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Early View

Original article

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Please cite this article as: Song X, Ji J, Reva B, *et al*. Post-anticoagulant D-dimer is a highly prognostic biomarker of COVID-19 mortality. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00018-2021).

Post-Anticoagulant D-dimer is a Highly Prognostic Biomarker of COVID-19 Mortality

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Take Home Message: In a retrospective study of 1835 severely ill COVID-19 patients on therapeutic anticoagulation for thromboprophylaxis during hospitalization, post-anticoagulant D-dimer levels and trends were highly significant and independent predictors of mortality.

COI disclosure: Authors have no competing interests to declare
Funding Source: None
Word count: Abstract: 250; Manuscript text: 3000; Tables: 1; Figures: 4
Keywords: COVID-19, D-Dimer, Anticoagulation, Mortality, Biomarker

Abstract:

Research Question: Clinical biomarkers that accurately predict mortality are needed for the effective management of patients with severe COVID-19 illness. In this study, we determine whether changes in D-dimer levels after anticoagulation are independently predictive of in-hospital mortality.

Study Design: Adult patients hospitalized for severe COVID-19 who received therapeutic anticoagulation for thromboprophylaxis were identified from a large COVID-19 database of the Mount Sinai Health System in New York City. We studied the ability of post-anticoagulant D-dimer levels to predict in-hospital mortality, while taking into consideration 65 other clinically important covariates including patient demographics, comorbidities, vital signs and several laboratory tests.

Results: 1835 adult patients with PCR-confirmed COVID-19 who received therapeutic anticoagulation during hospitalization were included. Overall, 26% of patients died in the hospital. Significantly different in-hospital mortality rates were observed in patient groups based on mean D-dimer levels and trend following anticoagulation: 49% for the high mean-increase trend (HI) group; 27% for the high-decrease (HD) group; 21% for the low-increase (LI) group; and 9% for the low-decrease (LD) group ($p<0.001$). Using penalized logistic regression models to simultaneously analyze 67 clinical variables, the HI (adjusted odds ratios [ORadj]: 6.58, 95% CI 3.81-11.16), LI (ORadj: 4.06, 95% CI 2.23-7.38) and HD (ORadj: 2.37; 95% CI 1.37-4.09) D-dimer groups (reference: LD group) had the highest odds for in-hospital mortality among all clinical features.

Conclusion: Changes in D-dimer levels and trend following anticoagulation are highly predictive of in-hospital mortality and may help guide resource allocation and future studies of emerging treatments for severe COVID-19.

Introduction

The COVID-19 pandemic has resulted in 46 million confirmed cases and 1.2 million deaths worldwide through November, 2020 [1]. Among patients with more severe illness requiring hospitalization, there is an urgent need for accurate clinical biomarkers to predict mortality risk in order to guide clinical decisions, allocate critical resources and inform study designs of emerging treatments. Currently, there is insufficient evidence to precisely identify patients at the highest risk of poor outcomes, and clinicians often consider a multitude of individual clinical factors (i.e., exam findings, laboratory tests) without predictive cut-off values for making treatment decisions. Therefore, quantifying the impact of laboratory markers used in clinical practice as prognostic biomarkers for mortality is critical for the effective management of COVID-19 patients.

D-dimer, a small protein fragment present in blood resulting from plasmin cleavage of cross-linked fibrin clots, is routinely used in clinical practice as a sensitive biomarker in the evaluation of venous thromboembolism (VTE) [2]. Recently, several studies have shown that elevated D-dimer levels at the time of hospital admission in COVID-19 patients are associated with higher mortality [3–6]. Furthermore, the use of anticoagulant therapy in hospitalized COVID-19 patients with elevated D-dimer levels resulted in a significant mortality benefit [3,7–10]. As a consequence, many guidelines and institutional protocols have recommended therapeutic anticoagulation strategies (using intermediate or full doses) for thromboprophylaxis in patients with severe COVID-19 infection [4–6]. However, while D-dimer measurements generally are followed throughout the

hospitalization, there remains no consensus or guidance as to how changes in D-dimer levels should be interpreted following anticoagulant therapy in COVID-19 patients.

In this study, we hypothesized that changes in D-dimer levels and trends following administration of therapeutic doses of anticoagulation in patients with severe COVID-19 infections are predictive of in-hospital mortality. To determine the role of D-dimer in this setting, we leveraged a large institutional database of COVID-19 hospitalized patients from the Mount Sinai Health System (MSHS) in New York City, one of the initial epicenters of the COVID-19 pandemic in the United States (US).

Study Design and Methods

Study Cohort

MSHS includes the Mount Sinai Hospital and 7 other urban hospitals throughout New York City, serving a diverse patient population with high representation of low-income minorities. This study utilized a comprehensive COVID-19 database, which includes de-identified clinical data extracted from the electronic medical records of all patients tested for and/or diagnosed with COVID-19 within the health system from February 25, 2020 to May 31, 2020. We included all adults (≥18 years of age) who were hospitalized for a new COVID-19 infection (based on RT-PCR COVID-19 assay using nasopharyngeal swabs), and were treated with therapeutic doses of anticoagulation for thromboprophylaxis. Included patients required follow up data for at least 3 days after the first anticoagulant dose and information on their hospitalization outcome (discharged vs. deceased). We then excluded patients who: 1) had high risk of bleeding from

therapeutic doses of anticoagulation due to either low platelet counts (<50,000/uL) or elevated international normalization ratio (INR>1.5) and 2) were given therapeutic doses of anticoagulation or tissue plasminogen activator (TPA) for a newly diagnosed VTE as large vessel thrombosis could affect post-anticoagulant D-dimer levels.

Study Variables

Patient Characteristics

For each patient, we obtained baseline sociodemographic data (i.e., age, sex, self-reported race and ethnicity), smoking status, body mass index (BMI), and 18 common comorbidities (**Table S1**). Baseline vital signs (temperature, systolic blood pressure, diastolic blood pressure, oxygen saturation, heart rate, respiratory rate) and laboratory tests obtained within 24 hours of admission and prior to receiving anticoagulation were collected. In cases where multiple vital signs were recorded during the first 24 hours of admission, we used the most clinically abnormal measurement concerning for systemic inflammatory response syndrome (SIRS) [11]. A preprocessing procedure was performed to exclude laboratory tests that were missing in > 50% of patients. The remaining 35 laboratory tests that were used for analysis included complete blood count (CBC) with differential, comprehensive metabolic panel (CMP), inflammatory markers (i.e., ferritin, C-reactive protein [CRP], lactate dehydrogenase [LDH]), liver function tests and baseline D-dimer. All together, 65 baseline variables were considered for each patient (**Table S1**).

Therapeutic dose of anti-coagulation treatment

The MSHS, alongside many other high acuity hospitals, has developed a standardized protocol for anticoagulant therapy in patients requiring hospital admission for COVID-19. All patients without confirmed VTE are recommended to receive thromboprophylaxis with heparin, enoxaparin and/or apixaban using either prophylactic doses for patients without severe respiratory compromise or therapeutic doses (intermediate or full) for patients with severe respiratory compromise (i.e., respiratory rate >24/minute, oxygen saturation <90%, or requiring supplemental oxygen >4L/min via nasal canula). Our study cohort included patients on therapeutic doses defined as: 1) heparin: >5,000 units subcutaneous (SQ) every 8 hours in patients with BMI<40 kg/m2 or >7,500 units SQ every 8 hours in patients with BMI ≥40 kg/m2; 2) enoxaparin: 1mg/kg SQ every 24 hours (intermediate dose) or 1mg/kg SQ twice daily (full dose); and 3) apixaban: >2.5mg by mouth every 24 hours.

Post-anticoagulant D-dimer values and groups

We recorded post-anticoagulant D-dimer levels as all measurements collected within the first 3 days after the administration of therapeutic doses of anticoagulation was started. This time frame was chosen after finding the incremental Area under the Curve (AUC) change for the predictive capability of our model was not significantly different for each additional day of D-dimer levels past day 3 (Figure S1). As the number of D-dimer measurements during this period varied dramatically (from 0 to 18 measurements) for each patient, we calculated both the mean and trend to summarize the data. The trend was defined, if at least 2 measurements were available, as the slope of a linear

regression model characterizing the dependence of the post-anticoagulant D-dimer values on the test collection time from anticoagulation.

