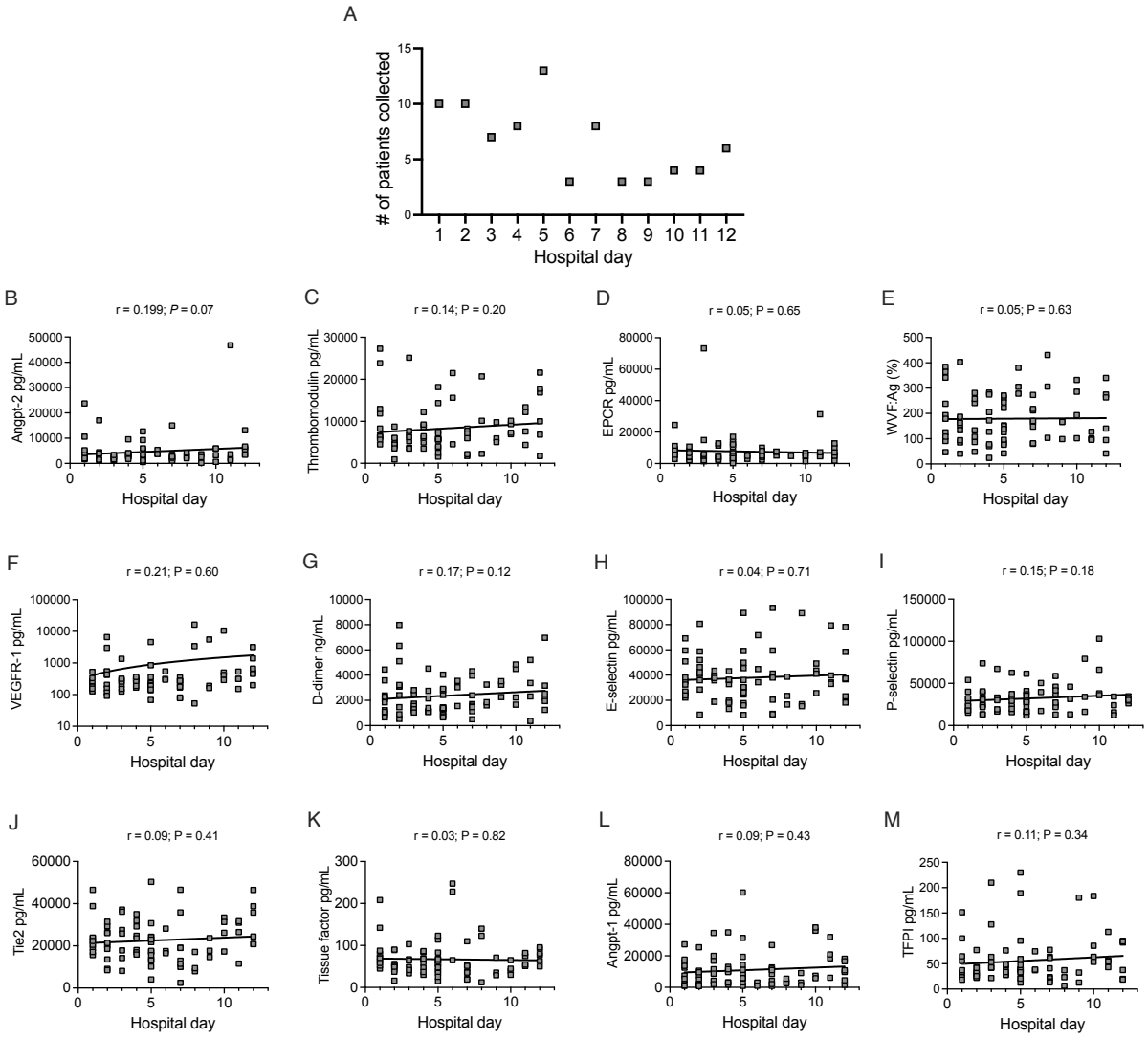
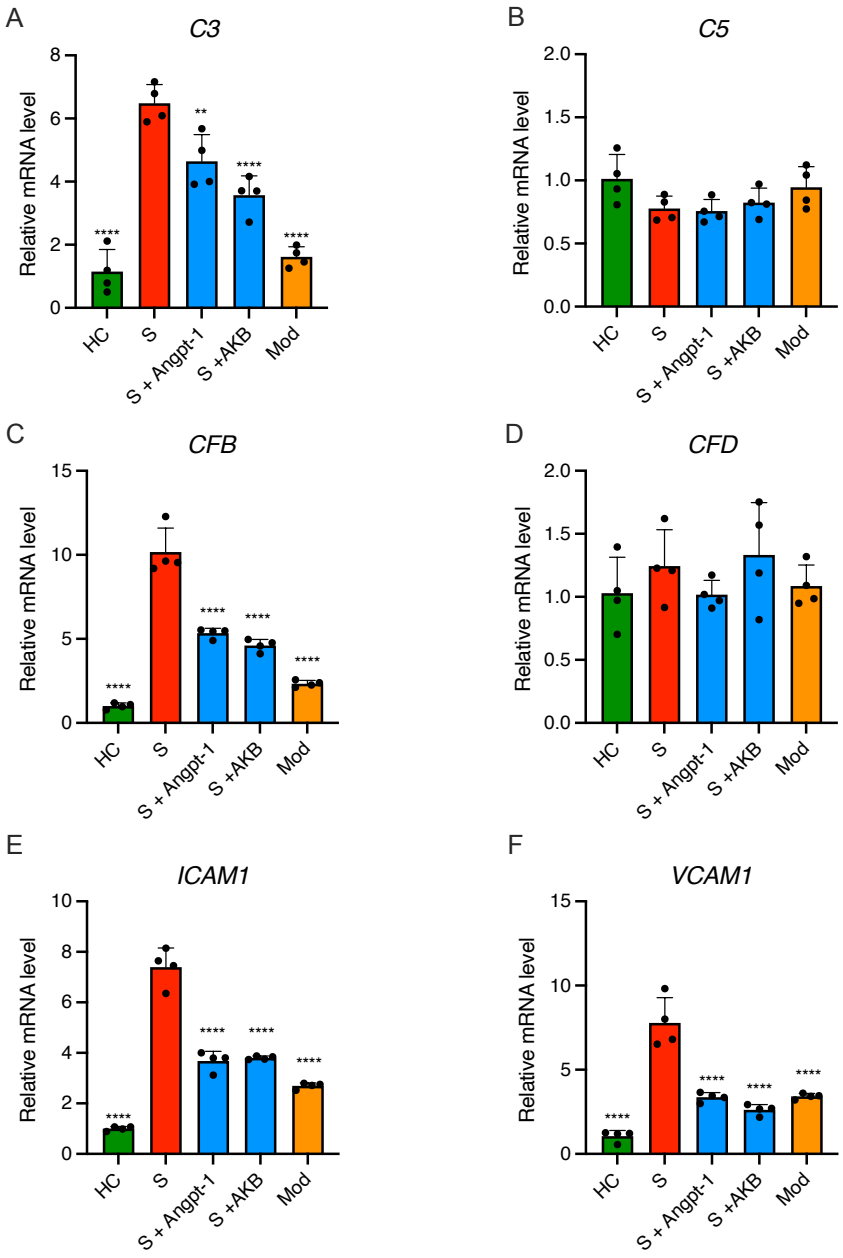
