**Supplementary Appendix**

**D-dimer and Death in Critically Ill Patients with COVID-19**

|  |  |
| --- | --- |
| **STOP_COVID-realigned** | **Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19** |

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**Supplemental Methods**

**Data Collection and Validation**

Data were collected using REDCap, a secure, HIPAA-compliant, web-based application. Wherever possible, data were captured using checkboxes rather manual entry to minimize keystroke errors. For data that required keystroke entry (e.g., laboratory values), we implemented validation ranges to flag potential errors in real-time. We also implemented automated data validation rules to flag errors in dates (e.g., if the date of death was entered as being before the date of ICU admission). Finally, all data were manually reviewed, and values that appeared incongruent or out of range were manually validated by confirming the accuracy of the data with the collaborator who entered it.

**Sensitivity Analysis of 28-day mortality in patients discharged from the hospital prior to 28 days**

In a subset of patients consisting of those who had been admitted to one of six hospitals in Boston, MA, and who had been discharged from the hospital prior to 28 days, we manually reviewed their charts or called them to ascertain their 28-day survival status. Among 50 patients reviewed, all 50 remained alive at 28 days.

**Multivariable Modeling of D-dimer’s Association with Mortality**

We prespecified the variables below for inclusion in the multivariable models based on clinical knowledge, biologic plausibility, and completeness of data. All patient data were abstracted through manual chart review by study staff. To minimize missingness of laboratory and physiologic data, we selected the worse value on ICU day 1 or 2.

1. D-dimer: highest value on ICU day 1 or ICU day 2, normalized by dividing value by assay-specific upper limit of normal (venous thromboembolism) cut-off. Categories: <2 times (x, ref), 2-3.9x, 4-7.9x, and ≥8x upper limit of normal
2. Age: 18-39 (ref); 40-49; 50-59; 60-69; 70-79; ≥80 years
3. Male sex
4. Race: White (ref), Black, Asian, and Other
5. Hypertension: per chart review
6. Diabetes mellitus: per chart review
7. Body mass index: <25; 25-29.9; 30-34.9; 35-39.9; and ≥40 kg/m2
8. Coronary artery disease: per chart review; any history of angina, myocardial infarction, or coronary artery bypass graft surgery
9. Congestive heart failure: per chart review, heart failure with preserved or reduced ejection fraction
10. Chronic obstructive pulmonary disease: per chart review
11. Current smoking status: per chart review, does not include vaping or non-tobacco products
12. Active malignancy: active malignancy (other than non-melanoma skin cancer) treated in the past year. Defined as cancer of the lung, breast, colorectal, prostate, gastric, pancreatic, melanoma, ovarian, brain, or other
13. Days from symptom onset to ICU admission: ≤3 vs. >3
14. Lymphocyte count (lowest value on ICU day 1 or day 2): <1000, ≥1000 per mm3, and missing
15. Invasive mechanical ventilation on ICU day 1 or day 2
16. Shock on ICU day 1 or day 2: defined as the requirement for ≥2 vasopressors
17. Renal, liver, and coagulation components of the Sequential Organ Failure Assessment (SOFA) score, highest score on ICU day 1 or day 2:

|  |  |
| --- | --- |
|  | Categories |
|  | 0a | 1 | 2b |
| SOFA Renal | Cr<1.2 and UOP≥500 | Cr 1.2-1.9 and UOP≥500 | Cr ≥2 or UOP<500c or acute RRT or ESRD |
| SOFA Liver (Bilirubin) | <1.2 | 1.2-1.9 | ≥2 |
| SOFA Coagulation (Platelets) | ≥150 | 100-149 | ≤99 |

aMissing data were categorized as 0.

bRenal, liver, and coagulation SOFA scores of 2, 3, or 4 were binned due to low frequency of events in categories “3” and “4”.

cIf the UOP was missing, the category was assigned according to the Cr

1. Home anticoagulation
2. Receipt of therapeutic anticoagulation on ICU day 1 or day 2, defined as the receipt of one of the following:
	1. Continuous drips of heparin, argatroban, or bivalirudin
	2. Subcutaneous regimens: enoxaparin (Lovenox) 1mg/kg twice per day, enoxaparin (Lovenox) 1.5mg/kg once per day, dalteparin (Fragmin) 150-200 units/kg once per day, dalteparin (Fragmin) 100 units/kg twice per day, fondaparinux (Aristra) at doses of 5mg or more daily
	3. Oral anticoagulants: warfarin (Coumadin), apixaban (Eliquis), rivaroxaban (Xarelto), edoxaban, or dabigatran (Pradaxa)
3. Receipt of aspirin on ICU day 1 or day 2
4. Receipt of steroids on ICU day 1 or day 2

**Mortality Risk Stratification**

To explore the ability of D-dimer to assist in rapid mortality risk stratification, we fit additional logistic regression models for 28-day mortality to the cohort data. Two models were used to determine the added benefit of D-dimer consideration in risk assessment with varying patient characteristics.