Using 2.5 ug/ml as a cutoff for the post-anticoagulant D-dimer mean value, and 0 as a cutoff for the post-anticoagulant D-dimer trend, we divided patients into four groups with similar sample sizes: HI--- high mean value (>=2.5 ug/ml) and increase trend (trend>=0); HD--- high mean value and decrease trend; LI --- low mean value and increase trend; and LD --- low mean value and decrease trend.

Study End Point

The study endpoint is a binary indicator of in-hospital mortality, defined as patients who died during their admission vs. patients who were discharged alive from the hospital, usually to home, nursing facility, acute/sub-acute rehab or long-term care facility.

Statistical Analysis

To test the associations between baseline and post-anticoagulant D-dimer variables with in-hospital mortality, χ^2 tests and two-sample Wilcoxon tests were used for categorical and continuous variables, respectively. Bonferroni correction for multiple testing provided $p<0.0007$ (=0.05/65) as the cutoff to determine significant associations with in-hospital mortality. Missing values in categorical variables were treated as a separate category, while multiple imputations were performed for missing values in numeric variables using the R package MICE [12].

Logistic regression models were employed to predict in-hospital mortality based on baseline and post-anticoagulant D-dimer levels. The predictive values were evaluated through 10-fold cross-validation. The Receiver Operating Characteristic (ROC) curve and the corresponding AUCs were used to assess and compare the performance of the prediction model based on baseline and post-anticoagulant D-dimer values.

We assessed whether the in-hospital mortality and the baseline characteristics of patients differed across the four D-dimer groups described above. χ^2 tests were used for categorical variables and Kruskal-Wallis tests for continuous variables. Variables that passed 5% significance level after Bonferroni correction were further examined for statistically significant differences in groups with high D-dimer levels (HI and HD combined) vs. groups with low D-dimer levels (LI and LD combined); as well as in groups with increasing D-dimer vs. those with decreasing D-dimer trends (HI vs. HD; LI vs. LD).

We assessed the predictivity of D-dimers for in-hospital mortality conditional on baseline characteristics of patients. To better estimate effect sizes of predictors, we randomly split the samples into discovery and validation subsets with equal sizes and performed variable selection on the discovery subset while inference of effect sizes on the validation subset to avoid post-selection inference, which results in biased estimates and confidence intervals (CIs). In the discovery subset, we utilized regularized logistic regression models with Lasso penalty[13] to select the most important predictors for in-hospital mortality from a large feature set of 67 important clinical variables (**Table S1**).

For the variables selected by the penalized logistic regressions, we performed an ordinary logistic regression using the validation subset to estimate odds ratios (ORs) and the corresponding 95% CIs. For the variables that were confirmed to be statistically significant, we calculated AUC differences between leave-one-predictor-out models and the full model in the validation subset to assess the relative importance of each predictor. Moreover, we performed parallel analyses using only baseline variables, and compared the predictive performance of these models with the above ones using post-anticoagulant D-Dimer information in the validation subset. We compared the 10-fold cross-validation prediction AUCs between the baseline model and the full model with post-anticoagulant D-dimer groups among 100 randomly selected bootstrap samples. All statistical analyses were repeated in complete case analysis among samples without missing post-anticoagulant D-dimer data, with similar results (**Table S3)**.

We analyzed a subset of 668 patients in our cohort that had at least two post-anticoagulant fibrinogen measurements in order to determine if changes in D-Dimer levels reflected onset of disseminated intravascular coagulopathy (DIC) or if a more COVID-specific process. As fibrinogen would not be affected by anticoagulation directly, we used the mean and trend as a proxy for DIC and added these covariates in the penalized logistic regression.

Results

Baseline Characteristics of Study Cohort

After applying the selection criteria to the COVID-19 database (n=65,501 patients), the final study cohort consisted of 1835 laboratory-confirmed COVID-19 positive adult patients who were hospitalized in the MSHS between February 25 and May 31, 2020 (**Figure 1**). Among them, 470 (26%) study patients died during hospitalization and 1365 (74%) were discharged alive. Patients who died during hospitalization were generally older, had more comorbidities, presented with signs of more severe respiratory distress (higher respiratory rates and lower minimum oxygen saturation), had worse kidney function, higher levels of inflammatory markers (ferritin, CRP, LDH) and higher baseline D-dimers ($p<0.001$ for all comparisons after Bonferroni correction). Although not statistically significant, patients who died during hospitalization also experienced a longer time between admission and the start of therapeutic doses of anticoagulation (**Tables 1 and S1)**.

Post-anticoagulant D-dimer levels and COVID-19 mortality

After beginning therapeutic doses of anticoagulation, the mean D-dimer was significantly higher for patients who died vs. those who were discharged from the hospital (median 3.71 ug/ml; [interquartile range, IQR 1.98, 8.05 ug/ml] vs. 1.69 ug/ml [IQR 0.86, 3.41 ug/ml], respectively; $p<0.001$). The difference in mean post-anticoagulant D-dimers between discharged vs. deceased groups was greater than the difference observed at baseline (2.02 ug/ml vs. 0.39 ug/ml, respectively; $p<0.001$). An increasing trend of post-anticoagulant D-dimers was observed for patients who died in the hospital (median slope: 0.09), while a decreasing trend was seen for those who were discharged (median slope: -0.05), with a significant difference between the

changes in slope (p<0.001) (**Figure 2A**). The predictive power for in-hospital mortality of the logistic regression model with post-anticoagulant D-dimer mean level and its trend (AUC 0.76; 95% CI 0.74, 0.78) was significantly greater than the model with the baseline D-dimer (AUC 0.59; 95% CI 0.55, 0.61). Including baseline D-dimer levels to the model based on post-anticoagulant D-dimer did not further improve the prediction (AUC 0.76; 96%CI [0.74, 0.78]) (**Figure 2B**).

By stratifying the study cohort into four similar sized groups combining high vs. low post-anticoagulant D-dimer means and increasing vs. decreasing trend, a significant difference was observed in the in-hospital mortality rates for patients within HI (49%) vs. HD (27%) vs. LI (21%) vs. LD (9%) groups (p<0.001) (**Figure 3A**). Patients with high mean post-anticoagulant D-dimer (>=2.5 ug/ml) were typically older, had more comorbidities, lower oxygen saturation, higher baseline D-dimers, higher leukocyte counts with lower lymphocyte percentages, worse kidney function and higher inflammatory markers than patients with low mean post-anticoagulant D-dimer (<2.5 ug/ml; p<0.001 for all comparisons) (**Table S2**). Among patients within the high or low mean post-anticoagulant D-dimer groups, only lower baseline D-dimer was associated with increasing D-dimer trends (p<0.001) (**Figure 3B**).

Post-anticoagulant D-dimer groups and in-hospital mortality

Jointly modeling post-anticoagulant D-dimer groups and 65 baseline covariates with penalized logistic regressions, 12 variables were selected to be predictive of in-hospital mortality through 10-fold cross validation based on the discovery subset. Among these,

10 variables were confirmed to be significantly associated with in-hospital mortality based on the validation subset (**Figure 4A)**. Compared to patients in the LD post-anticoagulant D-dimer group, patients in the HI post-anticoagulant D-dimer group were significantly the most likely to die during hospitalization (ORadj = 6.58; 95% CI [3.81,11.16]), followed by those in the LI post-anticoagulant D-dimer group (ORadj = 4.06; 95% CI [2.23, 7.38]) and HD group (ORadj = 2.37; 95% CI [1.37, 4.09]), after adjusting for the other pre-selected covariates. The post-anticoagulant D-dimer group was a stronger predictor of mortality than other covariates, such as acute kidney injury (ORadj = 1.99; 95% CI [1.34, 2.96]), or acute respiratory distress syndrome (ARDS; ORadj = 2.46; 95% CI 1.44-4.20) at admission (**Figure 4A)**. The baseline D-dimer value was not a significant predictor of mortality and was not selected in the final model. Additionally, we found consistent results that post-anticoagulant D-Dimer remained the most significant predictor of in-hospital mortality after adjusting for fibrinogen (Figure S2).

Robustness of the findings

When we evaluated the impact of individual predictors in the above model by calculating the change of the model's AUC after excluding one variable at a time, age resulted in the largest AUC change (0.041), followed by HD post-anticoagulant D-dimer group (0.039), HI post-anticoagulant D-dimer group (0.024), platelet count (0.020), minimum oxygen saturation (0.020) and then LI post-anticoagulant D-dimer group (0.019) (**Figure 4B**). The combined effects of the four post-anticoagulant D-dimer groups had the greatest impact on model prediction (AUC change 0.054). Furthermore, when we

compared the predictive powers of the above model based on post-anticoagulant D-dimer groups as well as the selected baseline variables with the predictive powers of a model based on only baseline variables, the AUCs of the post-anticoagulant D-dimer models are significantly higher than that of the baseline models based on 100 bootstrap data sets generated from the validation subset (**Figure 4C**).

