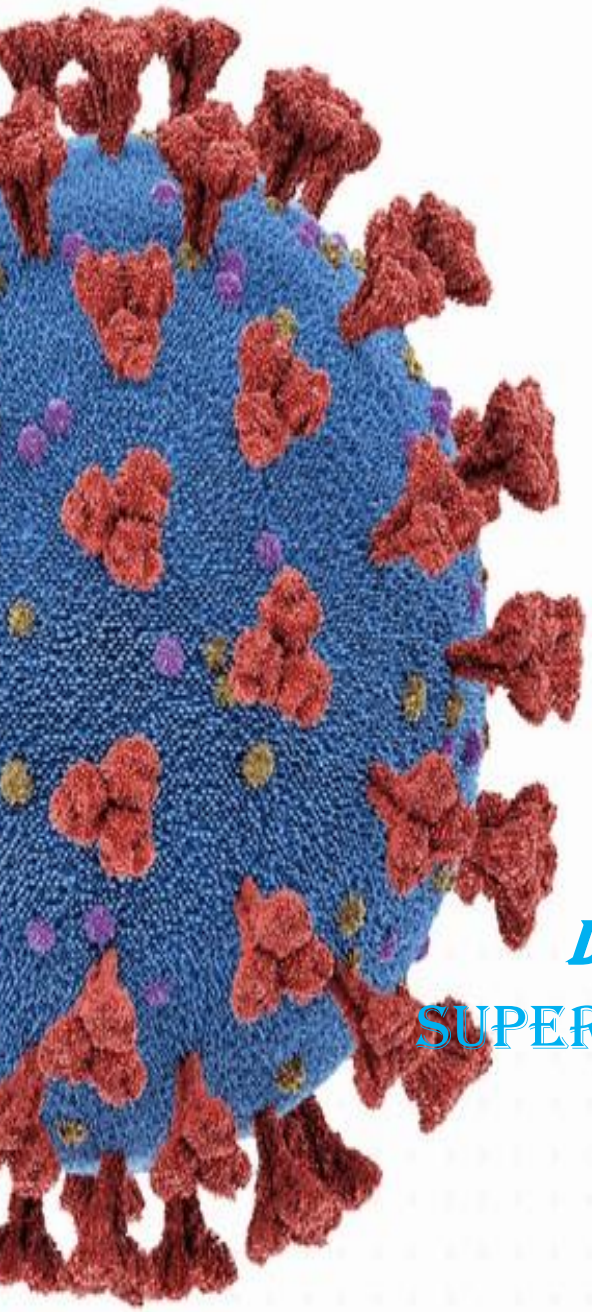
D-DIMER IN COVID-19



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INTRODUCTION

Coronavirus disease is now a global pandemic caused by rapid transmission between humans. It can cause a variety of respiratory, cardiovascular, and neurological diseases, ranging from mild to fatal. We wanted to see if high D-dimer levels are a predictor of COVID-19 progression to see if we could reduce mortality.

PURPOSE

The main goal of this research project is to investigate the prevalence of D-dimer and its connection to the morbidity and mortality of COVID-19 infection.

MATERIALS AND METHODS

Our large documented study looked at D-dimer levels in patients admitted to Baqubah General teaching Hospital department of alshifa no.8 during the COVID-19 pandemic. A rough sample of four patients was taken, based on the top D-dimer level (< 1, 1-9,9, 10-20 and > 20 ug/mL FEU). We examined and compared their populations with risk of death, including their ages, sex, hypertension, diabetes, troponin and Creatinine levels. We then assessed the therapy and its relationship to better results.