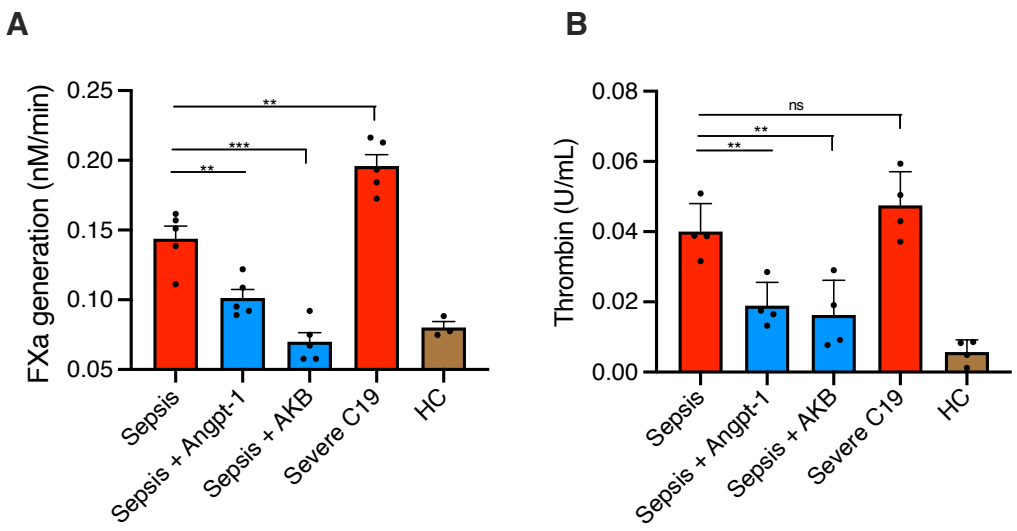