Discussion

In this retrospective study of 1,835 adult patients on therapeutic doses of anticoagulation for thromboprophylaxis during admission for severe COVID-19 illness, we found high and independent predictive power of post-anticoagulant D-dimer levels for in-hospital mortality, while taking into consideration 65 other important covariates including patient demographics, comorbidities, vital signs and laboratory tests at baseline. We further identified patient-specific trajectories of D-dimers values after anticoagulant therapy, which demonstrated significant differences in mortality rates and had the greatest impact on model prediction among all clinical characteristics under consideration. Therefore, changes in D-dimer levels and trends following initiation of therapeutic doses of anticoagulation are novel prognostic biomarkers that should be considered in the management of hospitalized COVID-19 patients.

Elevated D-dimer is among the most consistent markers of poor outcomes in COVID-19 patients. Several retrospective studies of hospitalized patients in Wuhan, China have demonstrated elevated D-dimer levels on admission with differing optimal cutoffs

(starting at >0.5 ug/ml) to be predictive of in-hospital mortality[3,6,14 5]. However, D-dimer at the time of admission was not a significant predictor of mortality in our hospitalized cohort of COVID-19 patients with severe illness on therapeutic doses of anticoagulation for thromboprophylaxis. Instead, we found post-anticoagulant D-dimer levels to be highly predictive of in-hospital mortality in this group, with patients in the HI group 6.58 times more likely to die during the hospitalization than patients in the LD group. Interestingly, patients in the LI post-anticoagulant D-dimer group had a higher risk of dying than those in the HD group, suggesting that the trend of the D-dimer following anticoagulation is more important than the three-day mean. With limited specific baseline patient characteristics associated with post-anticoagulant D-dimer trends, it is critical that serial D-dimer measurements are collected for accurate prediction of in-hospital mortality.

D-dimer is commonly measured throughout the hospitalization of severely ill COVID-19 patients. However, there is no consensus on how to interpret changes in D-dimer levels in this context[15]. We found that the ability of D-dimer to predict in-hospital mortality was not affected by fibrinogen levels, indicating the hypercoagulability is the result of a more COVID-specific process rather than DIC. Once on therapeutic doses of anticoagulation, elevated D-dimer levels could be expected to decrease or normalize reflecting the cessation of new clot formation. However, persistently elevated or rising D-dimer levels following anticoagulation in COVID-19 patients may signify continued risk of large vessel thrombotic events[16,17]. In a study of 608 patients who completed anticoagulation for VTE, patients with persistently elevated D-dimer levels were 2.27 fold more likely to

experience recurrent VTE than those who had normalization of D-dimer[16]. Furthermore, recent autopsy data from COVID-19 patients demonstrated severe endothelial injury associated with intracellular virus resulting in widespread micoangiopathy and pulmonary capillary microthrombi compared to matched autopsies from influenza A (H1N1) patients[18]. Therefore, D-dimer levels and trends appear to be capturing angiocentric progression associated with poor outcomes.

There are strengths and limitations to this study worth discussing. We were able to rapidly evaluate the impact of over 65 clinical features on in-hospital mortality for hospitalized COVID-19 patients with the highest risk of poor outcomes. In order to do so, we present the largest experience reporting the clinical outcomes of hospitalized COVID-19 patients receiving therapeutic doses of anticoagulation for thromboprophylaxis. However, patients treated at a single tertiary hospital network in New York City may not be representative of the general population in the US and worldwide. Other limitations include that there may be imprecisions of laboratory assays, which can alter the assessment of D-dimer. In addition, we were unable to account for unmeasured confounders that may affect D-dimer levels, a particular limitation inherent to all observational studies.

In summary, D-dimer levels and trends should be widely incorporated into the management protocols for hospitalized COVID-19 patients on anticoagulation. We highlight an important subset of patients associated with especially poor outcomes that may benefit from early escalation to Intensive Care Unit (ICU) care and, if proven

effective in this setting, emerging disease modifying treatments (i.e., remdesivir, corticosteroids) that may help reduce virus spread and/or COVID-associated hyperinflammation[19–21]. Conversely, patients in low-risk D-dimer groups following administration of therapeutic doses of anticoagulation may be appropriate for switch to prophylactic anticoagulant doses or de-escalation of care from ICU settings. Future studies should further validate changes in D-dimer following anticoagulation as a prognostic biomarker and consider D-dimer when determining the effectiveness of COVID-19 interventions in different risk groups.

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Acknowledgement
We would like to express our sincerest condolences to the patients and their families who were affected by the COVID-19 pandemic. We greatly appreciate the health care providers who contributed to the care of these patients. The Mount Sinai de-identified COVID-19 database was supported through the computational and data resources and staff expertise provided by Scientific Computing at the Icahn School of Medicine at Mount Sinai. The authors also acknowledge the support of the Biostatistics Shared Resource Facility, Icahn School of Medicine at Mount Sinai, and NCI Cancer Center Support Grant P30 CA196521-01.

Author Contributions: Conception and design, Manuscript Writing, Final approval: All authors; Collection, assembly, analysis and interpretation of data: XS, ET, PW, RRV.

COI disclosure: Authors have no competing interests to declare

Data Availability
The datasets analyzed during the current study are not publicly available due to United States Federal Health Insurance Portability and Accountability Act (HIPAA) compliance. A de-identified dataset may be available from the corresponding authors on reasonable request. The Icahn School of Medicine at Mount Sinai Institutional Review Board considered the study exempt. The lead author and all authors affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Table 1. Characteristics of Hospitalized COVID-19 Patients According to Survival Status

Characteristics	Discharged from Hospital (N=1365)	Deceased in Hospital (N=470)	P-value
Age (years), median (IQR[1])	65 [54, 75]	73 [65, 83]	< 2.2e-16*
Male sex, N (%)	805 (59.0)	262 (55.7)	0.242
Race/Ethnicity, N (%)			
White	275 (20.1)	111 (23.6)	0.374
Black	277 (20.3)	83 (17.7)	
Hispanic	404 (29.6)	138 (29.4)	
Other	236 (17.3)	73 (15.5)	
Missing	173 (12.7)	65 (13.8)	
Smoking Status, N (%)			
Never smoker	688 (50.4)	229 (48.7)	0.714
Ever smoker	384 (28.1)	132 (28.1)	
Missing	293 (21.5)	109 (23.2)	
Baseline comorbidities, N (%) (Details in Table S1)			
0	456 (33.4)	89 (18.9)	1.4e-08*
1-2	534 (39.1)	196 (41.7)	
>2	375 (27.5)	185 (39.4)	
BMI[2] (kg/m^2), median (IQR)	27.55 [23.88, 32.12]	27.46 [24.32, 32.48]	0.331
Admission Vital Signs, median (IQR)			
Systolic Blood Pressure maximum (mmHg)	143 [129, 159]	144 [129, 161]	0.531
Diastolic Blood Pressure maximum (mmHg)	83 [76, 92]	81 [73, 91]	0.017
Heart Rate maximum (beats/minute)	101.00 [90.75, 114.00]	103.00 [91.00, 120.75]	0.009
Respiratory Rate maximum (breaths/minute)	22 [20, 28]	24 [20, 30]	9.7e-06*
Temperature maximum (Fahrenheit)	99.8 [98.6, 101.3]	99.6 [98.6, 101.1]	0.064
Oxygen Saturation minimum (%)	93 [90, 95]	90 [84, 94]	3.4e-16*
Baseline Laboratory Tests, median (IQR)			
White Blood Cell (x10E3/uL)	7.60 [5.50, 10.40]	8.14 [5.90, 12.28]	0.011
Lymphocyte %	13.05 [8.30, 18.58]	11.00 [7.25, 16.95]	0.003
Neutrophil %	78.60 [70.45, 84.77]	81.90 [73.40, 87.10]	2.8e-05*
Hemoglobin (g/dL)	12.70 [11.10, 13.90]	12.90 [11.10, 14.10]	0.448
Platelet (x10E3/uL)	221.00 [167.00, 293.00]	187.00 [147.00, 244.00]	1.7e-09*
Serum Creatinine (mg/dL)	0.95 [0.73, 1.41]	1.20 [0.82, 2.00]	1.2e-4*

