Retrospective Analyses Associate Hemostasis Activation Biomarkers With Poor Outcomes in Patients With COVID-19

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ABSTRACT

Objectives: Patients with coronavirus disease 2019 (COVID-19) have thromboembolic complications. Assessment of coagulation and other markers could be useful to understand their coagulopathy.

Methods: We performed a retrospective study of inflammatory and coagulation parameters, including prothrombin fragment 1.2 (PF1.2), thrombin-antithrombin complexes (TATs), fibrin monomers, and D-dimer, in hospitalized patients with COVID-19. We compared the markers in patients with thrombosis, admission to the intensive care unit (ICU), and poor outcome.

Results: Of the 81 patients, 9 (11%) experienced an acute thrombotic event (4 with pulmonary embolism, 3 with venous thrombosis, and 2 with stroke). PF1.2 was elevated in 32 (39%) patients, TATs in 54 (67%), fibrin monomers in 49 (60%), and D-dimer in 76 (94%). Statistically significant elevation in PF1.2 and TATs was seen in patients admitted to the ICU, while D-dimer and fibrin monomers were significantly elevated in patients with poor outcomes. The presence of multiple abnormal coagulation parameters was associated with ICU admission. Other parameters with statistically significant results included abnormal WBC counts and elevated C-reactive protein, which were associated with ICU admission and poor outcomes.

Conclusions: Our data demonstrate that abnormalities of biomarkers of hemostasis activation and inflammatory markers are associated with poor outcomes in patients with COVID-19.

Key Points

- In patients with coronavirus disease 2019 (COVID-19), having multiple abnormal markers of coagulation and hemostasis activation is associated with poor outcomes.
- Fibrin monomers and D-dimer were significantly elevated in patients with COVID-19 who had poor outcomes (including death or discharge to hospice).
- Increase in prothrombin fragment 1.2 and thrombin-antithrombin is associated with admission to intensive care units in patients with COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has spread worldwide, becoming a pandemic, and it has become evident that coagulopathy occurs frequently in hospitalized patients with severe disease.1-4 The primary symptomatology and target organ of SARS-CoV-2 is the lung; however, invasion of endothelial cells via the angiotensin-converting enzyme 2 receptor indicates that the coagulopathy observed in these patients may have several causes, such as inflammation with recruitment of neutrophils and complement activation at the endothelial level as well as thrombin generation.5,6 At the start of the pandemic, elevations of D-dimer were found to have prognostic and therapeutic significance, and thromboprophylaxis was initiated based on increased levels.1-3 Other markers that have also been used to define risk of thrombosis in patients with COVID-19 include prothrombin time, fibrinogen, fibrinogen degradation products, prothrombin fragment 1.2 (PF1.2), thrombin-antithrombin complexes (TATs), platelet count, and others.6-9

D-dimer values above the reference range are seen in a variety of situations not necessarily related to activation of the coagulation system, including advanced
Moreover, D-dimer elevation may lag behind active clot excluding thrombotic events such as pulmonary embolus. Therefore, testing may be of value to further understand the coagulopathy in these patients. In our institution, we offer testing of three such biomarkers in a panel together with D-dimer and provide an interpretation. These biomarkers are as follows:

1. PF1.2, which assesses activation and thrombin generation
2. TATs, produced as a result of thrombin binding to antithrombin
3. Fibrin monomers, formed following conversion of fibrinogen to fibrin

This panel, called markers of coagulation and hemostasis activation (MOCHAs), has been used by clinical services in our institution to assess the risk of thrombosis in patients with stroke, pregnancy-associated morbidity, cardiothoracic surgery, atrial fibrillation, malignancy, and a variety of clinical scenarios in patients requiring antiplatelet therapy. Previous studies have shown significantly higher rates of coagulopathy-related morbidity and mortality in patients with two or more elevated MOCHA parameters compared with patients with elevation of one MOCHA parameter.15-16

In this study, our goal was to assess the MOCHA panel and other laboratory data in patients with COVID-19 with various outcomes, including development of thrombosis, admission to intensive care units (ICUs), and discharge disposition.