Model covariates were limited to prespecified clinical factors that were deemed to be readily apparent soon after ICU admission. The first model included the following clinical factors, without consideration of D-dimer level: age, sex, diabetes mellitus, hypertension, body mass index, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, current smoking status, active malignancy, need for invasive mechanical ventilation with two days following ICU admission, and shock within two days following ICU admission. The second model included each of these clinical factors, as well as the D-dimer category. Covariate definitions matched the primary analysis, as above.

After fitting these models to the cohort data, D-dimer’s ability to risk stratify was explored using two sets of hypothetical patients. In the first set, the characteristics of four patients deemed low-, moderate-, high-, or very high-risk were prespecified based on clinical knowledge. Point estimates for mortality risk were then calculated using each model, yielding five mortality risks for each patient: without D-dimer consideration, and with D-dimer values corresponding to each of the four D-dimer categories.

In a second set of hypothetical patients, the characteristics of 10,000 patients were generated at random. Point estimates for 28-day mortality were then calculated without D-dimer consideration, with a D-dimer level corresponding to the lowest category (<2x ULN), and with a D-dimer level corresponding to the highest category (>8x ULN). The point estimate for mortality with D-dimer corresponding to the lowest category was then subtracted from the point estimate corresponding to the highest category, yielding an absolute difference in mortality risk.

**Table S1. List of Participating Sites**

|  |
| --- |
| **Northeast** |
| Beth Israel Deaconess Medical Center |
| Brigham and Women’s Faulkner Hospital |
| Brigham and Women's Hospital |
| Cooper University Health Care |
| Hackensack Meridian Health Hackensack University Medical Center |
| Hackensack Mountainside Hospital |
| Johns Hopkins Hospital |
| Kings County Hospital Center |
| Lowell General Hospital |
| Massachusetts General Hospital |
| MedStar Georgetown University Hospital |
| Montefiore Medical Center |
| Mount Sinai  |
| Newton Wellesley Hospital |
| New York-Presbyterian Queens Hospital |
| New York-Presbyterian/Weill Cornell Medical Center |
| New York University Langone Hospital |
| Rutgers/New Jersey Medical School |
| Rutgers/Robert Wood Johnson Medical School |
| Temple University Hospital |
| Thomas Jefferson University Hospital |
| Tufts Medical Center |
| United Health Services Hospitals |
| University of Pennsylvania Health System |
| University of Pittsburgh Medical Center |
| Westchester Medical Center |
| Yale University Medical Center |
| **South** |
| Baylor College of Medicine, Houston |
| Baylor University Medical Center/Baylor Scott White and Health  |
| Duke University Medical Center |
| Mayo Clinic, Florida |
| Memphis VA Medical Center |
| Methodist University Hospital |
| Ochsner Medical Center |
| Tulane Medical Center |
| University of Alabama-Birmingham Hospital |
| University of Florida Health-Gainesville |
| University of Florida Health-Jacksonville |
| University of Miami Health System |
| University of North Carolina Hospitals |
| University of Texas Southwestern Medical Center |
| University of Virginia Health System |
| **Midwest** |
| Barnes-Jewish Hospital |
| Cook County Health |
| Mayo Clinic, Rochester |
| Froedtert Hospital |
| Indiana University Health Methodist Hospital |
| Northwestern Memorial Hospital |
| Promedica Health System |
| Rush University Medical Center |
| University Hospitals Cleveland Medical Center |
| University of Chicago Medical Center |
| University of Illinois Hospital and Health Sciences System  |
| University of Kentucky Hospital |
| University of Michigan Hospital |
| University of Oklahoma Health Sciences Center |
| **West**  |
| Loma Linda University Medical Center |
| Mayo Clinic, Arizona |
| Oregon Health and Science University Hospital |
| Renown Health |
| Stanford Healthcare |
| University of California-Davis Medical Center |
| University of California-Los Angeles Medical Center |
| University of California-San Diego Medical Center |
| University of California-San Francisco Medical Center |
| UCHealth University of Colorado |
| University Medical Center of Southern Nevada |
| University of Washington Medical Center |