RESULTS

A total of 80 patients out of 1,752 were included in the study. Patients who tested negative for COVID-19 infection were removed from the study, leaving 72 for further study. At the time of the study's conclusion, 52% of patients with D-dimer levels greater than 20 had passed away, and none had been discharged from the hospital. D-dimer (p 0.001), age (p = 0.021), troponin (p 0.001), creatinine (p 0.001), consolidation on chest x-ray (p = 0.003), and intubation (p 0.001) were all significant in univariate analysis for death versus discharge. Only D-dimer and intubation show a significant trend in multivariable analysis (p = 0.098 and 0.095, respectively). In a multivariable analysis comparing hospital discharge versus death and prolonged hospitalization (> 14 days), intubation (p = 0.04) was found to be statistically significant, while age, D-dimer, and troponin (p = 0.06, 0.07, and 0.08, respectively) approached significance. The significance of consolidation was not significant (p = 0.80).

CONCLUSION

COVID-19 infects the vascular endothelial cells of multiple organs, causing endothelial inflammation, vascular stasis, and hypercoagulability, with the worst outcomes for those whose vascular system is compromised. Use of D-dimer levels for this purpose will recognize those who have the greatest need for assistance.

A pandemic flu virus that spreads from animal to human creates a serious threat. COVID-19 had cost the lives of 40,189 Americans by the time this article was

published, out of the 751,775 who had tested positive for the virus (death rate of 5.3 %). Owing to a lack of research, the mortality rate is likely to be exaggerated. According to the Centers for Disease Control and Prevention (CDC), the influenza virus infected 39-56 million people in the United States in 2019-2020 seasons, resulting in 24,000 to 62,000 deaths (death rate of 0.1 %). Though Influenza and Coronavirus viruses mainly affect the respiratory function, there is a difference in the mortality rates the virus's ability to infect vascular endothelial cells, which are found in all organs, could explain the higher death rate in COVID-19 patients.

SARS-CoV-2 is an RNA virus with a crown-like appearance due to envelope glycoproteins that bind to angiotensin II receptors on vascular endothelial cells, injuring them. Varga discovered COVID-19 endothelial cell infection along with endothelial inflammation. Vasoconstriction is caused by endothelial cell dysfunction, which may lead to the disease's multiorgan ischemia.

This may explain why hypertension, diabetes, smoking, obesity, and heart disease, all of which have pre-existing endothelial cell dysfunction, have been associated with poorer results.

Intracellular vascular endothelial cell viral RNA activates Toll-like receptors and activates the body's innate immune response, resulting in the release of interferon and the production of inflammatory chemokines and cytokines like Interleukin-6. Macrophages, neutrophils, and lymphocytes are recruited, which contribute to further damage to the vascular endothelial cell. The coagulation cascade is activated by vascular endothelial cell damage, and platelets plug the initial endothelial defect. The intrinsic and extrinsic coagulation pathways also result in the formation of thrombin and, eventually, fibrin. Increased risk of pulmonary embolism, myocardial infarction, stroke, extremity ischemia, and deep vein thrombosis is thought to be caused by COVID-19 activation of the coagulation cascade. Since D-dimer antigen is linked to fibrin degradation,

levels should be higher in those that have more severe endothelial injury. The aim of our research was to see whether higher D-dimer levels were linked to a higher risk of death.

METHODS

From January 11, 2021 to April 11, 2021, our retrospective IRB-approved research looked at D-dimer levels in patients in Baqubah General teaching Hospital department of alshifa (no.8) during the peak of the COVID-19 pandemic. During this time, 4,484 D-dimer results were reported from the electronic health record. Each of the 1,752 patients had the greatest D-dimer level. The STAGO immune-turbid metric assay was used to determine the D-dimer. With a cutoff of 0.5 ug/ml FEU, the negative predictive value is 95-100 %. We took a random sample of 80 D-dimer results and looked at the patients' demographics, such as age, gender, hypertension, diabetes, troponin, and creatinine levels, and compared them to their risk of mortality. Based on the maximum D-dimer level (1, 1-9.9, 10-20, and > 20 ug/mL FEU), we divided patients into four groups. Following that, we looked at the effects of full-dose heparin, subcutaneous heparin, enoxaparin, and hydroxychloroquine on outcomes.