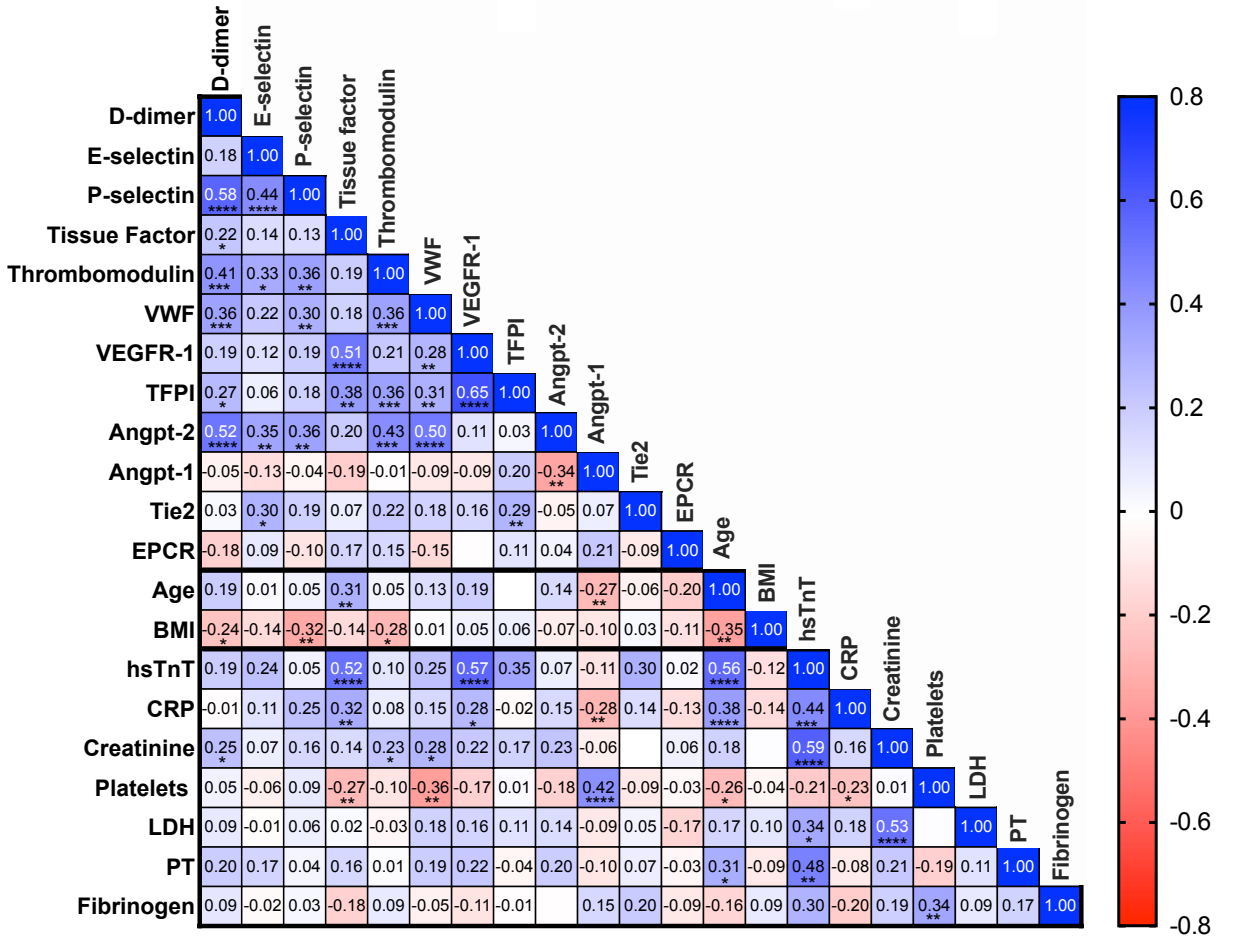
Supplemental Figure 1. Sample collection and day of hospitalization. A. The number of patient plasma samples in the COVID-19 cohort collected according to day of hospitalization. **B.** Measurement of plasma biomarkers according to day of hospitalization. Correlations were determined by Spearman's rank correlation. Angpt, angiopoietin; EPCR, endothelial protein C receptor; TFPI, tissue factor pathway inhibitor; VEGFR-1, vascular endothelial growth factor receptor 1; VWF Von Willebrand Factor.



