D-dimer in COVID-19 Patients

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Abstract

Purpose: Evaluate D-dimer levels and their relationship to morbidity and mortality of COVID-19 infection.

Materials and Methods: Our retrospective IRB approved study reviewed D-dimer levels in patients hospitalized at Columbia University Irving Medical Center during the height of the COVID-19 pandemic. We took a random sample of patients from four categories based on the patient’s highest D-dimer level (< 1, 1-9.9, 10-20 and > 20 ug/mL FEU). We reviewed their demographics including age, gender, hypertension, diabetes, troponin and creatinine levels and correlated them with risk of death. We then evaluated treatment and its relationship to improved outcomes.

Results: 80 patients of 1,752 were included. Patients who tested negative for COVID-19 infection were excluded leaving 72 for analysis. 52% of patients with D-dimer greater than 20 died and none was discharged from the hospital at the time of study completion. Univariate analysis for death versus discharge was significant for 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). On multivariable analysis only D-dimer and intubation trend towards significance (p = 0.098 and 0.095 respectively). Multivariable analysis comparing hospital discharge versus death and prolonged hospitalization (≥ 14 days) was significant for intubation (p = 0.04) and approached significance for age, D-dimer and troponin (p = 0.06, 0.07 and 0.08 respectively). Consolidation was not significant (p = 0.80).

Conclusion: COVID-19 infects the vascular endothelial cells of multiple organs leading to endothelial inflammation, vascular stasis and a hypercoagulable state with poorest outcomes for those whose vascular system is compromised. D-dimer levels help identify those with the highest risk of mortality.

Pandemic flu with animal to human transmission is a significant threat [1]. By the time this article was written, 40,189 American had already succumbed to COVID-19 out of the 751,775 who have tested positive for the infection (death rate of 5.3%). The death rate is likely inflated due to lack of available testing. The Centers for Disease Control and Prevention (CDC) report that for the 2019-2020 seasons in the United States, Influenza virus infected 39-56 million with 24,000 to 62,000 deaths (death rate of 0.1%). Both Coronavirus and Influenza viruses affect the lung parenchyma leading to respiratory compromise yet there is a discrepancy in the death rates. Perhaps the increased death rate in patients with COVID-19 is related to the virus’s ability to infect vascular endothelial cells, which are present in all organs.

SARS-CoV-2 is an RNA virus, which has a crown-like appearance due to envelope glycoproteins that bind to angiotensin-converting enzyme 2 receptors on vascular endothelial cells leading to their injury [2]. Varga identified direct COVID-19 endothelial cell infection with associated endothelial inflammation. Endothelial cell dysfunction causes vascular constriction and could contribute to the multiorgan ischemia associated with the disease. This would explain why worse outcomes have been associated with hypertension, diabetes, smoking, obesity, and heart disease, which have pre-existing

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Intracellular vascular endothelial cell viral RNA activates Toll-like receptors and stimulates the body’s innate immune response with interferon production and creation of inflammatory chemokines and cytokines including Interleukin-6. There is recruitment of macrophages, neutrophils, and lymphocytes leading to further vascular endothelial cell damage [1]. Vascular endothelial cell injury activates the coagulation cascade and platelets plug the initial endothelial defect. The intrinsic and extrinsic coagulation pathways induce thrombin and ultimately fibrin deposition [4]. COVID-19 activation of the coagulation cascade is believed to cause increased incidence of pulmonary embolism, myocardial infarction, stroke, extremity ischemia, and deep vein thrombosis [5]. D-dimer antigen is related to the degradation of fibrin [4] and so levels should be higher in those with more extensive endothelial injury. The purpose of our study was to evaluate if elevated D-dimer levels were associated with increased mortality.

**Methods**

Our retrospective IRB approved study reviewed the D-dimer levels in patients at Columbia University Irving Medical Center during the height of the COVID-19 pandemic from March 11, 2020 to April 11, 2020. The electronic medical record was mined and 4,484 D-dimer results were recorded during this time period. The highest D-dimer level was noted for each of 1,752 patients. The D-dimer was obtained using the STAGO immune-turbid metric assay. The negative predictive value is equal to 95-100% with cut off 0.5 ug/ml FEU. We obtained a random sample of 80 D-dimer results and reviewed the patient’s demographics including age, gender, hypertension, diabetes, troponin and creatinine levels and correlated them with patient risk of death. We separated patients into four categories based on the highest D-dimer level (< 1, 1-9.9, 10-20 and > 20 ug/mL FEU). Next, we looked at treatment with full dose heparin, subcutaneous heparin, enoxaparin and hydroxychloroquine and its relationship to outcomes.

