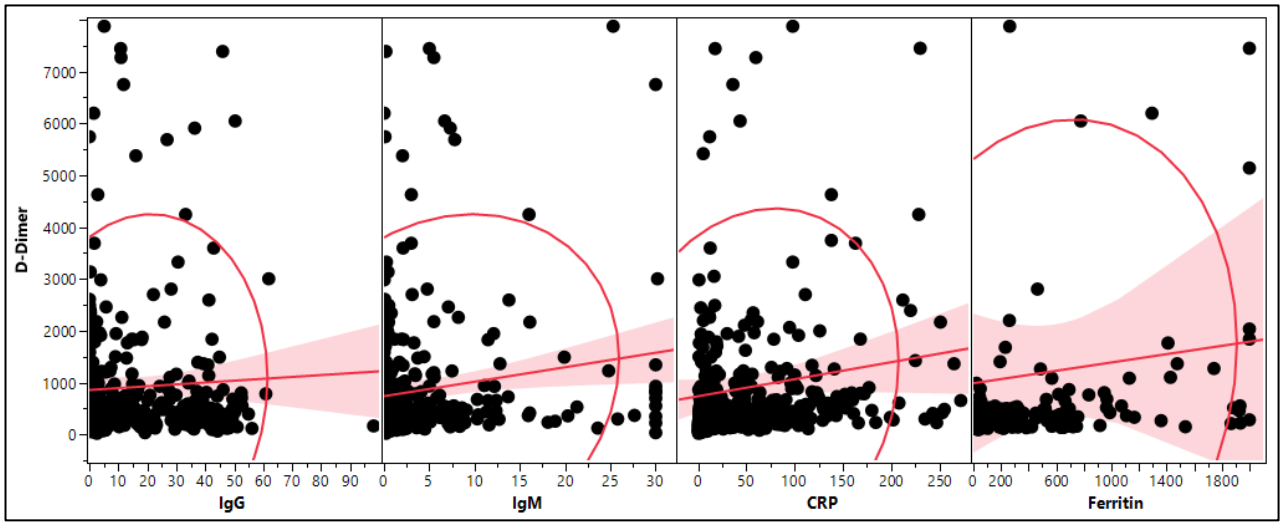


Figure 2: Correlation of D-dimer with IgG, IgM, CRP, and ferritin in patients with COVID-19

DISCUSSION

This study showed that patients with COVID-19 disease have a significantly higher prevalence of abnormal laboratory biomarkers. However, the inflammation was not shown to associate with thrombosis in COVID-19 patients. Thromboses are observed in acute settings weeks after critical illness. This observation recommends that the pro-thrombotic state may last for several weeks or even longer post-hospitalization.[14] The literature has reported different cumulative incidences of thromboembolic events in patients with COVID-19.[6]

The levels of CRP and D-dimer in COVID-19 disease have been examined in other countries as well. A study from Turkey showed that the COVID-19 patients had higher levels of CRP and D-dimer and lower levels of hemoglobin and lymphocyte.[15] A study from China reported that CRP levels are higher in the moderate patients than the COVID-19 patients in the mild group. In addition, the severe group had higher CRP levels compared to the moderate group. Also, the critical group of COVID-19 had higher levels of CRP compared to the severe group. In other words, the higher levels of CRP were positively correlated with the diameter of lung lesion and severe presentation.[16] In comparison with our study, a recent systematic review reported that elevated D-dimer is associated with severity of disease and higher mortality in patients with COVID-19. The early study from China reported that D-dimer levels ≥2.0 µg/mL had a higher incidence of mortality compared to those with D-dimer levels <2.0 µg/mL.[17]

The coronavirus family enters cells by binding angiotensin-converting enzyme 2, seen mainly on the alveolar epithelium and endothelium. Endothelial cell activation could be considered the primary driver for

the increasingly recognized complication of thrombosis in COVID-19 patients. Viral inclusion bodies are present in endothelial cells of different organs, such as the lungs.[18] "Pyroptosis" may trigger the immune dysregulation characteristic of severe COVID-19 infection. Pyroptosis is considered a proinflammatory form of apoptosis observed in macrophages.[19] The rapid viral replication results in a massive release of inflammatory mediators. The elevated level of D-dimer is the most consistent outcome. Despite the levels of D-dimer are increased with many inflammatory processes, the elevated D-dime levels could to some extent reflect intravascular thrombosis.[20] The elevated level of D-dimer (>1000 ng·mL-1) at admission in early studies is contributed to a higher risk of the COVID-19 patients' death in hospitals.[21]

Huertas, Montani [22] has described the early pathogenesis of COVID-19 pneumonia, characterized by widespread endotheliilitis in multiple organ systems. Possibly the presence of viral bodies within endothelial cells is accompanied by apoptosis, inflammatory cell infiltration, and microvascular thrombosis.[18]

The role of hyper-inflammation in the development of thrombosis in COVID-19 infection has been discussed elsewhere in a similar way. The SARS-CoV-2 infection leads to diffuse lung inflammation involving the extensive pulmonary vascular network. The clinical results recommend that an initial pulmonary intravascular coagulopathy is found in COVID-19 pneumonia.[23] The response of extensive cytokines in the pulmonary vasculature leads to intravascular coagulopathy. This response may result in a more systemic inflammatory response in severe COVID-19 cases.[24] D-dimer is considered a degradation product of fibrin. Therefore, its presence in the circulation reflects the fibrin polymers breakdown by plasmin and may contribute to the thrombus burden. But, maybe it does not specify the site of thrombus formation. In this regard, Panigada, Bottino [25] assessed many coagulation parameters in the COVID-19 infection. They used whole blood thromboelastography and determined hypercoagulability features as indicators of thrombosis. The indicators are decreasing time to fibrin formation, a decrease in time to clot formation, and an increase in clot strength.

Limitations of the study

We included as many as possible patients in this study, but we had no access to other precise inflammation biomarkers in the study due to the inherence of the study design. Elevated CRP levels are found in other diseases and comorbidities. Therefore, more concise studies are required by including other inflammation biomarkers; such as Hs. CRP. The high prevalence of obesity could be associated with the increased risk of PE. Also, we did not measure the BMI (Body Mass Index) in this study due to technical challenges.

The main weakness of this study is that we could not determine the time onset of initial symptoms owing to collecting laboratory-based information. In addition, the severity of the disease and patients' outcomes were not included in this study due to the inherence of the retrospective studies. The outcomes of interest were collected in one setting in this region. In addition, the thrombotic episodes were not determined in this study.

CONCLUSIONS

This study showed that patients with COVID-19 have a high prevalence rate of inflammation and abnormal laboratory measurements compared to their healthy subjects. A higher level of D-dimer was found to be the only factor to separate the COVID-19 from their healthy subjects in this study. The study did not confirm the role of inflammation in elevating D-dimer in COVID-19 patients. In addition, other factors; including age, IgG, IgM, and gender were not found to predict the D-dimer level in COVID-19 patients.

Future implications: The inflammatory and thrombosis markers are required to be measured in COVID-19 patients with different severities at various follow-up periods in a prospective study.

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