Estimated Glomerular Filtration Rate (ml/min/1.73m^2)	54.00 [30.15, 77.00]	41.28 [26.00, 58.33]	7.3e-11*
Alanine Aminotransferase (u/L)	30.00 [19.00, 50.00]	30.00 [20.25, 50.75]	0.885
Aspartate Aminotransferase (u/L)	40.00 [27.00, 63.50]	48.00 [33.00, 71.75]	1.7e-4*
Total Bilirubin (mg/dL)	0.60 [0.40, 0.80]	0.50 [0.40, 0.80]	0.356
C-Reactive Protein (mg/L)	113.50 [53.70, 194.30]	159.10 [90.82, 235.70]	1.0e-09*
Ferritin (ng/mL)	697.00 [330.00, 1512.00]	1038.00 [480.00, 2092.00]	8.9e-05 *
Lactate Dehydrogenase (u/L)	412.00 [312.00, 528.50]	516.50 [381.25, 660.75]	< 2.2e-16*
Baseline D-dimer (ug/mL)	1.37 [0.79, 2.46]	1.76 [1.08, 2.92]	1.6e-05*
Days from admission to start of anticoagulation, median (IQR)	0.55 [0.20, 1.68]	0.67 [0.24, 2.13]	0.017
[1] Interquartile Range; [2]Body Mass Index; * Significant after multiple testing			

Figure Legend:

Figure 1. Selection of Study Cohort to Evaluate Role of Post-Anticoagulant D-Dimer as Predictive Biomarker for Mortality.

Figure 2. D-dimer distribution and its association with patient outcomes. (A) Boxplot of baseline and post-A/C D-dimer values. (B) ROCs of prediction models with baseline D-dimer, post-A/C D-dimer and both (AUCs 0.59, 0.76 and 0.76, respectively).

Figure 3. In-hospital mortality and baseline patient characteristics of four Post-A/C D-dimer groups. (A) In-hospital mortality rates by post-A/C D-dimer groups. (B) Baseline characteristics of patients with different D-dimer groups after A/C therapy.

Figure 4. A multivariate prediction model for patients' outcome. (A) ORs estimates, 95% CI for variables selected in the post-A/C model. (B) AUC differences between leave-one-predictor-out models and the full model for variables selected in the post-A/C model. (C) Comparison of 10-fold CV AUCs between baseline model and post-A/C model in 100 bootstrap samples.

Figure S1: Incremental AUC by adding 1 more day of post-anticoagulant D-dimer measurements among a subset of 687 patients that have 7 day observation time. After 3 days, the incremental AUC is marginal.

Figure S2: Adjusted ORs estimates and 95% CI for model including post-anticoagulant fibrinogen levels in subset of 668 patients. Post-anticoagulant D-Dimer groups remain the most critical predictors of in-hospital mortality.

Figure 1

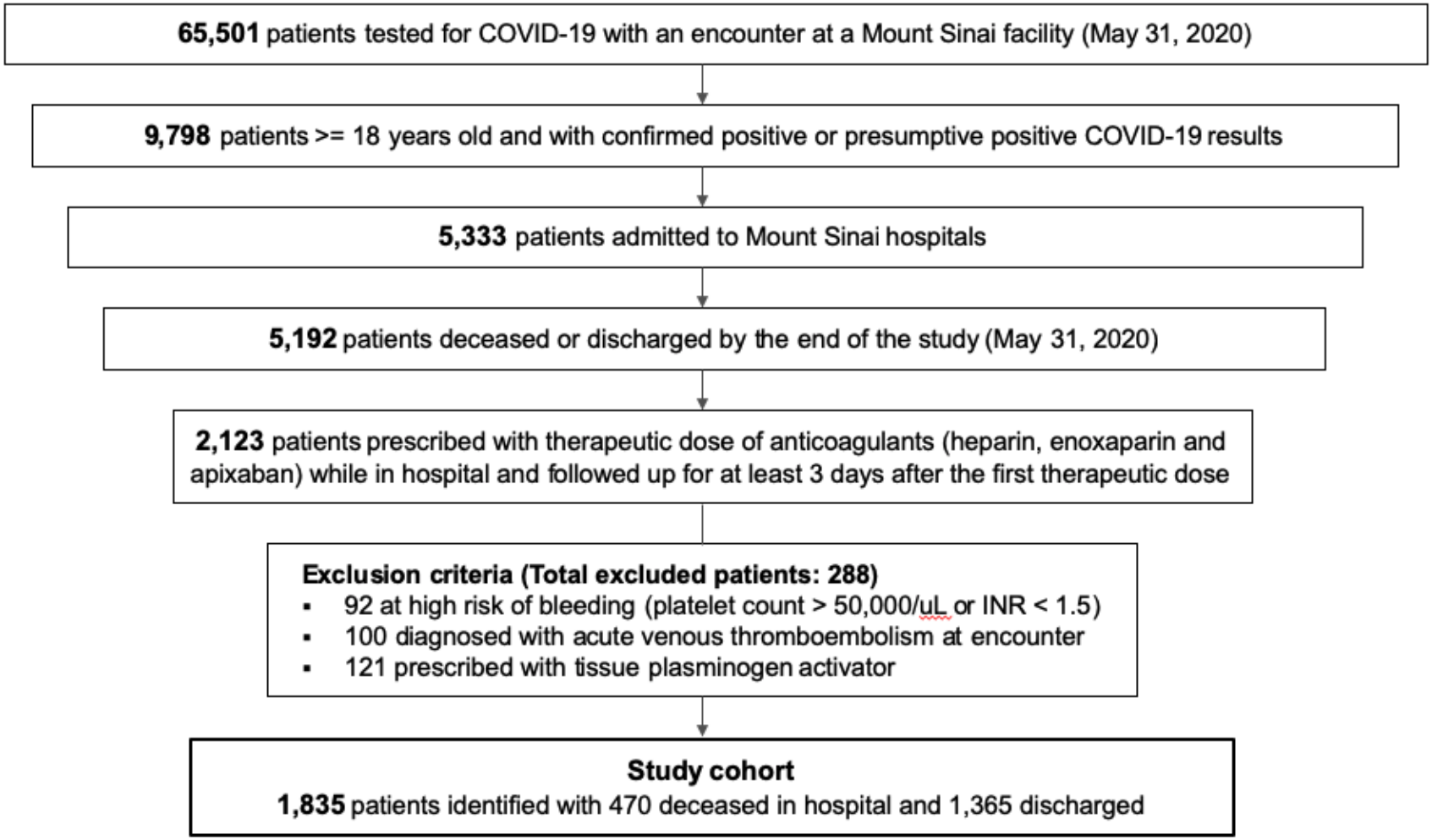

65,501 patients tested for COVID-19 with an encounter at a Mount Sinai facility (May 31, 2020)
9,798 patients >= 18 years old and with confirmed positive or presumptive positive COVID-19 results
5,333 patients admitted to Mount Sinai hospitals
5,192 patients deceased or discharged by the end of the study (May 31, 2020)
2,123 patients prescribed with therapeutic dose of anticoagulants (heparin, enoxaparin and apixaban) while in hospital and followed up for at least 3 days after the first therapeutic dose
Exclusion criteria (Total excluded patients: 288)
92 at high risk of bleeding (platelet count > 50,000/uL or INR < 1.5)
100 diagnosed with acute venous thromboembolism at encounter
121 prescribed with tissue plasminogen activator
Study cohort
1,835 patients identified with 470 deceased in hospital and 1,365 discharged

Figure 2.

