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Correlation of D-dimer and Outcomes in COVID-19 Patients

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Abstract

Background: The coronavirus disease 2019 (COVID-19) global pandemic has impacted daily life and medical practices around the world. Hospitals are continually making observations about this unique population as it relates to laboratory data and outcomes. Plasma D-dimer levels have been shown to be promising as a prognostic factor for outcomes in COVID-19 patients. This single institution retrospective study investigates the correlation between D-dimer and patient outcomes in our inpatient COVID-19 patient population.

Methods: COVID-19 confirmed positive patients who were admitted between March 2020 and May 2020 at our hospital were identified. Admission and peak D-dimer values and patient outcomes, including intubation and mortality, were retrospectively analyzed.

Results: Ninety-seven patients met criteria for inclusion in the study Mean age was 63.2 years, median admission D-dimer 2.35ug/mL, and median peak D-dimer 2.74ug/mL. Average time to peak D-dimer was 3.2 days. Patient's requiring intubation had higher admission D-dimers (3.79ug/mL vs. 1.62 ug/mL)

Discussion: Higher admission and peak D-dimer values were associated with worsening clinical outcomes, specifically with higher rates of intubation and mortality. Noting D-dimer trends early in a patients' COVID course, regardless of patients' clinical condition, may allow opportunities for physicians to provide early intervention to prevent these outcomes.

Keywords
COVID-19, D-dimer, thrombolytics

Background

The global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) otherwise known as coronavirus disease 2019 (COVID-19) has impacted daily life and medical practices around the world. Countless research and resources have been utilized to prevent, diagnose, treat, prognose, and improve outcomes for the COVID-19 patients. As the pandemic progresses, countries and hospitals are continually making observations about this unique population as it relates to laboratory data and outcomes.

One particular area of research interest relates to thrombosis seen with this unique viral pneumonia.[1] In contrast to community acquired pneumonia, the COVID-19 patient seems to exhibit an exaggerated thrombotic response to the virus.[2,3] The occurrence and burden of microthrombosis in these patients has been associated with poorer outcomes.[2-4]

D-dimer, a fibrin degradation product, as an indirect marker of thrombotic activity, is well established in venous thrombo-embolism (VTE) population risk assessment.[5] Additionally, D-dimer has been shown to be elevated in other hypercoagulable states including malignancy, sepsis, in pregnant women, and in the post-operative period.[5] With the suspicion of thrombosis in COVID-19 patients contributing to disease severity, and as a driving component of the respiratory difficulty

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encountered in this disease process, D-dimer has been valued as a useful clinical marker in this patient population.[6,7] Many international studies have been completed where plasma D-dimer levels have been indirectly associated with a thrombotic burden and applied as a prognostic measure for outcomes in COVID positive patients.[3,4,6,8-10]

COVID-19 patients have been shown to present with D-dimers twice as high on admission than patients with community acquired pneumonia.[3] Li et al[8] identified that the degree of variation in D-dimer values from those on admission were associated with outcomes in COVID- 19 patients. Furthermore, Zhang et al[4] found an admission D-dimer of >2.0 g/mL was associated with an increased risk of mortality. As an indirect measure of thrombotic burden, D-dimer values may have the potential to help guide treatment.

This single institution retrospective study investigates the correlation between D-dimer values, trends, and outcomes in our COVID-19 patient population.

Methods

This retrospective analysis was granted exemption status by our Institutional Review Board. COVID-19 confirmed positive patients who were admitted between March 2020 and May 2020 were identified. Patient laboratory values, demographics, clinical course, and outcomes were collected from the electronic medical record. Exclusion criteria included patients without the appropriate laboratory values, intubation of an unknown period prior to admission to our facility, tracheostomy in place prior to admission to our facility, or if they received thrombolytic therapy such as TPA. These patients received standard DVT prophylaxis to include lovenox and heparin and heparin drips for those with pulmonary embolism.

D-dimer laboratory data is expressed in micrograms per milliliter (ug/mL) of fibrinogen equivalent units (FEU). Our laboratory normal range for D-dimer is .00μg/mL to .45μg/mL. The upper level cut off detectable by our laboratory is 20ug/mL. D-dimer is detected via Immuno-Turbidimetric Assay using a STA-R™ coagulation analyzer and STA™ original reagents (Diagnostica Stago, Saint-Denis, France). All patients included in the study had a D-dimer measured on admission, as well during the first week of the hospital admission, and many had D-dimers measured intermittently during their hospital course. The highest D-dimer noted during their stay was recorded as the peak D-dimer. In our patient population, calculated measurements were expressed as mean and standard deviation for normal parametric variables, median and interquartile range (IQR) for non-parametric variables, and as number and percentage for categorical variables. Kolmogorov-Smirnov test determined normality in conjunction with the variables' QQ plots. Differences were derived from Fisher's exact test for categorical variables, t-tests for parametric variables, Mann-Whitney tests for non-parametric variables. Statistical significance level alpha was set to .05; tests were two-tailed. Statistical analysis was performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA).