Logistic regression models (for binary data) were used for association analysis. Fisher’s exact test was used to compare outcome of death versus discharge for full dose heparin and enoxaparin. P values < 0.05 were considered statistically significant. Statistical analysis was performed using R (version 3.6.2).

**Results**

**Demographics**

Demographics

| 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%) |
ized on average 21 days (range 17-26 days). Forty-three percent were discharged from the hospital. Forty-three percent of patients were intubated (Table 1).

Higher D-dimer levels were associated with worse outcomes. Fifty-two percent of patients with D-dimer greater than 20 ug/mL FEU died and none was discharged from the hospital at the time of study completion. Among those patients with the highest D-dimer levels 74% were intubated compared to 0% with the lowest D-dimer levels. Ninety-two percent of patients with the lowest D-dimer levels were discharged from the hospital (Table 1).

Univariate analysis for death versus discharge was significant for 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). However, on multivariable analysis only D-dimer and intubation were borderline significant (p = 0.098 and 0.095 respectively). Multivariable analysis comparing hospital discharge versus death or ongoing hospitalization was significant for intubation (p = 0.04) and trended towards significance for age, D-dimer, and troponin (p = 0.06, 0.07 and 0.08 respectively). Consolidation was not significant (p = 0.80) (Table 2).

**Imaging exams**

Despite the expected association of elevated D-dimer and thrombosis, the majority of patients (92%) were not found to have deep vein thrombosis (DVT), pulmonary embolism (PE),

### 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          | 0.884 | 0.77393-0.9826    | 1.0109-0.9977   | 0.07193757 |
| Age              | 0.899 | 0.80437-0.9820    | 1.00529-0.9921  | 0.06187754 |
| Hypertension     | 3.196 | 0.19254-0.0367    | 53.0542861      | 0.41753332 |
| Troponin         | 0.272 | 0.06066-0.3087    | 1.2203136       | 0.08914268 |
| Creatinine       | 0.499 | 0.10037-0.7769    | 2.4813599       | 0.39569142 |
| Consolidation    | 0.814 | 0.16035-0.3989    | 4.1347765       | 0.80426104 |
| Intubation       | 0.024 | 0.00066-0.8682    | 0.8562853       | 0.04086150 |

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

|                  | # of patients | Average age | Gender Male | Average D dimer (ug/mL FEU) | Average Troponin (ng/L) | Average creatinine (mg/dl) | Consolidation | Intubated | Full dose heparin | Subcutaneous heparin | Enoxaparin | Hydroxychloroquine |
|------------------|---------------|-------------|-------------|------------------------------|------------------------|---------------------------|----------------|-----------|-------------------|--------------------|------------|-------------------|
| Death            | 24            | 73          | 13/24 (54%) | 13.8                         | 179                    | 3.9                       | 20/20 (100%)  | 14/24 (58%) | 10/24 (42%)       | 2/24 (8%)          | 9/24 (38%) | 20/24 (83%)       |
| Ongoing hospitalization | 17            | 72          | 10/17 (59%) | 17.4                         | 431                    | 3.4                       | 17/17 (100%)  | 15/17 (88%) | 8/17 (47%)        | 5/17 (29%)         | 4/17 (24%) | 13/17 (76%)       |
| Hospital discharge | 31            | 62          | 15/31 (48%) | 5.6                          | 29                     | 1.2                       | 28/31 (90%)   | 2/31 (6%)  | 0/31 (0%)         | 5/31 (16%)         | 23/31 (74%) | 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%) |
stroke or extremity ischemia on imaging studies or physical exam (Table 3).

**Treatment**

Twenty-five percent of patients were treated with anticoagulation dose heparin and 17% were treated with subcutaneous heparin. The majority of the patients were treated with enoxaparin (50%). Seventy-two percent of the patients studied received hydroxychloroquine (Table 1). Of those who died, 42% were on full dose heparin and 83% received hydroxychloroquine (Table 4). Univariate comparison showed that the death/discharge outcome was significantly associated with anticoagulant dose heparin (p < 0.001) which is likely because sicker patients received heparin. The outcome of death versus discharge was not significantly associated with hydroxychloroquine (p = 0.133).