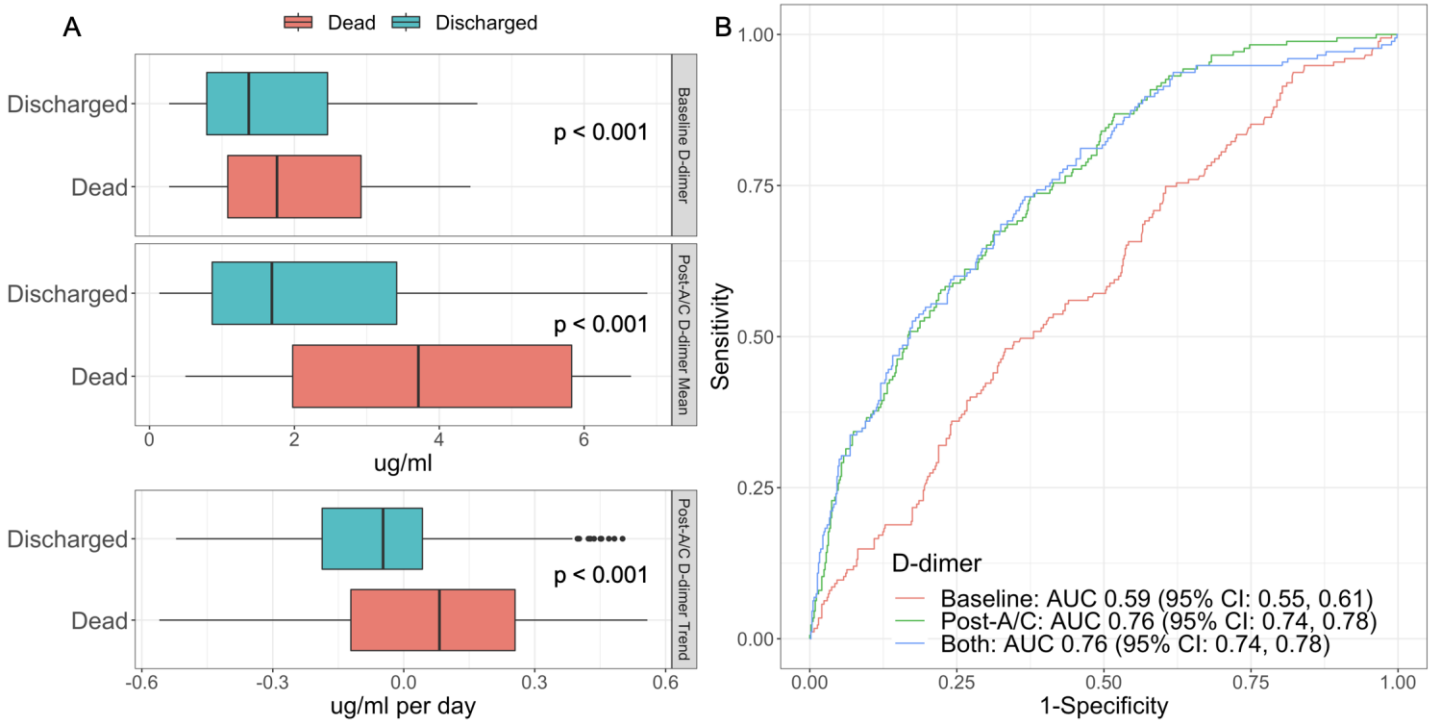

A
Dead
Discharged
Discharged
Dead
p < 0.001
Baseline D-dimer
Discharged
Dead
p < 0.001
Post-A/C D-dimer Mean
0
2
4
6
ug/ml
Discharged
Dead
p < 0.001
Post-A/C D-dimer Trend
-0.6
-0.3
0.0
0.3
0.6
ug/ml per day
B
1.00
0.75
0.50
0.25
0.00
Sensitivity
D-dimer
Baseline: AUC 0.59 (95% CI: 0.55, 0.61)
Post-A/C: AUC 0.76 (95% CI: 0.74, 0.78)
Both: AUC 0.76 (95% CI: 0.74, 0.78)
0.00
0.25
0.50
0.75
1.00
1-Specificity

Figure 3.

A

Mean post-A/C D-dimer	Change over time	No. of patients	Mortality rate
High (≥2.5 ug/ml)	Increase (≥0 ug/ml per day)	430	49%
	Decrease (<0 ug/ml per day)	508	27%
Low (<2.5 ug/ml)	Increase (≥0 ug/ml per day)	337	21%
	Decrease (<0 ug/ml per day)	560	9%

B

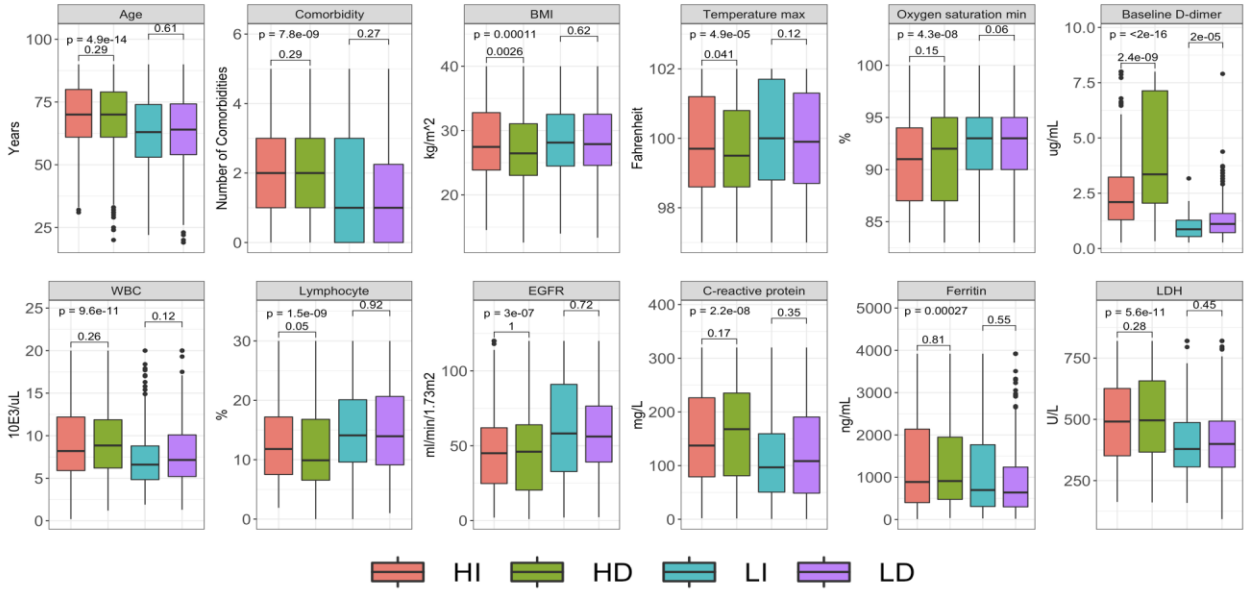
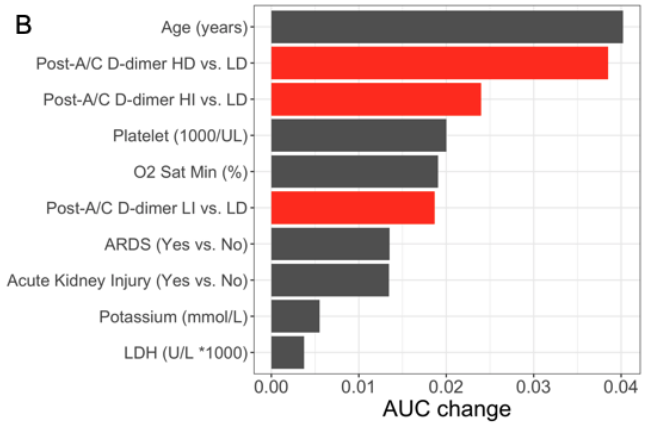


Figure 4.

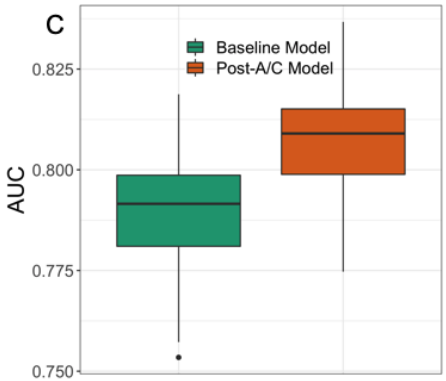
A

Variable	OR	95% CI
Post-A/C D-dimer HI vs. LD	6.52	(3.81,11.16)
Post-A/C D-dimer LI vs. LD	4.06	(2.23,7.38)
ARDS (Yes vs. No)	2.46	(1.44,4.20)
Post-A/C D-dimer HD vs. LD	2.37	(1.37,4.09)
Acute Kidney Injury (Yes vs. No)	1.99	(1.34,2.96)
Potassium (mmol/L)	1.29	(1.03,1.60)
Age (years)	1.06	(1.04,1.07)
LDH (U/L *1000)	1.33	(1.03,1.72)
Platelet (1000/UL)	0.99	(0.99,1.00)
O2 Sat Min (%)	0.94	(0.92,0.97)

B



C



Supplementary Figures and Tables:

Figure Legends:

Figure S1: Incremental AUC by adding 1 more day of post-anticoagulant D-dimer measurements among a subset of 687 patients that have 7 day observation time. After 3 days, the incremental AUC is marginal.