Materials and Methods

We performed a retrospective chart review in patients with a diagnosis of COVID-19 (positive nasopharyngeal swab by nucleic acid testing) in whom a MOCHA panel was ordered on admission before anticoagulation prophylaxis was started. The patients came from three different hospitals of the same health care system, which include two community hospitals with 400 to 500 beds and one tertiary referral hospital with 650 beds. Physicians from these hospitals agreed to have the MOCHA panel as an activated admission order for all patients with COVID-19 independent of severity of disease. The results presented in this study include patients admitted during March 2020. The MOCHA panel was not included in the order set of patients seen in the emergency room who were not admitted to the hospitals; thus, patients with mild disease were excluded from the study. In a number of cases, repeat MOCHA testing occurred and the trend of the parameters in relationship to anticoagulation is presented, but these subsequent MOCHA results are not included in the statistical analyses. Data collected included age, sex, ethnicity, underlying comorbidities, medications, admission type (inpatient ward vs ICU), thrombotic events, and disposition. Underlying comorbidities included all items within the problem list, primarily focusing on conditions associated with thrombosis, such as previous thrombotic events, pregnancy-related morbidity, or malignancy, as well as risk factors like hypertension, diabetes mellitus, and coronary artery disease. Laboratory data collected included routine coagulation studies (prothrombin time/ international normalized ratio, partial thromboplastin time, fibrinogen levels, antithrombin activity), CBC counts, and C-reactive protein (CRP) levels.

Plasma samples for testing MOCHA parameters were obtained in coagulation tubes containing 3.2% sodium citrate. D-dimer levels were measured using a high-sensitivity latex dimer assay (Instrumentation Laboratories). PF1.2 and TATs were measured using the Enzygnost ELISA kit (Siemens Healthcare). Soluble fibrin monomer assays were performed using a latex immunosassay (Stago).

We determined the median, range, and number of patients with values above the normal reference range for the different laboratory parameters. We used the Fisher exact test (univariate analysis) (GraphPad Software) to compare the numerical values and the number of elevated markers for the different laboratory parameters for the following groups: patients who developed acute thrombotic events vs those who did not, patients with admission to the ICU vs those with admission to regular wards, and patients with a poor outcome, including death or discharge to hospice, vs those with a favorable outcome, including discharge to home or rehabilitation facility. A P value less than .05 was considered statistically significant. For the four MOCHA parameters, patients were further stratified based on the number of elevated markers into the following groups: one or more, two or more, three or more, or all four markers abnormal; thus, patients with one or more elevated markers included those patients in groups with two, three, or all markers elevated. The number of abnormal MOCHA results has been used to determine hypercoagulable state in patients with stroke. 9,15

This investigation was deemed as an exempt protocol by the institutional review board. Deidentified tables with
raw data are presented as a Supplementary Table (all supplemental materials can be found at American Journal of Clinical Pathology online).

## Results

Table 1 presents the characteristics, demographics, and hospitalization details of the 81 patients studied. Acute thrombotic events during hospitalization included four cases of pulmonary embolism, three cases of deep venous thrombosis (two proximal and one distal), and two cases of stroke. The thrombotic events were diagnosed using ultrasound, doppler, or computed tomography angiography. Two patients who developed disseminated intravascular coagulation (DIC) in the setting of liver failure were excluded from the thrombotic group because they did not have a venous thrombotic event or stroke. No other patient in our cohort had DIC. An additional patient was excluded from the thrombotic group, as he developed heparin-induced thrombocytopenia and the thrombotic event was felt to be due to a comorbidity outside COVID-19. Of the 12 patients with poor outcome, acute thrombotic events were responsible for the poor outcome in 6 (7%), while the remainder was attributed to acute hypoxic failure. Of the nine patients who experienced acute thrombotic episodes in the hospital, eight had underlying cardiovascular disease, one had active cancer, and two had asthma, but none of these patients had a history of a thrombotic event. These nine patients received a variety of anticoagulation treatments during their hospitalization, including a direct thrombin inhibitor in one, low molecular weight heparin (LMWH) in another, and unfractionated heparin (UFH) in seven. One patient on UFH also continued to receive aspirin, which the patient was taking before admission.