**Discussion**

Our results are consistent with findings of other researchers and support the idea that the morbidity and mortality associated with COVID19 is at least in part related to microvascular changes [6-10], which promote 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 related to the degradation of fibrin [4]. Gao et al. studied 43 adult patients with COVID-19 and found that IL-6 and D-dimer levels were the best predictors of disease severity [11]. Zhou and collaborators reviewed 377 patients diagnosed with COVID-19, and found that age and D-dimer levels were best predictors of severe disease [12]. Cohen, et al. noted that acutely ill patients with elevated D-dimer levels had a 3.5-fold increased risk of venous thromboembolism [13]. Yu, et al. found significantly higher D-dimer levels in COVID-19 patients than in those with bacterial pneumonia [4].

Lippi, et al. found that troponin values were elevated with severe SARS-CoV-2 infection and that initial measurement and follow up levels might predict those with cardiac injury and a worse prognosis from COVID-19 [14]. Troponin elevation does not differentiate the causes of myocardial injury in COVID-19 patients, which can include myocarditis, and ischemic injury caused by microvascular injury and cytokine storm. Twenty percent of 416 patients in Wuhan China had troponin levels above the 99th percentile. They were older with more co-morbidities, more lung consolidation, and more cardiac complications. The mortality rate was higher in those with myocardial injury (51% versus 5%) [15]. In another study from Wuhan, troponin elevation was seen in 46% of those who died and only 1% of those who survived [15]. In our study, 30/53 (57%) patients with troponin levels less than 100 were discharged from the hospital compared to 1/19 (5%) with troponin level greater than 100. The troponin level trended towards significance (p = 0.08) in multivariable analysis comparing those who were discharged from the hospital to those who died or remained hospitalized ≥ 14 days.

Cheng and collaborators, studied 701 patients with COVID-19 in China of which 113 died in the hospital. The prevalence of elevated serum creatinine was 14.4%. Patients with kidney disease had a significantly higher risk for in-hospital death [16]. In contrast, Wang, et al., looked at 116 COVID-19 patients, 10.8% had a mild increase in blood urea nitrogen or creatinine and they concluded that acute kidney injury was uncommon in COVID-19 [17]. In our study 6/30 (20%) died with creatinine less than or equal to 1 mg/dl and 18/42 (43%) when greater than 1 mg/dl, however, it did not reach statistical significance (p = 0.39).

There is a known association between infection and hypercoagulability. Grimnes, et al. reported a 20-fold increase in venous thrombosis after infection and 141-fold increase if combined with immobilization [18]. Smeth, et al. studied the risks of DVT and PE after urinary and respiratory infections and found the risk to be highest in the first 2 weeks supporting a causal relationship [19]. Lindahl’s study found that stroke and myocardial infarction were increased after systemic respiratory infection and highest during the first three days [20]. Esmon and collaborators describe how inflammation elevates plasminogen activator inhibitor and decreases fibrinolysis. Furthermore, Interleukin 6 increases platelet count and shifts balance to clot formation [21]. Thrombosis alone is not enough to account for the poor outcomes in patients with COVID-19 infection. It does not explain why imaging studies for thrombosis are more often normal and why patients on anticoagulation frequently die. Varga, et al., describes how SARS-CoV-2 infects the host using the angiotensin-converting enzyme 2 receptor expressed on endothelial cells of the lung, heart, kidney, and intestine. Endothelial dysfunction leads to vasoconstriction and ultimately organ ischemia. COVID-19 causes an endothelliitis, which could explain the impaired microcirculation [3]. Perhaps the thrombosis occurs in conjunction with the vascular stasis created by hypertrophied and inflamed vascular endothelial cells as well as vasoconstriction where anticoagulation alone is not enough to reverse the ischemia.

**Implications for Treatment**

Multi-organ ischemia is part of the pathophysiology of COVID-19 infection leading to significant morbidity and mortality. Currently, combatting the inflammation and coagulopathy are strategies for treatment of the severely ill, hospitalized patients. Goeijenbier, et al. recommends that hospitalized patients with severe viral pneumonia should receive prophylactic low molecular-weight heparin unless they have an increased risk of bleeding [22]. In contrast, Tang and collaborators studied COVID-19 positive patients and found no difference in mortality between heparin users and non-users except for the sickest patients (p = 0.029) or when the D-dimer level was significantly elevated (P = 0.017) [23]. Jacobs and Obi reported that empiric anticoagulation protected against thrombotic events in patients with H1N1. It did so without increased hemorrhage supporting anticoagulation in critically ill ARDS patients with suspected H1N1 [24,25]. In our study, patients receiving full dose heparin did not have improved outcomes, which is likely the result of selection bias, as this group included the sickest patients.