Figure S2: Adjusted ORs estimates and 95% CI for model including post-anticoagulant fibrinogen levels in subset of 668 patients. Post-anticoagulant D-Dimer groups remain the most critical predictors of in-hospital mortality.

Figure S1:

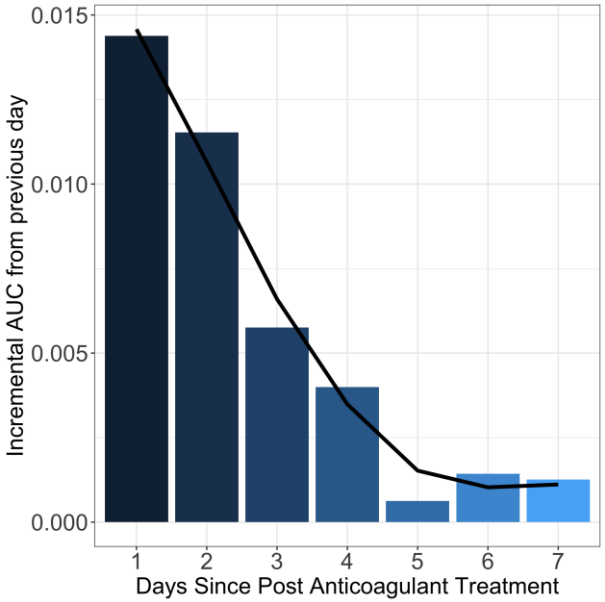


Figure S2:

Variable	OR	95% CI
Post-A/C D-dimer HI vs. LD	20.86	(6.87,63.31)
Post-A/C D-dimer LI vs. LD	7.8	(2.28,26.69)
Post-A/C D-dimer HD vs. LD	7.01	(2.3,21.31)
ARDS (Yes vs. No)	2.46	(1.29,4.71)
Age (years)	1.03	(1.01,1.05)
Monocyte (%)	0.89	(0.82,0.96)

Table S1: Characteristics of Hospitalized COVID-19 Patients Stratified by Survival			
Characteristic	**Discharged from Hospital**	**Deceased in Hospital**	**P-value**
N	1365	470	
Age in years - median [IQR]	65 [54, 75]	73 [65, 83]	<0.001*
Male sex — no. (%)	805 (59.0)	262 (55.7)	0.242
Race and ethnic group — no. (%)			0.374
Non-Hispanic white	275 (20.1)	111 (23.6)	
Non-Hispanic black	277 (20.3)	83 (17.7)	
Hispanic	404 (29.6)	138 (29.4)	
Other	236 (17.3)	73 (15.5)	
Missing data	173 (12.7)	65 (13.8)	
Smoking status — no. (%)			0.714
Never smoker	688 (50.4)	229 (48.7)	
Ever smoker	384 (28.1)	132 (28.1)	
Missing data	293 (21.5)	109 (23.2)	
Baseline diagnoses — no. (%)			
Asthma	88 (6.4)	26 (5.5)	0.55
Chronic obstructive pulmonary disease	62 (4.5)	30 (6.4)	0.146
Hypertension	489 (35.8)	211 (44.9)	0.001*
Obstructive sleep apnea	31 (2.3)	8 (1.7)	0.581
Obesity	115 (8.4)	38 (8.1)	0.894
Diabetes	348 (25.5)	117 (24.9)	0.844
Chronic kidney disease	161 (11.8)	68 (14.5)	0.152
HIV	24 (1.8)	7 (1.5)	0.855
Cancer	110 (8.1)	45 (9.6)	0.356
Coronary artery disease	162 (11.9)	84 (17.9)	0.001
Atrial fibrillation	84 (6.2)	50 (10.6)	0.002

Heart failure	86 (6.3)	35 (7.4)	0.45
Chronic viral hepatitis	21 (1.5)	2 (0.4)	0.103
Alcoholic nonalcoholic liver disease	28 (2.1)	8 (1.7)	0.781
Acute respiratory distress syndrome	107 (7.8)	110 (23.4)	<0.001*
Acute kidney injury	260 (19.0)	205 (43.6)	<0.001*
Cerebral infarction	61 (4.5)	26 (5.5)	0.418
Intracerebral hemorrhage	5 (0.4)	2 (0.4)	1
BMI (kg/m^2) - median [IQR]	27.55 [23.88, 32.12]	27.46 [24.32, 32.48]	0.331
Initial vital signs — median [IQR]			
Systolic blood pressure maximum — mm Hg	143 [129, 159]	144 [129, 161]	0.531
Diastolic blood pressure maximum — mm Hg	83 [76, 92]	81 [73, 91]	0.017
Heart rate maximum — beats/min	101.00 [90.75, 114.00]	103.00 [91.00, 120.75]	0.009
Respiratory rate maxmum — breaths/min	22 [20, 28]	24 [20, 30]	<0.001*
Temperature max — fahrenheit	99.80 [98.60, 101.30]	99.60 [98.60, 101.10]	0.064
Oxygen saturation minimum — %	93 [90, 95]	90 [84, 94]	<0.001*
Days from encounter to first therapeutic dose of anticoagulant — median [IQR]	0.55 [0.20, 1.68]	0.67 [0.24, 2.13]	0.017
Laboratory tests — median [IQR]			
Baseline D-dimer (ug/mL)	1.37 [0.79, 2.46]	1.76 [1.08, 2.92]	<0.001*

Platelet (x10E3/uL)	221.00 [167.00, 293.00]	187.00 [147.00, 244.00]	<0.001*
Mean platelet volume mpv (FL)	8.40 [7.70, 9.20]	8.70 [7.90, 9.53]	0.002
Red blood cell (RBC) count (x10E6/uL)	4.27 [3.79, 4.76]	4.36 [3.77, 4.75]	0.564
While blood cell (WBC) count (x10E3/uL)	7.60 [5.50, 10.40]	8.14 [5.90, 12.28]	0.011
Lymphocyte % (%)	13.05 [8.30, 18.58]	11.00 [7.25, 16.95]	0.003
Lymphocyte no. (x10E3/uL)	1.00 [0.70, 1.30]	0.90 [0.60, 1.30]	0.024
Neutrophil % (%)	78.60 [70.45, 84.77]	81.90 [73.40, 87.10]	<0.001*
Neutrophil no. (x10E3/uL)	5.90 [3.90, 8.71]	6.65 [4.50, 10.53]	0.002
Monocyte % (%)	6.40 [4.30, 9.10]	5.10 [3.30, 8.70]	<0.001*
Monocyte no. (x10E3/uL)	0.50 [0.30, 0.70]	0.40 [0.30, 0.70]	0.012
Basophil % (%)	0.20 [0.10, 0.40]	0.10 [0.00, 0.30]	<0.001*
Basophil no. (x10e3/uL)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.104
Eosinophil % (%)	0.20 [0.00, 0.70]	0.10 [0.10, 0.30]	0.018
Eosinophil no. (x10E3/uL)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.002
Mean corpuscular hemoglobin (MCH)	29.90 [28.30,	29.90	0.806

(pg)	31.10]	[28.10, 31.40]	
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	32.90 [32.10, 33.60]	32.65 [31.80, 33.40]	0.011
Mean corpuscular volume (MCV) (FL)	90.40 [86.50, 93.80]	91.15 [86.82, 94.90]	0.074
Serum creatinine (mg/dL)	0.95 [0.73, 1.41]	1.20 [0.82, 2.00]	<0.001*
C-reactive protein (mg/L)	113.50 [53.70, 194.30]	159.10 [90.82, 235.70]	<0.001*
Estimated glomerular filtration rate (EGFR) (ml/min/1.73m2)	54.00 [30.15, 77.00]	41.28 [26.00, 58.33]	<0.001*
Blood urea nitrogen (BUN) (mg/dL)	18.00 [12.00, 31.00]	26.00 [15.25, 47.75]	<0.001*
Alanine aminotransferase (ALT) (u/L)	30.00 [19.00, 50.00]	30.00 [20.25, 50.75]	0.885
aspartate aminotransferase (AST) (U/L)	40.00 [27.00, 63.50]	48.00 [33.00, 71.75]	<0.001*
Total bilirubin (mg/dL)	0.60 [0.40, 0.80]	0.50 [0.40, 0.80]	0.356
Glucose (mg/dL)	116.50 [97.00, 164.75]	133.00 [105.00, 186.50]	<0.001*
Lactate dehydrogenase (LDH) (U/L)	412.00 [312.00, 528.50]	516.50 [381.25, 660.75]	<0.001*
Hemoglobin (g/dL)	12.70 [11.10, 13.90]	12.90 [11.10, 14.10]	0.448
Ferritin (ng/mL)	697.00 [330.00, 1512.00]	1038.00 [480.00,	<0.001*

