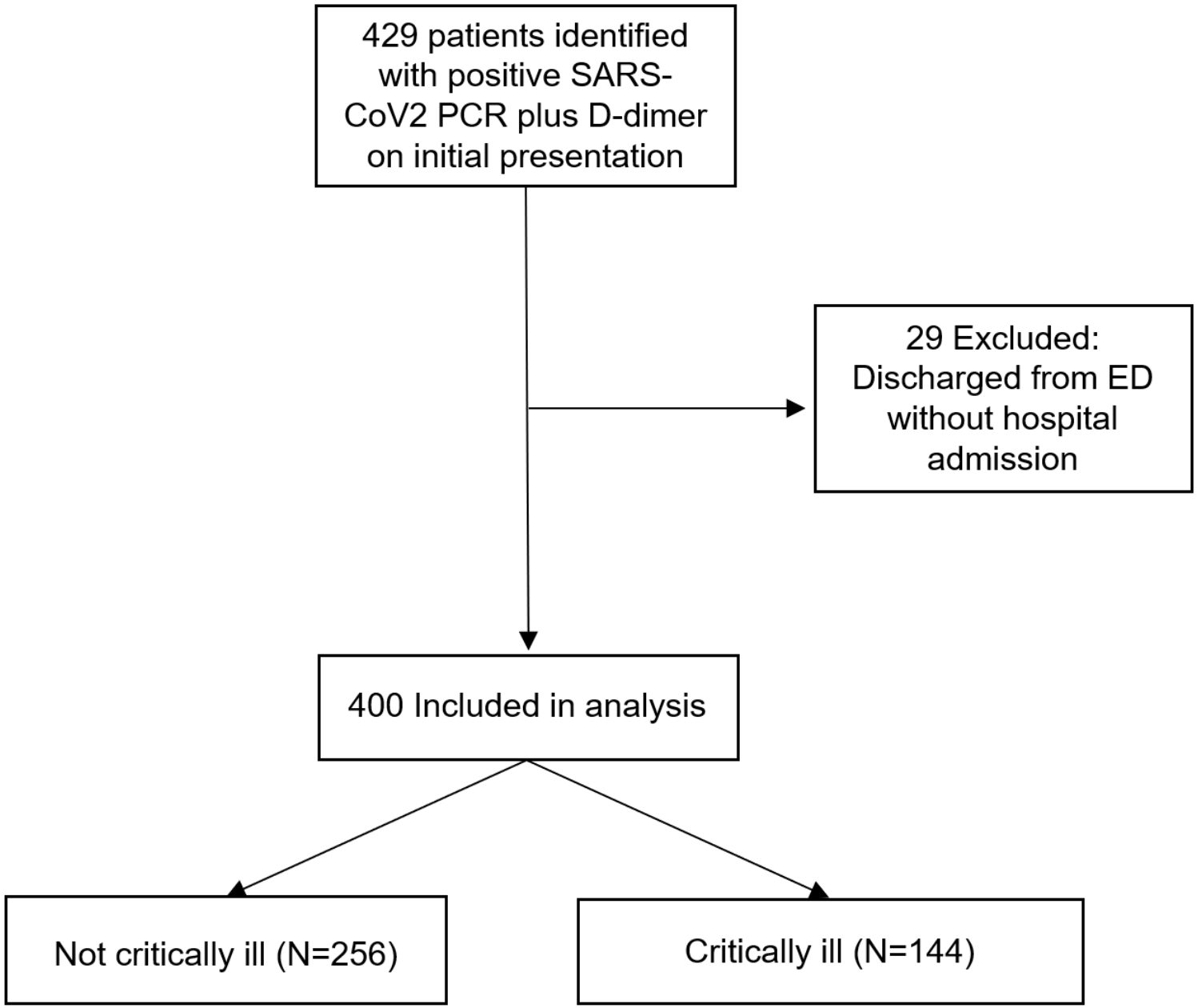
COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection

Supplemental Material

Supplemental Figure 1. Flow diagram of patients included in study.



Supplemental Table 1. Standard prophylactic anticoagulation agents and dosing incorporating institutional guidelines at all five hospitals during the study period. Guidelines were developed at the institutional level (and are not published guidelines from a professional society or group). Treating clinicians may have deviated from these institutional guidelines as they felt clinically indicated. SC, subcutaneous. Enoxaparin is usually selected except in patients with significant renal impairment (CrCl <30), for whom unfractionated heparin is generally chosen. For the purposes of prophylactic anticoagulation dosing, obesity was defined as BMI ≥40 or weight >120 kg for 3 institutions and weight >150 kg for 2 institutions.

Location	Medical Floor	Medical Floor (obese)	ICU	ICU (obese)
Agents and Dosing	Enoxaparin 40 mg SC daily OR Unfractionated heparin 5000 U SC every 8-12 hours	Enoxaparin 40 mg SC every 12 hours OR Unfractionated heparin 5000-7500 U SC every 8 hours	Enoxaparin 40 mg SC daily OR Unfractionated heparin 5000 U SC every 8-12 hours	Enoxaparin 40 mg SC every 12 hours OR Unfractionated heparin 5000-7500 U SC every 8 hours

Supplemental Table 2. Assays and assay manufacturers for each laboratory parameter by hospital. Reference ranges for each test were identical or very similar at each institution, and are summarized appropriately by the following: D-dimer, <500 ng/mL; prothrombin time, 11.5-14.5 sec; international normalized ratio, 0.9-1.1; partial thromboplastin time, 22.0-36.0 sec; fibrinogen, 150-450 mg/dL; platelet count, 150-450×10^9/L; C-reactive protein, <8.0 mg/L; erythrocyte sedimentation rate, <13 mm/h (men) and <20 mm/h (women); ferritin, 20-300 µg/L (men) and 10-200 µg/L (women); procalcitonin, <0.10 ng/mL; high-sensitivity cardiac troponin, <14 ng/L (men) and <9 ng/L (women).