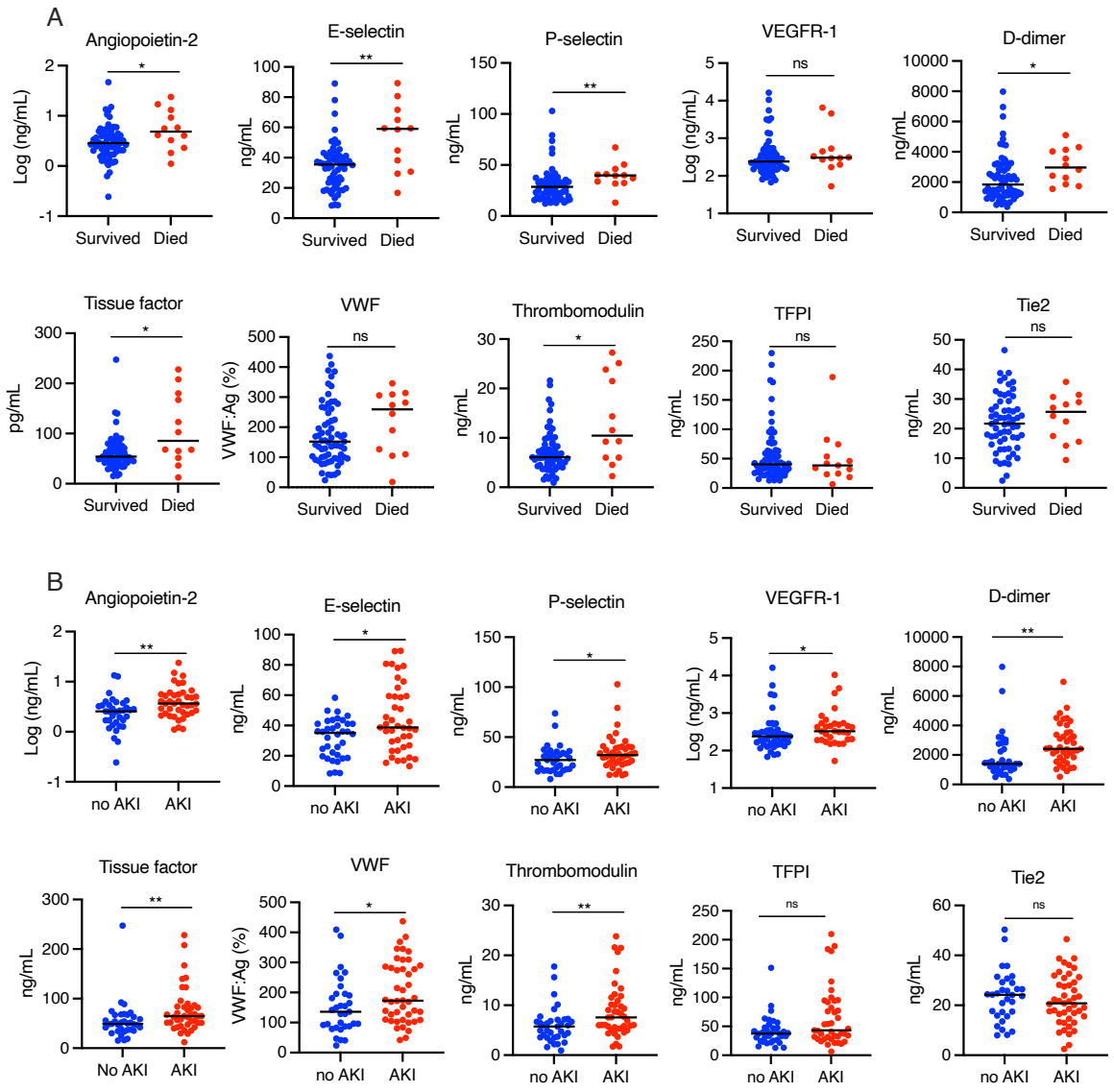
Supplemental Figure 2. Activation of complement and endothelial adhesion molecule gene expression by plasma from patients with COVID-19. HUVECs were cultured overnight in the presence of 10% pooled plasma from patients with severe (S, ICU patients), moderate (Mod, non-ICU hospitalized patients) COVID-19 or healthy controls (HC) and analyzed for relative fold mRNA expression change of complement *C3* (**A**), complement *C5* (**B**), complement factor B (*CFB*, **C**), complement factor D (*CFD*, **D**), intercellular adhesion molecule 1 (*ICAM1*, **E**) and vascular cell adhesion molecule 1 (*VCAM1*, **F**). When indicated, cells were pretreated with Angpt-1 (300 ng/mL) or AKB-9778 (5 μM) for 30 min prior to incubation with plasma (n = 3-4 biologic replicates performed in technical duplicate). Gene expression was normalized to that of actin and changes are shown relative to HC. Graphs represent the mean ± SD. Significance in comparison to severe (S) was determined by 1-way ANOVA using Dunnett post-test, $^{**}P < 0.01$, $^{****}P < 0.0001$.