		2092.00]	
Calcium (mg/dL)	8.30 [7.90, 8.70]	8.20 [7.70, 8.60]	0.001
Albumin (g/dL)	3.00 [2.70, 3.40]	2.90 [2.60, 3.20]	0.001
Sodium (MEQ/L)	138.00 [135.00, 140.00]	137.50 [134.00, 144.00]	0.102
Potassium (mmol/L)	4.20 [3.70, 4.60]	4.30 [3.83, 4.88]	0.002
Chloride (mEq/L)	103.00 [99.00, 106.00]	104.00 [100.00, 108.00]	<0.001*
Anion gap (mEq/L)	11.90 [10.00, 14.00]	12.20 [10.20, 15.00]	0.002
Post A/C D-dimer values			
Mean D-dimer (ug/ml)	1.69 [0.86, 3.41]	3.71 [1.98, 8.05]	<0.001*
Trend D-dimer (ug/ml per day)	-0.05 [-0.21, 0.04]	0.09 [-0.12, 0.60]	<0.001*

Table S2: Characteristics of Hospitalized COVID-19 Patients Stratified by post-anticoagulant D-dimer groups								
Characteristic	**Patients with high and increasing D-dimer**	**Patients with high and decreasing D-dimer**	**Patients with low and increasing D-dimer**	**Patients with low and decreasing D-dimer**	**P-value for Indepe-ndence**	**P-value for high vs low groups**	**P-value for Increasing vs decreasing in high group**	**P-value for Increasing vs decreasing in low group**
N	430	508	337	560				
In-hospital mortality — no. (%)	212 (49.3)	137 (27.0)	70 (20.8)	51 (9.1)				
Age in years - median [IQR]	70 [61, 80]	70.00 [61.00, 79.00]	63.00 [53.00, 74.00]	64.00 [54.00, 74.25]	<0.001	<0.001	0.293	0.609
Male sex — no. (%)	253 (58.8)	311 (61.2)	204 (60.5)	299 (53.4)	0.045	0.087	0.499	0.044
Race and ethnic group — no. (%)						0.303	0.882	0.122
Non-Hispanic white	89 (20.7)	103 (20.3)	67 (19.9)	127 (22.7)				
Non-Hispanic black	89 (20.7)	113 (22.2)	74 (22.0)	84 (15.0)				
Hispanic	126 (29.3)	143 (28.1)	100 (29.7)	173 (30.9)				
Other	66 (15.3)	86 (16.9)	56 (16.6)	101 (18.0)				
Missing data	60 (14.0)	63 (12.4)	40 (11.9)	75 (13.4)				
Smoking status — no. (%)						0.832	0.472	0.79

Never smoker	208 (48.4)	264 (52.0)	171 (50.7)	274 (48.9)				
Ever smoker	120 (27.9)	138 (27.2)	97 (28.8)	161 (28.7)				
Missing data	102 (23.7)	106 (20.9)	69 (20.5)	125 (22.3)				
No of baseline comorbidities — no. (%)					<0.001	<0.001	0.456	0.355
0	88 (20.5)	121 (23.8)	121 (35.9)	215 (38.4)				
1-2	193 (44.9)	215 (42.3)	117 (34.7)	205 (36.6)				
3+	149 (34.7)	172 (33.9)	99 (29.4)	140 (25)				
Baseline diagnoses — no. (%)								
Asthma	20 (4.7)	23 (4.5)	30 (8.9)	41 (7.3)	0.022	0.004	1	0.471
Chronic obstructive pulmonary disease	28 (6.5)	18 (3.5)	22 (6.5)	24 (4.3)	0.087	0.91	0.052	0.187
Hypertension	179 (41.6)	211 (41.5)	114 (33.8)	196 (35.0)	0.021	0.002	1	0.776
Obstructive sleep apnea	10 (2.3)	7 (1.4)	7 (2.1)	15 (2.7)	0.517	0.43	0.402	0.733
Obesity	37 (8.6)	30 (5.9)	36 (10.7)	50 (8.9)	0.084	0.07	0.141	0.455
Diabetes	112 (26.0)	140 (27.6)	79 (23.4)	134 (23.9)	0.446	0.138	0.655	0.932

Chronic kidney disease	62 (14.4)	79 (15.6)	36 (10.7)	52 (9.3)	0.007	0.001	0.695	0.572
HIV	6 (1.4)	12 (2.4)	4 (1.2)	9 (1.6)	0.543	0.549	0.403	0.825
Cancer	32 (7.4)	48 (9.4)	26 (7.7)	49 (8.8)	0.677	0.964	0.327	0.676
Coronary artery disease	58 (13.5)	73 (14.4)	48 (14.2)	67 (12.0)	0.656	0.515	0.769	0.376
Atrial fibrillation	35 (8.1)	33 (6.5)	29 (8.6)	37 (6.6)	0.536	1	0.4	0.328
Heart failure	33 (7.7)	27 (5.3)	26 (7.7)	35 (6.2)	0.398	0.799	0.181	0.479
Chronic viral hepatitis	3 (0.7)	7 (1.4)	4 (1.2)	9 (1.6)	0.634	0.598	0.489	0.825
Alcoholic nonalcoholic liver disease	6 (1.4)	8 (1.6)	10 (3.0)	12 (2.1)	0.395	0.189	1	0.582
Acute respiratory distress syndrome	94 (21.9)	73 (14.4)	24 (7.1)	26 (4.6)	<0.001	<0.001	0.004	0.157
Acute kidney injury	167 (38.8)	167 (32.9)	58 (17.2)	73 (13.0)	<0.001	<0.001	0.067	0.106
Cerebral infarction	17 (4.0)	31 (6.1)	18 (5.3)	21 (3.8)	0.245	0.506	0.18	0.336
Intracerebral hemorrhage	2 (0.5)	1 (0.2)	2 (0.6)	2 (0.4)	0.815	0.953	0.885	1
BMI (kg/m^2) - median [IQR]	27.46 [23.86, 32.79]	26.46 [23.04, 31.06]	28.13 [24.48, 32.53]	27.90 [24.58, 32.54]	<0.001	0.001	0.003	0.621
Initial vital signs — median [IQR]								
Systolic blood pressure maximum — mm Hg	146.00 [131.25, 163.75]	145.00 [131.00, 163.00]	140.00 [127.00, 156.00]	141.00 [127.00, 156.00]	<0.001	<0.001	0.748	0.944

Diastolic blood pressure maximum — mm Hg	82.50 [74.00, 92.00]	84.00 [76.00, 93.00]	82.00 [75.00, 90.00]	82.00 [74.00, 90.00]	0.021	0.01	0.135	0.516
Heart rate maximum — beats/min	102.00 [89.00, 118.00]	104.00 [92.00, 117.00]	102.00 [91.00, 114.00]	100.00 [90.00, 113.00]	0.063	0.022	0.236	0.437
Respiratory rate maxmum — breaths/min	22.00 [20.00, 30.00]	22.00 [20.00, 30.00]	21.00 [20.00, 26.00]	21.50 [20.00, 26.00]	<0.001	<0.001	0.796	0.393
Temperature max — fahrenheit	99.70 [98.60, 101.20]	99.50 [98.60, 100.80]	100.00 [98.80, 101.70]	99.90 [98.70, 101.30]	<0.001	<0.001	0.054	0.132
Oxygen saturation minimum — %	91.00 [87.00, 94.00]	92.00 [87.00, 95.00]	93.00 [90.00, 95.00]	93.00 [90.00, 95.00]	<0.001	<0.001	0.163	0.059
Time from encounter to first therapeutic dose of anticoagulant — median [IQR]	0.71 [0.24, 2.57]	0.68 [0.22, 1.96]	0.54 [0.21, 1.71]	0.49 [0.18, 1.41]	0.001	<0.001	0.426	0.163
Initial laboratory tests — median [IQR]								
D-dimer (ug/mL FEU)	2.10 [1.30, 3.23]	3.35 [2.05, 7.14]	0.87 [0.54, 1.28]	1.11 [0.72, 1.58]	<0.001	<0.001	<0.001	<0.001
Platelet (x10E3/uL)	203.00 [163.00, 282.00]	226.00 [163.00, 290.50]	194.00 [150.00, 256.00]	216.00 [159.00, 285.50]	0.038	0.119	0.191	0.036
Mean platelet volume mpv (FL)	8.50 [7.80, 9.40]	8.60 [7.70, 9.50]	8.40 [7.70, 9.20]	8.40 [7.70, 9.20]	0.613	0.195	0.724	0.9