Table 2 presents laboratory results (number of cases above normal range, median, and range of the results) stratified by grouping, and Figure 1 presents the range and median of the MOCHA parameters and the

| Table 1 | Patient Demographics, Comorbidities, and Hospitalization Details Including Anticoagulation Received |
|---------|------------------------------------------------------------------------------------------------------|
| **Characteristics** | **Cohort (n = 81)** | **Notes** |
| **Demographics** | | |
| Age, mean (range), y | 64 (23-94) | |
| Female, No. (%) | 44 (54) | |
| Race ethnicity (known in 78), No. (%) | | |
| Black | 55 (70) | |
| White | 18 (23) | |
| Hispanic | 3 (4) | |
| Asian | 2 (2) | |
| **Comorbidities, No. (%)** | | |
| No comorbidities | 1 (1) | |
| One comorbidity | 16 (20) | |
| Two comorbidities | 18 (22) | |
| Three or more comorbidities | 46 (57) | |
| Hypertension | 47 (58) | |
| Type 2 diabetes | 37 (46) | |
| Hyperlipidemia | 16 (20) | |
| Underlying lung disease | 11 (14) | 7 with asthma, 4 with COPD |
| Kidney disease | 10 (12) | |
| Autoimmune disease | 11 (14) | |
| Active malignancy | 6 (7) | |
| HIV/AIDS | 2 (2) | |
| Previous thrombotic event | 14 (17) | |
| On antplatelet therapy | 11 (14) | 10 on aspirin, 1 on clopidogrel (all continued during hospitalization) |
| **Hospitalization details** | | |
| Length in days, mean (range) | 13 (2-24) | |
| Admission to ICU, No. (%) | 49 (61) | |
| Thrombotic event, No. (%) | 9 (11) | |
| Poor outcome, No. (%) | 12 (15) | 8 died, 4 were discharged to hospice |
| **Anticoagulation during hospital stay, No. (%)** | | |
| Low molecular weight heparin | 38 (47) | |
| Unfractionated heparin | 31 (38) | |
| Direct thrombin inhibitor | 5 (6) | |
| Direct anti-Xa inhibitor | 4 (5) | |

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.
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Table 2
Comparison of the Different Laboratory Parameters in the Different Groups a

