Serial Thromboelastography and the Development of Venous Thromboembolism in Critically Ill Patients with COVID-19

Supplementary Appendix

Contents

SUPPLEMENTAL TABLES

Supplemental Table S1: Enrollment Coagulation Parameters Grouped by Bleeding Events

Laboratory Measures	Reference Range	All Patients n=98	Bleeding n=11	No Bleeding n=87	P-value
Fibrinogen (mg/dL) [N=96]	188-450	678 (574.5 - 843.5)	649 (594 - 863)	680 (568 - 836)	0.93
Platelet count ($x10^3/\mu L$) [N=97]	135 - 371	242 (169 - 300)	232 (130 - 271)	255 (169 - 304)	0.21
INR [N=96]		1.2 (1.1 - 1.3)	1.2 (1.1 - 1.2)	1.2 (1.1 - 1.3)	0.79
PT (seconds) [N=96]	11.9 - 14.5	14.6 (14.0 - 15.7)	14.6 (14 - 15.4)	14.6 (13.9 - 15.7)	0.92
aPTT (seconds) [N=94]	23.5 - 33.5	31.1 (28.2 - 35.3)	33.7 (31.1 - 39.7)	30.4 (28.1 - 35)	0.14
D-dimer (mcg/mL FEU)	0.27 - 0.49	2.16 (0.96 - 6.81)	1.48 (1.39 - 13.43)	2.20 (0.87 - 6.68)	0.64
DIC Score (ISTH)		2 (2 - 3)	2.5 (2 - 4)	2 (1 - 3)	0.28
Thromboelastography [N=95]					
MA (mm)	50 - 70	67.0 (63.7 - 70.7)	63.8 (61.7 - 67.9)	67.2 (64.1 - 70.8)	0.18
α (degrees)	53 - 72	73.2 (68.7 - 76.4)	67.9 (66.0 - 71.0)	73.8 (69.5 - 76.4)	<0.01
R (minutes)	5 - 10	3.7 (3.2 - 4.8)	4.9 (3.3 - 5.8)	3.6 (3.2 - 4.3)	0.06
G ($dyne/cm^2$)	4.5-11	10.2 (8.8 - 12.1)	9.2 (8.1 - 10.6)	10.2 (8.9 - 12.1)	0.19
Clotting Index	-3.0 - +3.0	3.4 (2.9 - 3.9)	2.9 (2.3 - 3.5)	3.4 (2.9 - 4.0)	0.07
Ly30 (%)	0 - 8	0.6 (0 - 1.4)	0.75 (0.1 - 2.5)	0.6 (0 - 1.4)	0.50

α = alpha angle, aPTT = activated partial thromboplastin time, Bleeding = Major bleeding defined by ISTH guidelines. DIC = disseminated intravsascular coagulation, dL = deciliter, G = shear elastic modulus (complete clot strength), INR = international normalized ratio, IQR = interquartile range, ISTH = International Society on Thrombosis and Haemostasis, Ly30 = percent lysis at 30 minutes, MA = maximum amplitude, mg = milligram, PT = prothrombin time, R = reaction time,

P-values from two-sided Mann-Whitney U test for continuous variables.

Supplemental Table S2: Enrollment Coagulation Parameters for the Additional 58 patients Excluding the previously reported 40 patients