RBC count (x10E6/uL)	4.25 [3.69, 4.72]	4.13 [3.56, 4.69]	4.39 [3.98, 4.79]	4.33 [3.96, 4.80]	<0.001	<0.001	0.247	0.623
WBC count (x10E3/uL)	8.20 [5.90, 12.20]	8.85 [6.20, 11.88]	6.60 [4.84, 8.80]	7.15 [5.20, 10.10]	<0.001	<0.001	0.257	0.115
Lymphocyte % (%)	11.80 [7.50, 17.20]	9.90 [6.55, 16.80]	14.10 [9.60, 20.10]	13.95 [9.12, 20.65]	<0.001	<0.001	0.049	0.908
Lymphocyte no. (x10E3/uL)	0.90 [0.70, 1.30]	0.90 [0.60, 1.30]	0.90 [0.70, 1.30]	0.90 [0.70, 1.30]	0.425	0.108	0.715	0.785
Neutrophil % (%)	80.80 [72.62, 86.80]	81.85 [74.30, 87.00]	77.00 [69.60, 83.50]	77.10 [68.93, 84.18]	<0.001	<0.001	0.241	0.788
Neutrophil no. (x10E3/uL)	6.50 [4.25, 10.15]	7.35 [4.90, 10.45]	5.06 [3.50, 7.40]	5.40 [3.70, 7.80]	<0.001	<0.001	0.062	0.184
Monocyte no. (x10E3/uL)	0.50 [0.30, 0.70]	0.50 [0.30, 0.70]	0.50 [0.30, 0.70]	0.40 [0.30, 0.60]	0.045	0.04	0.67	0.048
Monocyte % (%)	6.05 [3.68, 9.23]	5.60 [4.00, 8.20]	6.60 [4.80, 9.60]	6.30 [4.00, 9.07]	0.011	0.01	0.225	0.114
Basophil number (x10e3/uL)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.192	0.253	0.078	0.797
Basophil percent (%)	0.10 [0.10, 0.30]	0.20 [0.10, 0.40]	0.20 [0.10, 0.40]	0.20 [0.10, 0.40]	0.006	0.001	0.147	0.861
Eosinophil no. (x10E3/uL)	0.00 [0.00, 0.00]	0.00 [0.00, 0.10]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.04	0.044	0.061	0.439
Eosinophil % (%)	0.20 [0.10, 0.40]	0.20 [0.00, 0.70]	0.10 [0.00, 0.50]	0.20 [0.00, 0.50]	0.198	0.132	0.123	0.646
MCH (pg)	29.80 [27.80,	30.20 [28.30,	29.50 [28.10,	29.90 [28.40,	0.263	0.816	0.225	0.111

	31.10]	31.20]	30.90]	31.10]				
MCHC (g/dL)	32.60 [32.00, 33.40]	32.70 [31.70, 33.50]	33.00 [32.10, 33.60]	33.00 [32.30, 33.60]	0.002	<0.001	0.694	0.677
MCV (FL)	90.40 [86.60, 94.70]	91.30 [86.95, 95.40]	89.80 [86.40, 92.40]	90.70 [86.85, 93.93]	0.018	0.027	0.2	0.056
Serum creatinine (mg/dL)	1.11 [0.83, 2.00]	1.14 [0.81, 2.02]	0.89 [0.70, 1.21]	0.87 [0.71, 1.20]	<0.001	<0.001	0.966	0.706
C-reactive protein (mg/L)	137.30 [79.03, 226.30]	167.82 [81.00, 235.15]	96.70 [50.52, 159.38]	108.35 [48.55, 190.49]	<0.001	<0.001	0.17	0.35
Estimated glomerular filtration rate (EGFR) (ml/min/1.73m2)	45.00 [24.75, 62.00]	46.00 [20.34, 64.00]	58.19 [32.75, 91.00]	56.14 [39.09, 76.50]	<0.001	<0.001	0.996	0.73
Blood urea nitrogen (BUN) (mg/dL)	23.00 [14.00, 43.00]	24.00 [15.00, 45.00]	16.00 [11.00, 26.00]	16.00 [11.00, 26.00]	<0.001	<0.001	0.343	0.904
Alanine aminotransferase (ALT) (u/L)	31.00 [19.00, 51.00]	30.00 [20.00, 50.00]	27.00 [19.00, 48.00]	32.00 [19.00, 50.00]	0.615	0.852	0.918	0.187
aspartate aminotransferase (AST) (U/L)	43.00 [30.00, 70.00]	43.00 [29.00, 69.50]	39.00 [27.00, 58.00]	42.00 [28.00, 63.00]	0.276	0.066	0.95	0.474
Total bilirubin (mg/dL)	0.60 [0.40, 0.80]	0.60 [0.40, 0.83]	0.50 [0.40, 0.80]	0.50 [0.40, 0.80]	0.076	0.015	0.352	0.641
Anion gap (mEq/L)	12.00 [10.00, 14.50]	12.50 [10.00, 15.00]	11.70 [10.00, 13.55]	11.30 [9.60, 13.00]	<0.001	<0.001	0.395	0.077

Albumin (g/dL)	3.00 [2.60, 3.30]	2.80 [2.50, 3.20]	3.10 [2.90, 3.50]	3.10 [2.80, 3.40]	<0.001	<0.001	0.009	0.093
Calcium (mg/dL)	8.30 [7.90, 8.70]	8.20 [7.70, 8.70]	8.20 [7.90, 8.70]	8.30 [8.00, 8.70]	0.011	0.013	0.067	0.183
Chloride (mEq/L)	104.00 [100.00, 107.00]	103.00 [99.00, 108.00]	103.00 [99.00, 106.00]	103.00 [99.00, 107.00]	0.007	0.001	0.413	0.59
Ferritin (ng/mL)	888.00 [399.50, 2137.50]	909.50 [476.25, 1947.75]	697.00 [308.00, 1768.00]	638.50 [299.50, 1239.50]	<0.001	<0.001	0.805	0.546
Glucose (mg/dL)	130.00 [100.00, 181.50]	128.00 [99.25, 184.00]	114.00 [96.00, 157.00]	115.00 [97.00, 152.50]	<0.001	<0.001	0.938	0.704
Hemoglobin (g/dL)	12.35 [10.70, 14.00]	12.50 [10.55, 13.80]	12.90 [11.80, 14.10]	13.10 [11.80, 14.10]	<0.001	<0.001	0.611	0.59
Lactate dehydrogenase (LDH) (U/L)	491.00 [351.25, 626.00]	496.00 [366.25, 657.00]	379.00 [306.00, 487.00]	399.50 [304.75, 492.75]	<0.001	<0.001	0.279	0.445
Potassium (mmol/L)	4.20 [3.90, 4.70]	4.30 [3.80, 4.80]	4.10 [3.70, 4.50]	4.10 [3.70, 4.50]	<0.001	<0.001	0.357	0.421
Sodium (MEQ/L)	138.00 [135.00, 141.00]	137.00 [134.00, 142.75]	138.00 [135.00, 140.00]	138.00 [135.00, 140.00]	0.443	0.181	0.38	0.995

Table S3: Unimputed Analysis						
term	OR	OR_lower	OR_upper	p.value	auc_change	p_bonferroni
Post-A/C D-dimer HI (Ref: LD)	8.6	3.3	22.8	1.49143E-05	0.045	0.000164057
ARDS	3.3	1.5	7.4	0.002982326	0.029	0.03280559
Post-A/C D-dimer LI (Ref: LD)	3.3	1.1	9.4	0.027278089	0.014	0.300058977
Acute Kidney Injury	2.5	1.3	5.0	0.006749455	0.025	0.074244004
Post-A/C D-dimer HD (Ref: LD)	1.9	0.7	5.4	0.209672822	0.018	1
basophil_percent	1.7	0.7	4.0	0.214340486	0.005	1
Age	1.0	1.0	1.1	0.000761589	0.030	0.008377481
sodium	1.0	1.0	1.1	0.434094472	0.019	1
LDH	1.0	1.0	1.0	0.334443227	0.003	1
Platelet	1.0	1.0	1.0	0.000123421	0.046	0.001357635
O2 Sat Min	0.9	0.9	1.0	0.00014103	0.019	0.001551334