| Characteristic | ICU  
| Non-ICU  
| P Value | Thrombotic Events  
| Without Thrombosis  
| P Value | Deceased  
| Alive  
| P Value |
|---|---|---|---|---|---|---|
| PT (9.4-12.5 seconds) | 42 (86) 21 (65) .05 | 9 (100) 54 (75) .19 | 10 (83) 53 (77) .61 |
| No. (%) above normal | 14.2 13.4 .44 | 13.5 13.9 .92 | 14.4 13.7 .47 |
| Median | 10.4-21 11.2-22.4 12.8-17.7 10.4-22.4 | 11.2-22.4 10.4-22.4 | 11.2-18.8 10.4-22.4 |
| Range | APTT (25.2-36.5 seconds) | 16 (33) 5 (16) .12 | 3 (33) 18 (25) .68 | 3 (25) 18 (26) .93 |
| No. (%) above normal | 33.4 31.5 .85 | 31.5 32.5 .84 | 30.5 32.5 .72 |
| Median | 24.3-188.5 22.6-249 25.8-66.6 22.6-249 | 25.8-66.6 22.6-249 | 24.7-75 22.6-249 |
| Range | Prothrombin fragment 1.2 (<288 pmol/L) | 23 (47) 9 (28) .1 | 3 (33) 29 (40) .74 | 3 (25) 29 (42) .34 |
| No. (%) above normal | 274 176 .03 | 212 233 .74 | 197 248 .22 |
| Median | 46-1,116 53-670 161-563 46-1,116 | 161-563 46-1,116 | 169-447 46-1,116 |
| Range | Thrombin-antithrombin (<5.5 µg/L) | 35 (71) 19 (59) .33 | 6 (66) 48 (67) .1 | 10 (83) 44 (64) .31 |
| No. (%) above normal | 8.9 5.9 .04 | 10.2 78 .78 | 13.1 71 .76 |
| Median | 2.5-104 23-59.5 3.4-31.3 2-104 | 3.4-31.3 2-104 | 3.9-31.3 2-104 |
| Range | Fibrin monomers (<7 µg/mL) | 32 (63) 17 (53) .35 | 7 (78) 42 (58) .3 | 11 (92) 38 (55) .02 |
| No. (%) above normal | 12 7.3 .72 | 9 9.6 .07 | 25 8 .04 |
| Median | 7-150 7-145 7-145 7-150 | 7-145 7-150 | 7-150 7-150 |
| Range | D-dimer (<574 ng/mL) | 48 (98) 28 (87) .07 | 9 (100) 67 (93) 1 | 12 (100) 64 (92.7) 1 |
| No. (%) above normal | 3,592 1,005 .16 | 5,457 1,891 .2 | 7,460 1,891 .004 |
| Median | 3,592 1,005 5,457 1,891 | 5,457 1,891 | 7,460 1,891 |
| Range | Platelets (150,000-400,000 cells/µL) | 10 (20) 10 (31) .3 | 3 (33) 17 (23) 1 | 3 (25) 17 (25) 1 |
| No. (%) above normal | 257 265 .99 | 202 270 .08 | 241 265 .14 |
| Median | 273-604 92-811 273-367 73-811 | 273-367 73-811 | 103-351 27-811 |
| Range | C-reactive protein (<40 mg/L) | 46/48 (96) 25/29 (86) .09 | 6/8 (75) 65/69 (94) .19 | 10/11 (91) 61/66 (92) 1 |
| No. (%) above normal | 215 105 <.001 | 239.9 149.3 .92 | 239 139 .03 |
| Median | 5.2-468.4 6.6-296 5.2-299.4 73-468.4 | 5.2-299.4 73-468.4 | 10-468 5.2-375 |
| Range | WBCs (4,000-10,000 cells/µL) | 27 (55) 12 (37) .17 | 5 (55) 34 (47) .73 | 9 (11) 30 (37) .06 |
| No. (%) above normal | 10.3 6.55 .01 | 11.6 7.7 .06 | 11.6 7.6 .004 |
| Median | 3.3-42.1 2.8-26 4.4-42.1 2.8-29.7 | 4.4-42.1 2.8-29.7 | 2.8-42.1 2.9-29.7 |
| Range | aP values are presented for the number of cases above normal and for the result value for each parameter between the three different groups. Bold values are statistically significant.

PTT, activated partial thromboplastin time; ICU, intensive care unit; PT, prothrombin time.

Statistically significant P value for each of the MOCHA parameters. Result of the MOCHA panel showed the following: PF1.2 and TATs had statistically significant elevation in patients admitted to the ICU, and D-dimer and fibrin monomers were significantly elevated in patients with poor outcomes (deceased or sent to hospice). Other coagulation parameters with statistically significant elevations included increased fibrinogen in patients admitted to the ICU and increased prothrombin time in patients admitted to the ICU. Since our institution interprets MOCHA parameters as a profile, we were interested in the number of cases with abnormal results. PF1.2 above the normal reference range (65-288 pmol/L) was found in 32 (39%) patients and was interpreted by a pathologist as evidence of prothrombin-driven hemostatic activation. Of the patients with increased levels of PF1.2, three (4%) had a thrombotic event (levels of 419, 438, and 463 pmol/L). Fifty-four (67%) patients had elevation of TATs (reference range, 1.0-5.5 µg/L), 49 (60%) had increased levels of fibrin monomers (reference range <7 µg/mL), and 76 (94%) had elevations of D-dimer (reference range <574 ng/mL). There were 18

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(22%) patients with D-dimer between 1,000 and 2,000 ng/mL, 26 (32%) patients between 2,001 and 10,000 ng/mL, and 15 (18%) patients above 10,000 ng/mL. Only two of the patients with thrombotic events had D-dimer levels above 10,000 ng/mL.