Laboratory Measures Median (IQR)	Reference Range	All Patients	VTE n=14	No VTE n=44	P-value
Fibrinogen (mg/dL) [N=56]	188-450	673.5 (578 - 797)	546 (365 - 626)	688 (631 - 828)	<0.001
Platelet count (x10^3/μL) [N=57]	135 - 371	324 (164 - 287)	162.5 (117 - 259)	253 (196 - 301)	0.02
INR [N=57]		1.2 (1.1 - 1.3)	1.2 (1.0 - 1.3)	1.2 (1.1 - 1.3)	0.62
PT (seconds) [N=57]	11.9 - 14.5	14.9 (14.1 - 15.8)	15.3 (13.3 - 16.3)	14.8 (14.1 - 15.8)	0.75
aPTT (seconds) [N=57]	23.5 - 33.5	30 (27.8 - 35.3)	29.9 (27.4 - 31)	32.2 (27.8 - 36.2)	0.35
D-dimer (mcg/mL FEU)	0.27 - 0.49	2.08 (0.84 - 5.51)	20 (6.81 - 20)	1.62 (0.78 - 3.32)	<0.001
DIC Score (ISTH)		2 (0 - 3)	3 (3 - 3)	2 (0 - 3)	0.01
Thromboelastography [N=55]					
MA (mm)	50 - 70	66.7 (63.7 - 68.4)	60.3 (53.7 - 65.2)	67.3 (65.2 - 69.8)	<0.001
α (degrees)	53 - 72	73.8 (68.6 - 76.4)	67.0 (60.2 - 73.7)	75.3 (69.9 - 76.6)	<0.001
R (minutes)	5 - 10	3.7 (3.1 - 4.4)	3.4 (2.8 - 3.8)	4.1 (3.2 - 4.8)	0.08
G (dyne/cm^2)[d]	4.5-11	10 (8.8 - 11.4)	7.6 (5.8 - 9.4)	10.3 (9.4 - 11.6)	<0.001
Clotting Index	-3.0 - +3.0	3.4 (2.6 - 3.8)	2.6 (1.5 - 3.4)	3.5 (3.0 - 3.8)	0.002
Ly30 (%)	0 - 8	0.5 (0 - 1.6)	1.0 (0.1 - 1.6)	0.4 (0 - 1.1)	0.37

α = alpha angle, aPTT = activated partial thromboplastin time, DIC = disseminated intravsascular coagulation, dL = deciliter, G = shear elastic modulus (complete clot strength), INR = international normalized ratio, IQR = interquartile range, ISTH = International Society on Thrombosis and Haemostasis, Ly30 = percent lysis at 30 minutes, MA = maximum amplitude, mg = milligram, PT = prothrombin time, R = reaction time, VTE = venous thromboembolism.

P-values from two-sided Mann-Whitney U test for continuous variables.

Supplemental Table S3: Sensitivity Analyses

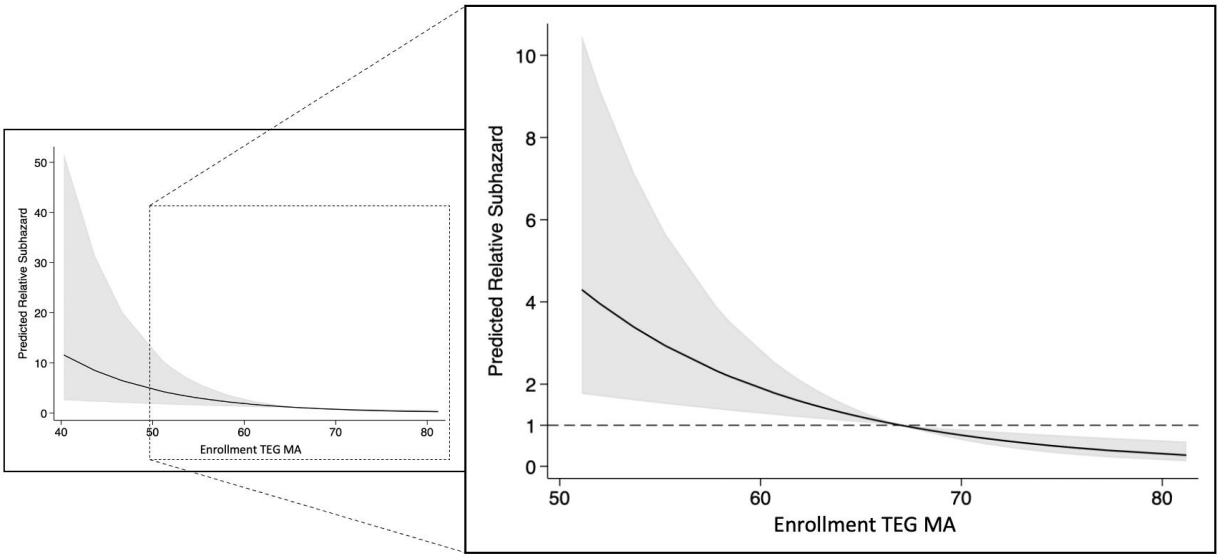
	n	SHR	95% Confidence Interval	p-value
Sensitivity Analysis (1)				
Enrollment	70	0.91	0.86 - 0.97	0.003
Peak	85	0.92	0.89 - 0.95	<0.001
Sensitivity Analysis (2)				
Enrollment	80	0.93	0.88 - 0.98	0.007
Peak	83	0.85	0.79 - 0.91	<0.001
Sensitivity Analysis (3)				
Enrollment	69	0.92	0.87 - 0.98	0.008
Peak	71	0.85	0.80 - 0.91	<0.001
Adjusting for age, sex, SOFA score, antiplatelet exposure, and anticoagulant dose				
Enrollment	95	0.92	0.87 - 0.98	0.005
Peak	98	0.84	0.78 - 0.91	<0.001

