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Coronavirus Pandemic

Predictive value of D-Dimer and thromboplastin time as coagulation indicators for COVID-19 patients

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Abstract

Introduction: Coronavirus 2019 symptoms include coagulopathy and thromboembolic risk. Using one parameter to diagnose coagulopathy has little predictive value.

Objective: This study will examine if D-dimer and APTT testing can predict COVID-19 severity and aid triage and manage patients.

Methods: 214 COVID-19 patients were enrolled and classified into two categories based on their respiratory manifestations; mild (126 cases) and severe (88 cases). Patient data regarding age, gender, D-Dimer level, and APTT level were collected. When both D-Dimer and APTT levels were abnormal, in this study, the patient was considered to have a coagulation disorder. Indicators of coagulation in the COVID-19 patients were collected and compared between the two groups. Chi-square (χ^2) tests were used to determine the significant differences between coagulation disorders in the two groups.

Results: Our findings showed that patients with coagulopathies were more likely to belong to the severe group. Within the two groups of patients, the rate of coagulation disorders was as follows: mild = 8.8 % within coagulation disorders, 4.8% within the two Groups; severe = 91.2 % within coagulation disorders, 77.8 % within the two Groups. There was a statistically significant relationship between coagulation disorder and severe COVID-19 patients compared to mild patients ($p < 0.05$).

Conclusions: Coagulation disorders are more likely to occur in severe COVID-19 patients. D-Dimer and APTT tests are significant indicators for predicting COVID-19 severity. Our research found an abnormal pattern of coagulation disorders and COVID-19 severity that should be considered in the COVID-19 treatment protocol.

Key words: COVID-19 disease; D-dimer; partial thromboplastin time; coagulation disorder; COVID-19 severity.

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Introduction

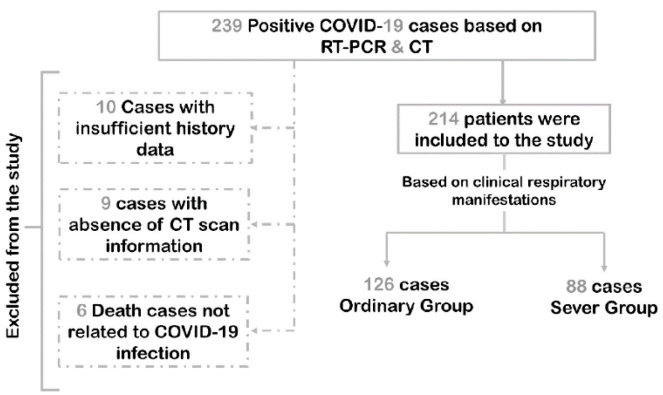
2019 featured the global spread of the novel coronavirus illness, or COVID-19, which began in Wuhan, China and quickly became the fifth pandemic to be officially recorded since 1918 [1]. With so many COVID-19 variations and sequences being reported globally, the pandemic's future is now unclear. To ascertain a patient's coagulation status, several laboratory tests were developed, including activated partial thromboplastin time (APTT), prothrombin time (PT), and D-Dimer. These tests aid in the diagnosis of blood clotting and coagulation disorders in patients. Therefore, coagulopathy has been linked to increased mortality in several studies that have looked at the

clinical features of COVID-19 patients [2-4]. One component of fibrin breakdown that may help blood clots is D-Dimer. There is a correlation between alterations in the D-Dimer level and COVID-19 prognosis and a higher risk of thrombotic factors, especially in the more severe stages [5,6]. D-Dimer levels higher than 1 μg/m have been linked to an elevated risk of in-hospital death and have been shown to be more common in deceased COVID-19 patients [3,7]. According to the studies, COVID-19 patients who are bedridden and have defective coagulation functions should receive special clinical care about their risk of venous thromboembolism [2,8,9].

For instance, Tang *et al.* studied 183 COVID-19 patients in Wuhan, China, and looked at coagulation parameters such as PT, PTT, and D-Dimer levels. They discovered that in the later stages of the COVID-19 infection, patients had considerably higher D-Dimer levels and extended PT and PTT [7]. Nonetheless, COVID-19 individuals have higher D-Dimer levels but lower APTT values [2,4,7]. Venous and artery thromboembolism is common, even in patients with mild COVID-19 [10–12]. These test results, which show elevated thromboembolism rates, imply that coagulation disorders exist at various COVID-19 stages.