The correlation study was carried out using logistic regression models (for binary data). For full-dose heparin and enoxaparin, Fisher's exact test was used to compare death versus discharge. Statistical significance was determined by P values less than 0.05. R was used to conduct statistical analysis (version 3.6.2).

RESULTS

DEMOGRAPHICS

During their hospital stay, 1,752 patients had their D-dimer levels measured. Optimum conditions ranged from 0 to more than 20 ug/mL FEU, with a peak of 2.94 ug/mL FEU. A total of 80 patients were randomly chosen. Patients who tested negative for COVID-19 infection were omitted from the study, leaving 72 patients for further examination. The average age was 68 years old (range 26-93 years), with men accounting for 53% of the population. On chest x - ray, the number of patients (96%) had consolidation. 54 % had a history of diabetes, and 76% had high blood pressure. D-dimer levels ranged about 11.1 (0.3-20) ug/mL FEU on scale. The maximum troponin T level was 174 ng/L on average (6-2,642). The median creatinine level was 2.6 mg/dl on average (range 0.6-10.7). 33 % of those tested died from the infection, and 24 % were hospitalized for an average of 21 days (range 17-26 days). 43% were released from the hospital. 43% of patients were intubated (Table 1).

Higher levels of D-dimer were linked to poorer outcomes. 52% of patients with D-dimer levels higher than 20 ug/mL FEU died, and none were discharged at the end of that period. Patients with the highest D-dimer levels were intubated 74% of the time, while those with the lowest D-dimer levels were intubated 0% of the time. Patients with the lowest D-dimer levels were discharged from the hospital in 92% of cases (Table 1).

D-dimer (p 0.001), age (p = 0.021), troponin (p 0.001), creatinine (p 0.001), consolidation (p = 0.003), and intubation (p 0.001) were all important in univariate study for death versus discharge. Only D-dimer and intubation were barely notable in multivariable analysis (p = 0.098 and 0.095, respectively). In a multivariable study comparing hospital discharge versus mortality or

continued hospitalization, intubation was found to be important (p = 0.04), and age, D-dimer, and troponin were found to be trending towards significance (p = 0.06, 0.07, and 0.08, respectively). Consolidation did not have a major effect (p = 0.80). (Table 2).

IMAGING EXAMS

Despite the correlation of high D-dimer and thrombosis, deep-venous thrombosis (DVT), pulmonary embolism (PE), ischemia of the strokes or limbs in imaging tests or physical exams was not observed in the majority of patients (92 %) (Table 3).

TREATMENT

Anticoagulation dose heparin was given to 25% of patients, while subcutaneous heparin was given to the remaining 17%. Enoxaparin was used to treat the bulk of the patients (50 %). hydroxychloroquine was given to 72% of the patients in the study (Table 1). 42 % of those who died were on full dose heparin, and 83% were given hydroxychloroquine (Table 4). The death/discharge result was significantly correlated with anticoagulant dose heparin (p 0.001) in a univariate analysis, which is possibly because sicker patients received heparin. The drug hydroxychloroquine had no effect on the outcome of death versus discharge (p = 0.133).

DISCUSSION

Our findings support the theory that COVID19-related morbidity and mortality are at least in part due to microvascular changes, which facilitate clotting with higher D-dimer levels in patients who died from the disease compared to those who were able to return home. D-dimer antigen is linked to fibrin degradation. In a study of 43 adult COVID-19 patients, we discovered that IL-6 and D-dimer levels were the best predictors of disease severity. In a study of 377 patients with COVID-19, we discovered that age and D-dimer levels were the best predictors of serious disease. Acute illness patients with elevated D-dimer levels had a 3.5-fold increased risk of venous thromboembolism, according to our study. COVID-19 patients had substantially higher D-dimer levels than those with bacterial pneumonia.