Supplemental Figure 3. Plasma from patients with non-COVID-19 sepsis complicated by acute respiratory distress syndrome (ARDS) promotes activation of coagulation on endothelial cells similar to plasma from patients with severe COVID-19. HUVECs were cultured overnight in the presence of 10% pooled plasma from patients with severe sepsis/ARDS (sepsis), severe COVID-19 (Severe C19) or healthy controls (HC) and analyzed for their ability to generate factor Xa (**A**) or thrombin (**B**). When indicated, cells were pretreated with Angpt-1 (300 ng/mL) or AKB-9778 (5 μM) for 30 min prior to incubation with plasma. The rate of reaction for factor Xa and thrombin were converted to nM/min and U/mL, respectively, by comparison to standard curve. For factor Xa and thrombin generation assays, each data point represents the mean of 3 technical replicates, with 3-5 biologic replicates performed in total. Graphs represent mean ± SD. Significance was determined by 1-way ANOVA using Dunnett's post-test, $^{**}P < 0.01$, $^{***}P < 0.001$.



Supplemental Figure 4. Correlation matrix of measured analytes among hospitalized COVID-19 patients. Spearman rank correlations were performed for markers of endothelial and thrombotic activation, demographics, and clinical metrics. Positive correlations are indicated in blue and negative correlations indicated in red. Numbers within the square indicate r values. Angpt, angiopoietin; BMI, body mass index; CRP, C-reactive protein; EPCR, endothelial protein C receptor; hsTnT, high-sensitivity troponin, LDH, lactate dehydrogenase; PT, prothrombin time; TFPI, tissue factor pathway inhibitor; VEGFR-1, vascular endothelial growth factor receptor 1; VWF, Von Willebrand Factor, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.



Supplemental Figure 5. Endothelial and thrombotic activation and clinical endpoints among patients hospitalized with COVID-19. Plasma samples obtained from patients hospitalized with COVID-19 and values of measured proteins are shown for patients according to death (**A**) or development of acute kidney injury (**B**). Acute kidney injury (AKI) was defined as a rise in serum creatinine of ≥ 0.3 mg/dL or ≥ 1.5 times baseline. TFPI, tissue factor pathway inhibitor; VEGFR-1, vascular endothelial growth factor receptor 1; VWF, Von Willebrand Factor. Bar indicates median value. Significance was determined by a 2-tailed Mann-Whitney test. **P*<0.05, ***P*<0.01,

Supplemental Data 1

COVID-19 Autopsy specimens

Three characteristic findings were apparent in the lung specimens isolated from COVID-19 autopsies—1) alveolar spaces with pulmonary edema and fresh hemorrhage, without significant interstitial inflammation 2) chronic interstitial inflammation and edema, with type II pneumocyte hyperplasia and multinucleation, and 3) diffuse alveolar damage with organizing fibrin in alveolar spaces and associated microvascular thrombi(33)