Table 3 presents the correlation of number of abnormal MOCHA parameters within the three groups. Of note, three or more abnormal MOCHA markers was statistically significant in patients with an increased risk of poor outcome. Fibrinogen was available in 51 patients; it was normal (200-393 mg/dL) in 9 (18%) and above 500 mg/dL in 34 (67%). Fibrinogen was above 500 mg/dL in 4 (57%) of 7 patients with thrombosis, 6 (75%) of 8 patients with poor outcomes, and 29 (80%) of 36 patients in the ICU. The latter was statistically significant in patients admitted to the intensive care unit (ICU), while D-dimer and fibrin monomers were significantly elevated in patients with poor outcomes.

Table 3: Correlation of the Number of Abnormal MOCHA Parameters in the Different Groups

| No. of MOCHA Markers Above Normal (No.) | Thrombosis, No. (%) | Not Thrombosis, No. (%) | P Value | ICU, No. (%) | Not ICU, No. (%) | P Value | Poor Outcome, No. (%) | Favorable Outcome, No. (%) | P Value |
|----------------------------------------|---------------------|------------------------|---------|--------------|-----------------|---------|----------------------|-----------------------------|---------|
| All (20)                               |                      |                        |         |              |                 |         |                      |                             |         |
| >3 (46)                                | 6 (26)              | 40 (49)                | .72     | 33 (41)      | 13 (16)         | .21     | 12 (15)              | 52 (64)                      | .09     |
| >2 (64)                                | 9 (11)              | 55 (68)                | .19     | 42 (52)      | 22 (27)         | .06     | 12 (15)              | 52 (64)                      | .09     |
| >1 (81)                                | 9 (11)              | 72 (89)                | 1       | 49 (60)      | 32 (39)         | 1       | 12 (15)              | 69 (85)                      | 1       |

ICU, intensive care unit; MOCHA, marker of coagulation and hemostasis activation.

*There were no cases with all MOCHA parameters in the normal range. Abnormal values include prothrombin fraction 1.2 >289 pmol/L, thrombin-antithrombin >5.6 μg/L, fibrin monomers >7.1 μg/mL, and D-dimer >575 ng/mL. P values compare the number of abnormal results for each group (thrombus vs no thrombus, ICU vs no ICU, and unfavorable outcome vs favorable outcome). The row with three or more parameters includes patients in the row above (four abnormal parameters), the row with two or more includes the patients in the two rows above, and the last row with one or more includes the patients from the rows above.
Discussion

In our study, we found that acute thrombotic events occurred in 11% of cases, and 44% of them had poor outcomes. Depending on the series published, thrombotic complications in ICU patients and mortality due to coagulopathy in patients with COVID-19 can be lower or higher compared with our series. 3,17,18 Our COVID-19 cohort showed that PF1.2 and TATs were significantly associated with admission to the ICU. The association of PF1.2 and TAT with admission to the ICU suggests these may be relevant biomarkers of disease severity. Similar to other publications, our study demonstrated that TATs are significantly associated with admission to the ICU. 6 Elevations of PF1.2 have been associated with thrombotic events in patients with COVID-19, although admission to the ICU was not explored by previous authors. 9 We also found that a MOCHA panel with three or more increased biomarkers showed a significant association with increased likelihood of admission to the ICU. This indicates that additional MOCHA markers are useful to define severity in these patients rather than the use of only D-dimer.