Numerous investigations have demonstrated that the symptoms of COVID-19 individuals, whether they are severe or not, are identical. These symptoms include fever, coughing, fatigue, myalgia, arthralgia, anosmia, pharyngitis, and dysgeusia [7,13–16]. As such, determining the COVID-19 severity for patients who are infected poses an even greater challenge to public health and healthcare professionals. Early identification of individuals with severe COVID-19 would therefore improve their prognosis and save medical expenses. Furthermore, it was discovered that the predictive power of a single coagulation measure, such as the D-Dimer level, to predict thrombosis was restricted [17]. Consequently, the APTT test should be used to determine clotting time [18]. D-Dimer and APTT levels, two coagulation markers, were therefore employed in this investigation to determine if the patients had coagulation problems. To the best of our knowledge, no research has been done assessing coagulation abnormalities in COVID-19 patients from the Hashemite Kingdom of Jordan. This project intends to evaluate the role of dynamic variations in D-Dimer and APTT levels for COVID-19 severity prediction, to help manage and treat COVID-19 disease.

Figure 1. Flow chart for inclusion of the study participants.



Methods

In collaboration with Hakeem System for Electronic Health Solutions, 239 patients at the Prince Hamza Hospital in Jordan who had positive results from computed tomography (CT) scans and real-time reverse transcription polymerase chain reaction (RT-PCR) were examined as a case study to verify our methodology (Ethical Approval number: MH/RESEARCHERS/2766). Before taking any anticoagulants, the D-Dimer and APTT laboratory results for COVID-19 patients were documented and gathered. A total of 25 individuals were removed from the research for the following reasons: (1) 10 cases had inadequate history and laboratory results; (2) 9 cases had no information from a CT scan; and (3) 6 instances resulted in death that was unrelated to COVID-19 infection. For 214 patients, patient data such as age, gender, D-Dimer level, and APTT level were gathered.

Based on the patients' clinical respiratory function, two groups (mild or severe groups) were created. The respiratory function deteriorates more and more in the severe stage. Hence, low saturation oxygen levels (below 93%) and/or rapid respiratory rates (more than 30 times/min) were indicative of severe patients [19,20] (Figure 1).

Version 28 of IBM SPSS, the Statistical Package for the Social Sciences, was used to perform statistical analyses after data were assembled in Microsoft Excel. At $p < 0.05$, the threshold for statistical significance was established. To compare categorical variables, the chi-squared test (χ^2) was employed.

Results

The overall number of COVID-19 patients enrolled in the study was 214. The Cases were classified based on their clinical respiratory manifestations into mild (126 cases) and severe (88 cases) groups (Table 1). Male was reporting with more predominant severe cases in comparison to females (n = 62, 49.21%, vs n =

32, 36.36%). Previous studies have found an increase in the percentage of infected males as compared to females [3,4,21,22]. Bacteria and viruses are more likely to infect males than females, because females have stronger innate and adaptive immune system [23,24].

Elderly age groups (46.59%, $p < 0.001$), patients with elevated blood pressure (87.50%, $p < 0.001$), diabetes mellitus (55.26%, $p = 0.002$), chest pain (80.00%, $p < 0.001$), expectoration (86.67%, $p < 0.001$), dyspnea (80.95%, $p < 0.001$), renal disorders (77.78%, $p < 0.001$), cardiovascular disorders (85.71%, $p < 0.001$), hepatic disorders (88.24%, $p < 0.001$), and coagulation Disorders (91.18%, $p < 0.001$).

Discussions

D-Dimer levels alone should not be used to decide if anticoagulation is necessary, according to the study's conclusions. According to the study, there was little predictive significance for a single coagulation measure, D-Dimer, in predicting thrombosis [17]. Thus, in this investigation, APTT and D-Dimer levels were utilized as markers of coagulation abnormalities.

The investigations conclude that coagulation abnormalities in COVID-19 patients have been linked to venous thrombosis, pulmonary embolisms, and mortality rates. Furthermore, coagulopathy is associated with worse outcomes in COVID-19 patients, particularly in the elderly [25–27]. Clot development may be influenced by endothelial cell activation or malfunction. Evidence has been found that the presence of the virus is one of the factors that cause inflammation and malfunction. Therefore, both endothelial cell stimulation and malfunction may be responsible for the hypercoagulation condition observed in COVID-19 patients. These alterations may potentially mediate leukocyte infiltration, produce endothelial inflammation, and encourage procoagulant conditions [28].

Our results indicate a substantial correlation between coagulation abnormalities and the severity of COVID-19 disease. Our results are consistent with other studies that have linked coagulation abnormalities

Table 1. Demographic, outcomes, and clinical manifestations among ordinary and severe COVID-19 cases.