Laboratory Test	Assay, Manufacturer
PT/INR, aPTT, fibrinogen	Performed using reagents from Stago (Neoplastine Cl Plus, PTT-A, and Sta-fibrinogen, respectively) except for one laboratory that used reagents from Instrumentation Laboratory (HemosIL RecombiPlasTin 2G, SynthASil, Q.F.A. Bovine Thrombin, respectively).
D-dimer	All tests reported results in FEU with a reference range of <500 ng/mL FEU. Performed using Vidas (bioMerieux) in two laboratories, Sta-Liatest (Stago) in two laboratories, and HS 500 (Instrumentation Laboratory) in one laboratory.
ESR	Performed using iSed (Alcor) except for one laboratory that used Inversa (Mechatronics).
Platelet counts	Obtained using Sysmex analyzers in all laboratories.
CRP, procalcitonin, ferritin, high-sensitivity cardiac troponin	Performed with Cobas (Roche) in all laboratories.

Supplemental Table 3. Pre-existing clinical conditions imparting a high risk for COVID-19 included in multivariable logistic models in addition to age, sex, BMI, baseline anticoagulation intensity, and residence in a long-term care facility.

Risk Factor	Included Conditions
Chronic lung disease	Chronic obstructive pulmonary disease, moderate-to-severe asthma, restrictive or fibrotic lung disease, cystic fibrosis, lung cancer
Diabetes mellitus	Type 1, type 2, or gestational diabetes mellitus
Cardiovascular disease	Heart failure, coronary artery disease, congenital heart disease, cardiomyopathy, pulmonary hypertension, systemic hypertension (stage 2 or worse)
Chronic kidney disease requiring dialysis	Patients on hemodialysis or peritoneal dialysis
Immunocompromise	HIV/AIDS or other immunodeficiencies, use of immunosuppressive medications, receipt of cancer chemotherapy within 4 weeks of presentation
Chronic liver disease	Pathologic (fibrosis or cirrhosis) or clinical diagnosis of chronic liver disease including alcoholic liver disease, non-alcoholic fatty liver disease, and other chronic liver diseases

Supplemental Table 4. Sensitivity analysis for predictors of thrombosis (see Figure 1 in primary manuscript for full analysis) analyzing those parameters (D-dimer, platelet count, C-reactive protein, and erythrocyte sedimentation rate) predictive of thrombosis in the full analysis (that included all thrombotic complications). Cases in sensitivity analysis included only radiographically-confirmed VTE or arterial thrombosis and myocardial infarction.

Marker Initial Value	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
D-dimer				
≤1000	1 (reference)	--	1 (reference)	--
1001-2500	1.75 (0.69-4.42)	0.24	1.78 (0.65-4.84)	0.26
>2500	4.40 (1.60-12.08)	0.004	5.28 (1.74-15.96)	0.003
Platelet count				
≤450	1 (reference)	--	1 (reference)	--
>450	2.53 (0.89-7.20)	0.081	3.29 (1.03-10.57)	0.045
C-reactive protein				
≤100	1 (reference)	--	1 (reference)	--
>100	3.42 (1.47-7.95)	0.004	3.04 (1.24-7.47)	0.015
Erythrocyte sedimentation rate				
≤40	1 (reference)	--	1 (reference)	
>40	1.82 (0.89-4.84)	0.23	1.66 (0.59-4.65)	0.34

Supplemental Table 5. Sensitivity analysis for predictors of bleeding (see Figure 2 in primary manuscript for full analysis) analyzing those parameters (D-dimer and platelet count) predictive of bleeding in the full analysis (that included all bleeding events). Cases in sensitivity analysis included only major bleeds (WHO grade 3 or 4).

Marker Initial Value	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
D-dimer				
≤1000	1 (reference)	--	1 (reference)	--
1001-2500	1.53 (0.31-7.72)	0.60	1.40 (0.25-7.74)	0.70
>2500	4.54 (0.89-23.23)	0.069	4.73 (0.85-26.21)	0.076
Platelet count				
<150	4.07 (1.07-15.46)	0.040	4.42 (1.09-17.91)	0.037
≥150	1 (reference)	--	1 (reference)	--

Supplemental Table 6. 95% confidence intervals for Spearman correlation coefficients for correlation matrix demonstrating strength of correlation between D-dimer and evaluated inflammatory parameters (Figure 5 in primary manuscript). All correlations were statistically significant (*P*<0.0001).

	D-Dimer	CRP	ESR	Ferritin	Procalcitonin
D-Dimer		0.47 to 0.62	0.33 to 0.52	0.25 to 0.43	0.38 to 0.55
CRP	0.47 to 0.62		0.60 to 0.73	0.32 to 0.50	0.49 to 0.63
ESR	0.33 to 0.52	0.60 to 0.73		0.20 to 0.42	0.17 to 0.39
Ferritin	0.25 to 0.43	0.32 to 0.50	0.20 to 0.42		0.33 to 0.51
Procalcitonin	0.38 to 0.55	0.49 to 0.63	0.17 to 0.39	0.33 to 0.51	