**Table S2: Baseline characteristics by D-dimer measurement status.** Body mass index data was missing in 4.0% of patients, lymphocyte count data was missing in 8.6% of patients, and data for at least one SOFA score component score was missing in 9.9% of patients. All other data are complete. IQR, interquartile range; SOFA; Sequential Organ Failure Assessment.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **All Patients****(N=4949)** | **Measured D-Dimer****(N = 3418)** | **No D-Dimer****(N = 1531)** |
| **Demographics** |  |  |  |
| Age (yr), median (IQR) | 62 (52-71) | 62 (51-71) | 63 (53-71) |
| Male sex – no. (%) | 3123 (63.1) | 2170 (63.5) | 953 (62.2) |
| Race – no. (%) |  |  |  |
|  White | 1901 (38.4) | 1315 (38.5) | 586 (37.8) |
|  Black | 1516 (30.6) | 1030 (30.1) | 486 (31.7) |
|  Asian | 290 (5.9) | 190 (5.6) | 100 (6.5) |
|  Other | 1239 (25.0) | 880 (25.7) | 358 (23.4) |
| Hispanic – no. (%) | 1143 (23.1) | 858 (25.1) | 285 (18.6) |
| Body mass index – median (IQR) | 30 (26-36) | 30 (27-36) | 30 (26-36) |
| Pregnant – no. (%) | 39 (0.8) | 34 (1.0) | 5 (0.3) |
| **Coexisting conditions – no. (%)** |  |  |  |
| Diabetes mellitus | 2076 (41.9) | 1444 (42.2) | 631 (41.2) |
| Hypertension | 3040 (61.4) | 2089 (61.1) | 951 (62.1) |
| Chronic obstructive pulmonary disease | 427 (8.6) | 272 (8.0) | 155 (10.1) |
| Current smoker | 256 (5.2) | 160 (4.7) | 160 (4.7) |
| Coronary artery disease | 666 (13.5) | 436 (12.8) | 142 (4.2) |
| Congestive heart failure | 503 (10.2) | 332 (9.7) | 171 (11.2) |
| Active malignancy | 224 (4.5) | 142 (4.2) | 85 (5.4) |
| **<3 days of symptom duration before ICU admission** | 1080 (21.8) | 726 (21.2) | 354 (23.1) |
| **Severity of illness within 2 days after ICU admission – no. (%)** |  |  |
| Mechanical ventilation | 3363 (67.9) | 2359 (69.0) | 1004 (65.6) |
| Shock  | 817 (16.5) | 609 (17.8) | 208 (13.6) |
| Lymphocyte count <1000 per mm3 | 2044 (41.3) | 1501 (43.9) | 543 (35.5) |
| Coagulation component of SOFA score |  |  |  |
|  0 | 3845 (77.7) | 2684 (78.5) | 1160 (75.8) |
|  1 | 803 (16.2) | 533 (15.6) | 270 (17.6) |
|  >2  | 302 (6.1) | 201 (5.9) | 101 (6.6) |
| Liver component of SOFA score |  |  |  |
|  0 | 4299 (86.8) | 2933 (85.8) | 1365 (89.2) |
|  1 | 449 (9.1) | 330 (9.7) | 119 (7.8) |
|  >2 | 202 (4.1) | 155 (4.5) | 47 (3.1) |
| Renal component of SOFA score |  |  |  |
|  0 | 2049 (41.4) | 1353 (39.6) | 695 (45.4) |
|  1 | 913 (16.2) | 641 (18.8) | 272 (17.8) |
|  >2 | 1988 (40.2) | 1423 (41.7) | 564 (36.8) |
| **Medications affecting hemostasis – no. (%)** |  |  |  |
| Home anticoagulation | 438 (8.8) | 292 (8.5) | 146 (9.5) |
| Therapeutic anticoagulation | 1189 (24.0) | 916 (26.8) | 273 (17.8) |
| Aspirin receipt | 779 (15.7) | 527 (15.4) | 252 (16.5) |
| Steroid receipt | 1101 (22.2) | 858 (25.1) | 243 (15.9) |
| **28-day mortality – no. (%)** | 1785 (36.1) | 1180 (34.5) | 605 (39.5) |
| Mortality within 2 days after ICU admission – no. (%) | 222 (4.5) | 140 (4.1) | 82 (5.4) |
| Time to death (days) – median (IQR) | 10 (5-18) | 10 (5-18.5) | 9 (5-17) |

**Table S3: Logistic regression models for 90-day mortality.** Within 90 days following ICU admission, 1353 patients (39.6%) had died, 2029 (59.4%) were discharged alive, and 36 (1.0%) remained hospitalized. Model 1 is unadjusted. Model 2 is adjusted for demographics and comorbidities. Model 3 adds severity of illness measures in the first two days after ICU admission. Model 4 adds medications impacting hemostasis received within 2 days of ICU admission. ULN stands for upper limit of normal, as determined by the assay manufacturer.