Patient 1 (10 day admission) had a relatively benign course. He presented with low-grade fever and malaise, and negative chest x-ray without pulmonary symptoms. His labs showed lymphopenia and elevated inflammatory markers (CRP 110 mg/L Ferritin 1169 ng/mL) with a positive nasopharyngeal swab for COVID-19. He had profound hypotension following dialysis sessions, and progressive decline in strength and mental status. He was transitioned to comfort measures and died on day 10. Autopsy findings showed lungs with patchy pulmonary edema and acute alveolar hemorrhage.

Patient 2 (16 day admission) presented with fever, hypoxia, and respiratory distress requiring oxygen supplementation. She was septic with metabolic acidosis. After response to antibiotic and fluid resuscitation, she tested positive for COVID-19 by swab and was discharged to in-patient hospice where her respiratory status declined until death. Autopsy findings matched the clinical picture of lung injury and sepsis. The lungs showed diffuse alveolar damage and microvascular thrombosis. In less involved areas, sections showed a prominent septal lymphocytic infiltrate and type-II pneumocyte hyperplasia with multinucleated forms.

Patient 3 (40 day admission) presented with 10 days of fever, chills, and dry cough as well as nausea/vomiting and diarrhea. For the few days prior to presentation she had worsening dyspnea. At presentation she had bilateral lung field infiltrates on x-ray, lymphopenia and rapidly progressing hypoxia with positive COVID test. She was intubated and required pressor support to treat hypotension. She required mechanical ventilation and hemodialysis for acute kidney injury complicated. She was extubated on day 21, but readmitted to intensive care with aspiration pneumonia from tube feeds. She developed sepsis and died 4 days later. At autopsy, the lungs with prominent interstitial lymphocytic infiltrate and abundant alveolar macrophages likely related to recent pneumonias.

Case 4 (15 day admission) presented from dialysis for end stage kidney disease with 2 days of shortness of breath, cough and fatigue. On arrival her oxygen saturation was 82% requiring oxygen supplementation, and chest x-ray with multifocal pneumonia. She was lymphopenia and her CRP was 226 mg/L, and COVID testing was positive. In spite of antibiotics, her respiratory status worsened. She was intubated on day 2 with persistent hypoxemia and she developed adults respiratory distress syndrome (ARDS) and persistent shock requiring pressor support and died. At autopsy, her lungs showed patchy pulmonary edema and acute alveolar hemorrhage with prominent interstitial lymphocytic pneumonia with type-II pneumocyte hyperplasia and abundant alveolar macrophages and fibrin deposition in the microvasculature.

Case 5 (31 day admission) presented with 4 days of fever and malaise and was admitted for CoVID positive pneumonia requiring intubation on day 3. He required pressor for sepsis-related blood pressure support throughout his admission. He developed renal failure requiring

hemodialysis, and candidate sepsis from a line infection. He was improved at week 3 into his admission, but arrested with ventricular fibrillation. At autopsy, his lungs showed diffuse alveolar damage with associated microvascular thrombosis and organizing alveolar hemorrhage which correspond to diffuse radiographic infiltrates seen on daily chest x-rays.

Supplementary Table 1. Clinical characteristics and laboratory values for patients included in the cohort. Highest value during hospitalization is listed. (HTN – hypertension, ESRD – end stage renal disease, PE – pulmonary emboli, DM2 – diabetes mellitus type 2, TIA –transient ischemic attack, CKD – chronic kidney disease, AFib – atrial fibrillation).

	Age/ gender	**Hospital admission length**	**Intubated**	**Comorbidities**	**D- Dimer**	**cTropnT**
1	91M	10	no	ESRD on dialysis, h/o prostate ca, h/o PE, HTN	1174	0.17
2	82F	16	no	HTN, DM2, TIA, dementia	>21600	0.08
3	58F	40	yes	HTN, DM2, obesity, mild CKD	>21600	0.25
4	79F	15	no	ESRD on dialysis, HTN	>21600	0.23
5	75M	31	yes	Myasthenia gravis, HTN, AFib	20937	1.35

Supplemental acknowledgments

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