Results

There were a total of 97 patients who met criteria for inclusion in the study. Mean age of all patients was 63.2 (±15.7) years. Gender distribution was male N = 46 and female N = 51. The median D-dimer on admission for all patients was 2.35μg/mL. The median peak D-dimer for all patients was 2.74μg/mL. Significant respiratory distress was seen in patients requiring an overall intubation rate of 33% (N = 32). Overall mortality was 25% (N = 24). All of the patients included in this population incidentally had an underlying medical comorbidity which varied from obstructive sleep apnea to coronary artery disease, chronic obstructive pulmonary disease, and hypertension.

The patients were analyzed by those who required intubation vs those who did not during their hospital course. Intubation criteria were based on respiratory and physician judgment. Significant respiratory distress was seen in these patients requiring an overall intubation rate of 33% (N = 32). The mean age of the non-intubated patient was 63.6 years (±16.2) vs 62.4 years (±15.1) in patients requiring intubation (p .74). Gender was also similar in both groups. The median admission D-dimer was noted to be 1.62μg/mL (IQR 1.87) in those who did not require intubation vs 3.79μg/mL (IQR 8.31) in patients who required intubation (P <.01). The median peak D-dimer in the non-intubated group was 2.00μg/mL (IQR 2.13) vs 7.58μg/mL (IQR 16.7) in those patients requiring intubation (P <.01).

Patients whose hospital course resulted in mortality compared to those who survived were also analyzed. Mean age was 61.1 years in survivors vs 69.2 years in non-survivors (p .026). There was no statistical difference in gender between the groups. Admission D-dimer in survivors vs non-survivors was 1.69μg/mL vs 3.21μg/mL (P <.01), respectively. Peak D-dimer in survivors was 2.29μg/mL compared to 5.64μg/mL in non-survivors (P <.01).

Patients with an admission D-dimer of <2ug/mL compared to those with admission D-dimer of ≳2ug/mL were noted to have no significant difference in age (60.8 ± 15.3 years vs 65.4 ± 15.9 years, p .15). Similarly, there was not a significant difference in age of those with peak D-dimers of <2 mg/mL compared to

peak D-dimers ≳2 mg/mL (60.4 ± 15.3 vs 64.7±15.6 years, p .21). Patients who had an admission D-dimer of <2ug/mL vs ≳2 mg/mL were observed to be intubated 15% vs 48.1% (P <.01) and mortality was noted to be 7.5% vs 40.7% (P <.01), respectively. Patients with a peak D-dimer of <2ug/mL vs ≳2 mg/mL were observed to be intubated 3.1% vs 49.2% (P <.01) and mortality was noted to be 3.1% vs 38.1% (P <.01), respectively.

Furthermore, we categorized patients into groups based on their peak D-dimer range to identify trends in outcomes. The number of patients requiring intubation and total number of patients with mortality was calculated for each category. As the peak D-dimer rises, so does the rate of intubation and rate of mortality.

Discussion

Elevated D-dimer levels have emerged as a consistent finding in severely ill COVID-19 patients.[4] Researchers around the world are working towards the understanding of this consistent laboratory trend and the clinical impact that it reflects. It has become generally accepted that COVID-19 patients endure a hypercoagulable state and that the elevations in the D-dimer levels are in response to this prothrombotic phenomenon.[6,11] Multiple studies have identified an association between higher D-dimer levels and an increased risk of mortality in the COVID-19 patient population.[3-5]

In our study, D-dimer values appeared to correlate with mortality rates, a finding consistent with earlier international works. Admission and peak D-dimer values were noted to be twice as high in our non-surviving patients. Additionally, age was noted to be statistically higher in the non-survivors compared to survivors. Age has previously been shown to be an independent risk factor for mortality in patients with COVID-19.[11]

Despite similarities in age and gender, patients who required intubation demonstrated a 3-fold or higher D-dimer value (both admission and peak) than those patients who avoided intubation. This suggests the admission and peak D-dimers could be utilized as a prognostic factor for determining intubation risk. To the author's knowledge, no study to date has paired D-dimer value elevations with intubation risk.

Patients with admission and peak D-dimer values of less than 2ug/mL were observed to have statistically lower rates of intubation and mortality compared to those with D-dimer values greater than 2ug/mL, a trend of which was also noted by Zhang et al.[4] Furthermore, we observed that as the peak D-dimer values increased, the rates of intubation and mortality increased.

Our study has several limitations. It is a single institution retrospective review which limits its sample size, power, and applicability across non-similar populations. In addition, although all patients were treated in the same hospital by the same group of providers, variations in practice patterns that could contribute to less ideal patient outcomes cannot be completely predicted.

Conclusion

The findings provided by our retrospective study corroborate other, international works correlating D-dimer values with outcomes in COVID-19 patients. Higher admission and peak D-dimer values seem to be associated with worsening clinical outcomes, specifically with higher rates of intubation and mortality. Further studies could be done to evaluate the role of therapeutic anticoagulation on D-dimer trends.

Author Contributions

HMN: Literature search, study design, data collection, data analysis, data interpretation, and writing. AL: Literature search, study design, data collection, and writing. DBC: Literature search, study design, data analysis, data interpretation, writing, and critical revision. AM: Data analysis and data interpretation. DA: Study design, writing, and critical revision.

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