Variables	COVID-19 cases Frequency (N[1], %)		*p* value[2]
	Ordinary cases	Severe cases	
Gender			
Male	64 (50.79)	62 (49.21)	0.070
Female	56 (63.64)	32 (36.36)	
Age Group[3]			
21- 41 years	49 (38.89)	5 (5.68)	< 0.001*
42- 53 years	43 (34.13)	10 (11.36)	
54- 63 years	24 (19.05)	32 (36.36)	
64- 84 years	10 (7.94)	41 (46.59)	
Elevated D-Dimer levels (> 0.50 µg/mL)	112 (57.14)	84 (42.86)	0.728
Prolonged APTT[4] results (> 35 seconds)	62 (91.18)	6 (8.82)	< 0.001*
Outcomes			
Survive	121 (59.31)	83 (40.69)	0.393
Death	5 (50.00)	5 (50.00)	
Clinical Manifestations			
Nonspecific (general)			
Fever	106 (58.24)	76 (41.76)	0.402
Myalgia	22 (50.00)	22 (50.00)	0.121
Headache	34 (58.62)	24 (41.38)	0.542
Chronic disorders			
Elevated blood pressure	4 (12.50)	28 (87.50)	< 0.001*
Diabetes Mallitus	34 (44.74)	42 (55.26)	0.002*
Respiratory disorders			
Cough	100 (55.56)	80 (44.44)	0.017*
Chest pain	6 (20.00)	24 (80.00)	< 0.001*
Pharyngitis	4 (33.33)	8 (66.67)	0.062
Expectoration	4 (13.33)	26 (86.67)	< 0.001*
Dyspnea	8 (19.05)	34 (80.95)	< 0.001*
Renal disorders	8 (22.22)	28 (77.78)	< 0.001*
Cardiovascular disorders	4 (14.29)	24 (85.71)	< 0.001*
Hepatic disorders	4 (11.76)	30 (88.24)	< 0.001*
Abdominal pain/diarrhea	6 (50.00)	6 (50.00)	0.362
Coagulation Disorders	6 (8.82)	62 (91.18)	< 0.001*
Total	**126**	**88**	**-**

[1]N: Number; [2]*p* value was calculated based on Chi-squared test; [3]Age groups were classified based on Quartiles; [4]APTT: Activated Partial Thromboplastin Clotting Time; *Significant correlation.

to the severity of COVID-19 infection [3,29,30]. These investigations' findings indicate that severe COVID-19 patients have considerably higher levels of coagulopathy. For instance, in a multicenter prospective cohort study, D-Dimer and fibrinogen levels were high in almost 95% of patients, especially in those with severe COVID-19 symptoms.

In line with our findings, several studies showed that D-Dimer and APTT tests were significantly associated with severe and COVID-19 patients. In these studies, D-Dimer and APTT tests were found to be good indicators for predicting patients who are likely to progress to severe cases, which is similar to our results [31-35].

Moreover, our results align with the research carried out by Long *et al.,* wherein D-dimer and APTT showed a strong prediction power for the prognosis of the disease [36]. D-Dimer and APTT indicators were linked to patients with significant COVID-19 infection in our investigation. This may be explained by the fact that procoagulant pathways at various levels, including induction and activation of coagulation by proinflammatory cytokines of Tumor Necrosis Factor (TNF), Interleukin-1 (IL-1), IL-6, and IL-12, as well as hemodynamic changes that raise the risk of clotting and thrombosis, cause plaque rupture when systemic pro-inflammatory cytokines are released through local inflammation [31].

Therefore, when treating COVID-19 patients, clinicians should be aware of their coagulation indicator levels. Therefore, in order to give an early diagnosis and the best possible therapy, it is critical to pay close attention to these clinical signs and symptoms in order to assess the severity of COVID-19 disease. It is imperative for doctors and healthcare providers to take into account the coagulation indicator levels of individuals diagnosed with COVID-19. Therefore, in order to provide the best treatment and an early diagnosis for COVID-19 disease, it is imperative to include these clinical findings when establishing the severity of the condition.

Conclusions

It is probable that patients with a severe stage of COVID-19 had coagulopathy. Compared to patients with moderate instances, those with severe COVID-19 had considerably higher D-Dimer and APTT levels. In COVID-19 patients with severe infection, the rate of coagulopathy was 91.2%. Therefore, it is important to monitor coagulation indicators such as the D-Dimer and APTT tests to identify coagulopathy and thrombotic problems as soon as feasible. To lower the risk of coagulation abnormalities and provide the best care possible for individuals infected with COVID-19, preventive treatment is necessary.

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Authors' Contributions

M.A and T.A.A formulated the conceptualization and methodology. S.A.A and H.H performed the statistical analysis. M.A, O.K, A.A.O and A.M performed the data collection. M.A, S.M.F.A. and S.R.E. performed writing proper draft preparation. M.A and S.R.E and R.A.G performed writing, reviewing, and editing for the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Ethics Approval

Ethical approval was obtained from the Research Ethics Board of Prince Hamza Hospital (Ethical Approval number: MH/RESEARCHERS/2766).

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