|  |  |
| --- | --- |
|  | **Odds ratios (95% CI) for 90-day mortality (N = 3418)** |
| **Model** | **D-dimer** **<2x ULN****(N = 938)** | **D-dimer** **2-3.9x ULN****(N = 875)** | **D-dimer** **4-7.9x ULN****(N = 582)** | **D-dimer****>8x ULN****(N = 1023)** |
| 1 | 1 (ref) | 1.67 (1.37-2.05) | 2.23 (1.79-2.78) | 3.15 (2.61-8.82) |
| 2 | 1 (ref) | 1.61 (1.30-2.00) | 1.94 (1.53-2.45) | 2.82 (2.29-3.47) |
| 3 | 1 (ref) | 1.42 (1.13-1.78) | 1.47 (1.14-1.88) | 1.83 (1.47-2.30) |
| 4 | 1 (ref) | 1.38 (1.11-1.74) | 1.39 (1.08-1.79) | 1.70 (1.35-2.15) |

**Table S4: Logistic regression models for 28-day mortality for patients measured with the most common assay.** The most common assay among participating sites was the STA Liatest®, both in number of included patients (N = 1111) and number of centers (N = 21). Model 1 is unadjusted. Model 2 is adjusted for demographics and comorbidities. Model 3 adds severity of illness measures in the first two days after ICU admission. Model 4 adds medications impacting hemostasis. ULN stands for upper limit of normal, as determined by the assay manufacturer venous thromboembolism threshold.

|  |  |
| --- | --- |
|  | **Odds ratios (95% CI) for 28-day mortality in patients** **measured with the most common assay (N = 1111)** |
| **Model** | **D-dimer** **<2x ULN****(N = 227)** | **D-dimer** **2-3.9x ULN****(N = 255)** | **D-dimer** **4-7.9x ULN****(N = 255)** | **D-dimer****>8x ULN****(N = 374)** |
| 1 | 1 (ref) | 1.67 (1.14-2.42) | 1.88 (1.30-2.75) | 3.46 (2.44-4.93) |
| 2 | 1 (ref) | 1.90 (1.26-2.87) | 1.74 (1,16-2.65) | 3.48 (2.37-5.15) |
| 3 | 1 (ref) | 1.65 (1.07-2.55) | 1.11 (0.71-1.75) | 1.87 (1.21-2.88) |
| 4 | 1 (ref) | 1.58 (1.02-2.45) | 1.03 (0.65-1.62) | 1.65 (1.06-2.57) |

**Table S5: Linear regression models for 28-day mortality for patients measured with the most common assay.** The most common assay among participating sites was the STA Liatest®, both in number of included patients (N = 1111) and number of centers (N = 21). For this assay, 1 ULN is equal to 500 ng/mL FEU. Model 1 is unadjusted. Model 2 is adjusted for demographics and comorbidities. Model 3 adds severity of illness measures in the first two days after ICU admission. Model 4 adds medications impacting hemostasis. ULN stands for upper limit of normal, as determined by the assay manufacturer venous thromboembolism threshold.

|  |  |  |
| --- | --- | --- |
| **Model** | **Odds ratio, per each ULN increase** | **95% CI** |
| 1 | 1.17 | 1.12-1.23 |
| 2 | 1.16 | 1.11-1.22 |
| 3 | 1.07 | 1.01-1.13 |
| 4 | 1.05 | 0.99-1.11 |

**Figure S1: Forest plot of fully adjusted model for 28-day mortality.**

**Figure S2: Restricted cubic spline plots of models for mortality in patients measured by the most common assay.** Lines represent the predicted mortality risk and the shading represents 95% confidence intervals. ULN stands for assay upper limit of normal. The fully adjusted model is adjusted for age, sex, race, body mass index, diabetes, coronary artery disease, chronic obstructive pulmonary disease, current smoking status, active malignancy, mechanical ventilation, shock, lymphocyte count, renal, liver and coagulation, SOFA component scores, therapeutic anticoagulation, home anticoagulation, aspirin, and steroids.

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**Figure S3**: **Mortality risk according to D-dimer category by hypothetical risk status.** Mortality risk was predicted by a model including the listed covariates. Risk was predicted for 4 patients with pre-specified characteristics (A) and 10,000 patients with randomly generated characteristics (B). Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; MV, mechanical ventilation; ULN, upper limit of normal.