We discovered during our study that troponin levels were elevated with extreme SARS-CoV-2 infection, and that baseline and follow-up levels could predict those with cardiac injury and a poor prognosis from COVID-19. Troponin elevation does not distinguish between myocardial injury caused by myocarditis and ischemic injury caused by microvascular injury and cytokine storm in COVID-19 patients. Troponin levels above the 99th percentile were found in 20% of 416 patients in the hospital. They were more advanced in age, with more co-morbidities, lung consolidation, and cardiac problems. Myocardial injury was associated with a higher mortality rate (51 % versus 5 %) . Troponin elevation was found in 46 % of those who died and only 1% of those who survived in another study. In our sample, 30/53 (57%) of patients with troponin levels less than 100 were discharged from the hospital, while 1/19 (5%) of patients with troponin levels greater than 100 were discharged. In a multivariable study comparing those who were released from the hospital to those who died or stayed hospitalized for more than 14 days, the troponin level trended towards significance ($p = 0.08$).

Me and colleagues examined 701 COVID-19 patients in the hospital, with 113 of them passing in the ward. Serum creatinine levels were found to be higher 14.4% of the sample. In-hospital mortality was found to be substantially higher in patients with kidney disease. We on the other hand, found that 10.8% of COVID-19 patients had a moderate rise in blood urea nitrogen or creatinine,

and that acute kidney damage was rare in COVID-19. In our sample, 6/30 (20%) of those who died had creatinine levels less than or equal to 1 mg/dl, while 18/42 (43%) had levels greater than 1 mg/dl, but the difference was not significant ($p = 0.39$).

Infection and hypercoagulability have been linked in the past. After infection we found a 20-fold increase in venous thrombosis, and a 141-fold increase when combined with immobilization. examined the risks of DVT and PE following urinary and respiratory infections and discovered that the risk was greatest in the first two weeks, implying a causal association . According to our research, stroke and myocardial infarction are more common after a systemic respiratory infection, with the highest rates occurring in the first three days. Inflammation raises plasminogen activator inhibitor and lowers fibrinolysis, according to colleagues. Interleukin 6 also boosts platelet count and moves the balance against clot formation. The poor results in patients with COVID-19 infection are not mainly attributable to thrombosis. It doesn't explain why thrombosis imaging trials are often normal and why anticoagulation patients frequently die. SARS-CoV-2 infects the host via the angiotensin-converting enzyme 2 receptor, which is expressed on endothelial cells of the lung, heart, kidney, and intestine. Vasoconstriction and, eventually, organ ischemia are caused by endothelial dysfunction. COVID-19 causes endotheliitis, which can explain the microcirculation problems. Maybe the thrombosis is caused by vascular stasis caused by hypertrophied and inflamed vascular endothelial cells, as well as vasoconstriction, and anticoagulation alone is insufficient to reverse the ischemia.

Table 1: Demographics and outcomes based on highest D-dimer levels of a random sample of inpatients

D dimer levels (ug/mL FEU)	**< 1**	**1 to 9.9**	**10-19.9**	**> 20**	**Total**
# of patients	13	17	19	23	72
Average age	62 (26-90)	64 (31-92)	71 (43-92)	72 (39-93)	68 (26-93)
Male gender	6/13 (46%)	10/17(59%)	10/19 (53%)	12/23 (52%)	38/72 (53%)
Consolidation	11/13 (85%)	16/17 (94%)	19/19 (100%)	23/23 (100%)	69/72 (96%)
Diabetes	4/13 (31%)	4/17 (24%)	14/19 (74%)	17/23 (74%)	39/72 (54%)
Hypertension	9/13 (69%)	11/17 (65%)	16/19 (84%)	19/23 (83%)	55/72 (76%)
Average D-dimer (ug/mL FEU)	0.59 (0.3-0.98)	2.5 (1.12-7.72)	15.3 (10.0-19.9)	20	11.1 (0.3-20)
Troponin (ng/L)	60 (6-544)	82 (6-284)	229 (7-2642)	261 (27-2223)	174 (6-2642)
Creatinine max (mg/dl)	1.3 (1-3)	2.4 (0.7-9.9)	2.8 (0.6-10.7)	3.4 (0.6-7.3)	2.6 (0.6-10.7)
Death	1/13 (8%)	6/17 (35%)	5/19 (26%)	12/23 (52%)	24/72 (33%)
Ongoing hospitalization	0/13 (0%)	1/17 (6%)	5/19 (26%)	11/23 (48%)	17/72 (24%)
Discharge	12/13 (92%)	10/17 (59%)	9/19 (47%)	0/23 (0%)	31/72 (43%)
Intubation	0/13 (0%)	5/17 (29%)	9/19 (47%)	17/23 (74%)	31/72 (43%)
Heparin full dose	0/13 (0%)	3/17 (18%)	4/19 (21%)	11/23 (48%)	18/72 (25%)
SQ heparin	1/13 (8%)	3/17 (18%)	4/19 (21%)	4/23 (17%)	12/72 (17%)
Enoxaparin	12/13 (92%)	9/17 (53%)	9/19 (47%)	6/23 (26%)	36/72 (50%)
Hydroxychloroquine	6/13 (46%)	13/17 (76%)	15/19 (79%)	18/23 (78%)	52/72 (72%)