Jantsch and collaborators, found that in 106 patients with severe ARDS, 33% had multiple thrombi and 15% had a single thrombus. The mortality rate was highest in those with multi-
ple thrombi [26]. Li’s meta-analysis revealed that low molecular weight heparin given within 7 days of ARDS onset reduced mortality and improved oxygenation [27]. Camprubi-Rimblass, et al., advocates for the use of anti-coagulation in ARDS patients and suggests that nebulized heparin might have a direct effect without the complications [28]. Interestingly, Mahmoud and collaborators found that inhaled streptokinase in patients with severe ARDS caused improved oxygenation and lung mechanics more quickly than heparin [29].

The majority of our patients were treated with hydroxychloroquine, which interferes with lysosomal acidification and antigen presentation by lymphocytes, inhibits Toll-like receptor signals, inhibits T and B cell receptors and decreases macrophage cytokine production. The inhibition of cytokines decreases the amount of tissue damage and endothelial inflammation [30,31]. Rand, et al. described how hydroxychloroquine has anticoagulation effects and can be used for treatment of anti-phospholipid syndrome [32]. We did not show improved outcomes for patients treated with hydroxychloroquine.

SARS-CoV-1 is a coronavirus like SARS-CoV-2 that causes severe lower respiratory tract infections. Nearly 20 to 30% of infected patients required mechanical ventilation. Diffuse alveolar damage was the hallmark finding in the lung parenchyma as is seen with COVID-19. In addition, there was edema of the walls of pulmonary vessels and vascular thrombi [33]. Endothelial cells desquamated with inflammation of blood vessel walls (vasculitis). Thrombosis occurred in parts of small veins [34]. There was capillary engorgement and microthrombosis [35]. Vascular endothelial damage of small- and medium pulmonary vessels was noted [36]. SARS caused both narrowing of vessels with stasis and thrombosis. Multiple treatments may be necessary to address the endovascular dysregulation to improve patient outcomes.

Georgescu, et al. found that enoxaparin diminished the contractility of the arterial wall in aged and aged-diabetic hamsters and these effects were more pronounced compared to heparin. The vascular relaxation complemented anticoagulant properties and could improve circulation in elderly and diabetic people [37]. Samama, et al. found that enoxaparin effectively decreased venous thrombosis in acutely ill patients [38]. In our study, 74% of those who were discharged received treatment with Enoxaparin whereas 38% of those who died were treated with this medication.

Hypertension, obesity, diabetes, aging, and smoking cause reduced nitrous oxide levels. Nitrous oxide causes vasodilation. It also has anti-thrombotic effects by inhibiting platelet adhesion [39]. Chen, et al. described the use of inhaled nitric oxide (NO) for patients with severe acute respiratory syndrome (SARS). The patients had improved oxygenation and airway pressures. Chest radiography showed decreased lung infiltrates, and the benefits remained after completion of therapy [40]. Nitrous oxide might be beneficial for patients with COVID-19 because of its ability to act as a vasodilator while minimizing thrombus; but controlled studies will be necessary to prove this hypothesis.

The limitations of this study are that it is a single center retrospective study with a limited sample size. There were confounding variables that may have generated selection bias within subgroups. The retrospective nature of this study did not allow us to assess long-term outcomes in patients who survived their illness. Future studies should continue to look at the role of ischemia as it relates to mortality and evaluate treatment strategies that optimize blood flow to vital organs as well as minimize complications. Imaging for ischemia will need to evaluate the microcirculation because the smallest vessels are at greatest risk which does not appear to be an embolic phenomenon.

SARS-CoV-2 infects the vascular endothelial cells of multiple organs leading to both endothelial inflammation resulting in stasis and a hypercoagulable state. This leads to poor outcomes for many patients especially those whose vascular system is compromised by advanced age, diabetes, and hypertension. D-dimer levels help identify those with the highest risk of mortality.

Disclosures

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