In our study, D-dimer was increased in over 90% of the cases and was significantly associated with unfavorable outcomes. Measurement of D-dimer has been proposed as a valuable marker for poor outcomes in patients with COVID-19 in multiple publications. 4,5,19-21 The presence of D-dimer indicates that a fibrin clot has formed and is subsequently undergoing fibrinolysis. Elevations of D-dimer can occur in those with intravenous lines or the elderly without the presence of thrombosis such as pulmonary emboli. 10-13 Thus, measurement of other markers could be beneficial. Here we demonstrate that fibrin monomers were significantly associated with unfavorable outcomes and that fibrinogen above 500 mg/dL was significantly associated with ICU admission. The statistically significant elevation in fibrinogen in patients with poor outcomes is consistent with findings in early studies of patients with COVID-19. 1 Although measurements of PF1.2, TATs, fibrin monomers, and fibrinogen appear significant to define outcomes, the effect of age requires additional study.

We sought to understand better the significance of earlier hemostasis markers to determine the pathophysiology driving thrombosis in patients with COVID-19. PF1.2 and TAT are markers that indicate thrombin formation, while fibrin monomers indicate thrombin-catalyzed fibrin generation. Others have found that patients with COVID-19 have normal in vitro thrombin generation by the use of rotational thromboelastography while having increased TATs and D-dimer as markers of in vivo thrombin generation. 22 The influence of WBC and CRP has been explored in other publications showing that increases in WBC counts are found in patients with COVID-19 admitted to the ICU while CRP has been observed as a predictor of respiratory failure and thrombotic complications. 23-25 In our series, we found that WBC and CRP were found in patients admitted to the ICU and those with poor outcome. Underlying comorbidities and hospital immobilization, which are known risk factors for venous thrombosis, 26 were present in most of our patients, suggesting that the risk of thrombosis in patients with COVID-19 is likely multifactorial.

In our study, 77 (95%) patients received anticoagulant prophylaxis or treatment, primarily with heparin or LMWH (88% of total patients receiving an anticoagulant). The remaining patients who did not receive anticoagulation either refused treatment or were deemed as noncandidates due to a high bleeding risk by their providers. Despite prophylactic or therapeutic anticoagulation, a significant portion of patients still had adverse outcomes not related to thrombosis. Heparin and especially LMWH have been recommended by
expert consensus groups due to preliminary findings of improved prognosis in patients with COVID-19–related coagulopathy. A trend toward normalized MOCHA parameters was observed in our patients who were initiated on anticoagulants during their hospitalization, although clinical outcome was variable and likely depended on other variables that occurred during hospitalization.

Limitations of our study include the retrospective nature of data collection; thus, not all patients had complete laboratory profiles (eg, not all patients had CRP or fibrinogen ordered). Although the MOCHA panel was approved by the medical practice in our hospitals as an activated admission order, we do not know if physicians decided to inactivate the order for the MOCHA panel (unick the order) during the study period, which could potentially create a bias. The patients studied are those who required admission; thus, we do not know the MOCHA panel results of patients with mild disease, creating a bias toward having higher prevalence of abnormalities. Also, since the patient had to be SARS-CoV-2 polymerase chain reaction positive by using a nasopharyngeal swab, those patients negative on the molecular test but who later tested positive for antibodies were not captured in this study. Practices in the three different hospitals and by different physicians may not be necessarily identical, which may have created variability in anticoagulant prophylaxis or treatment. Moreover, the inclusion of patients with COVID-19 with complex medical histories can confound the study, as these patients are more prone to have preexisting abnormalities on MOCHA testing. The outcomes in our cohort included mostly elderly Black patients with more than one underlying medical comorbidity, all of which suggest that several variables come into play, as have been defined in a published meta-analysis. Last, this was a retrospective univariate analysis.

In summary, early detection and monitoring of coagulopathy are essential in patients with COVID-19, and we believe that the MOCHA panel provides data that can be useful for prognosis and treatment. Our study underscores the variable mechanisms of COVID-19 coagulopathy and the role that study of inflammatory and MOCHA biomarkers plays in better understanding the disease process.

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