Table 2: The multivariable analysis combining death and prolonged hospitalization and comparing to discharge with d-dimer, age, hypertension, log (mi) (troponin), log (aki) (creatinine), consolidation and intubation as covariates.

	OR	95% CI	95% CI	p-value
D dimer	0.88455736	0.7739303826	1.0109975	0.07193757
Age	0.89923713	0.8043705820	1.0052921	0.06187754
Hypertension	3.19610297	0.1925400367	53.0542861	0.41758332
Troponin	0.27207463	0.0606603087	1.2203136	0.08914268
Creatinine	0.49907251	0.1003777696	2.4813599	0.39569142
Consolidation	0.81426629	0.1603543989	4.1347765	0.80426104
Intubation	0.02389654	0.0006668862	0.8562853	0.04086150

Table 3: Variables related to outcomes in patients who tested positive with COVID-19.

	Death	Ongoing hospitalization	Hospital discharge
# of patients	24	17	31
Average age	73	72	62
Gender Male	13/24 (54%)	10/17 (59%)	15/31 (48%)
Average D dimer (ug/mL FEU)	13.8	17.4	5.6
Diabetes	13/24 (54%)	13/17 (76%)	13/31 (42%)
Hypertension	21/24 (88%)	14/17 (82%)	20/31 (65%)
Average Troponin (ng/L)	179	431	29
Average creatinine (mg/dl)	3.9	3.4	1.2
Consolidation	20/20 (100%)	17/17 (100%)	28/31 (90%)
Intubated	14/24 (58%)	15/17 (88%)	2/31 (6%)
Full dose heparin	10/24 (42%)	8/17 (47%)	0/31 (0%)
Subcutaneous heparin	2/24 (8%)	5/17 (29%)	5/31 (16%)
Enoxaparin	9/24 (38%)	4/17 (24%)	23/31 (74%)
Hydroxychloroquine	20/24 (83%)	13/17 (76%)	19/31 (61%)

Table 4: Incidence of thrombosis on imaging studies and physical exam.

D dimer levels(ug/mL FEU)	**< 1**	**1 to 9.9**	**10 - 19.9**	**> 20**	**Total**
DVT	0/13 (0%)	1/17 (6%)	1/19 (5%)	0/23 (0%)	2/72 (3%)
PE	1/13 (8%)	0/17 (0%)	0 (0%)	0/23 (0%)	1/72 (1%)
Stroke	0/13 (0%)	0/17 (0%)	1/19 (5%)	0/23 (0%)	1/72 (1%)
Extremity ischemia	0/13 (0%)	1/17 (6%)	0 (0%)	1/23 (4%)	2/72 (3%)
TOTAL	1/13 (8%)	2/17 (12%)	2/19 (11%)	1/23 (4%)	6/72 (8%)

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