n = number of patients, SHR = subdistribution hazard ratio, SOFA = sequential organ failure assessment

SUPPLEMENTAL FIGURES

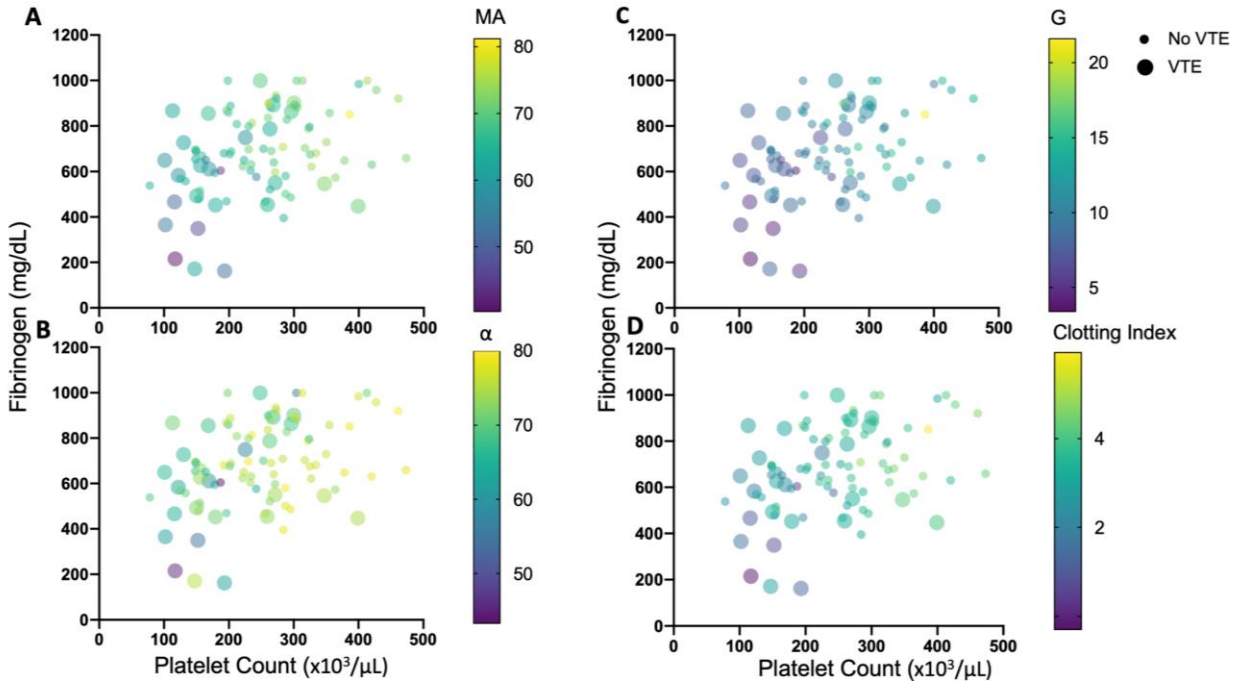
Supplemental Figure S1: Predicted Relative Subhazard for Maximum Amplitude

Left panel: Predicted relative subhazard for the risk of venous thromboembolism compared to the median enrollment thromboelastography maximum amplitude (TEG MA). Right panel: Zoomed in image including 97% of enrollment measures. The dotted line at a predicted subhazard ratio of 1 represents the reference line and intersects with the curve at the median enrollment TEG MA.



Supplemental Figure S2: Multivariable scatter plot showing the relationship between enrollment fibrinogen, platelet count, and thromboelastography parameters.

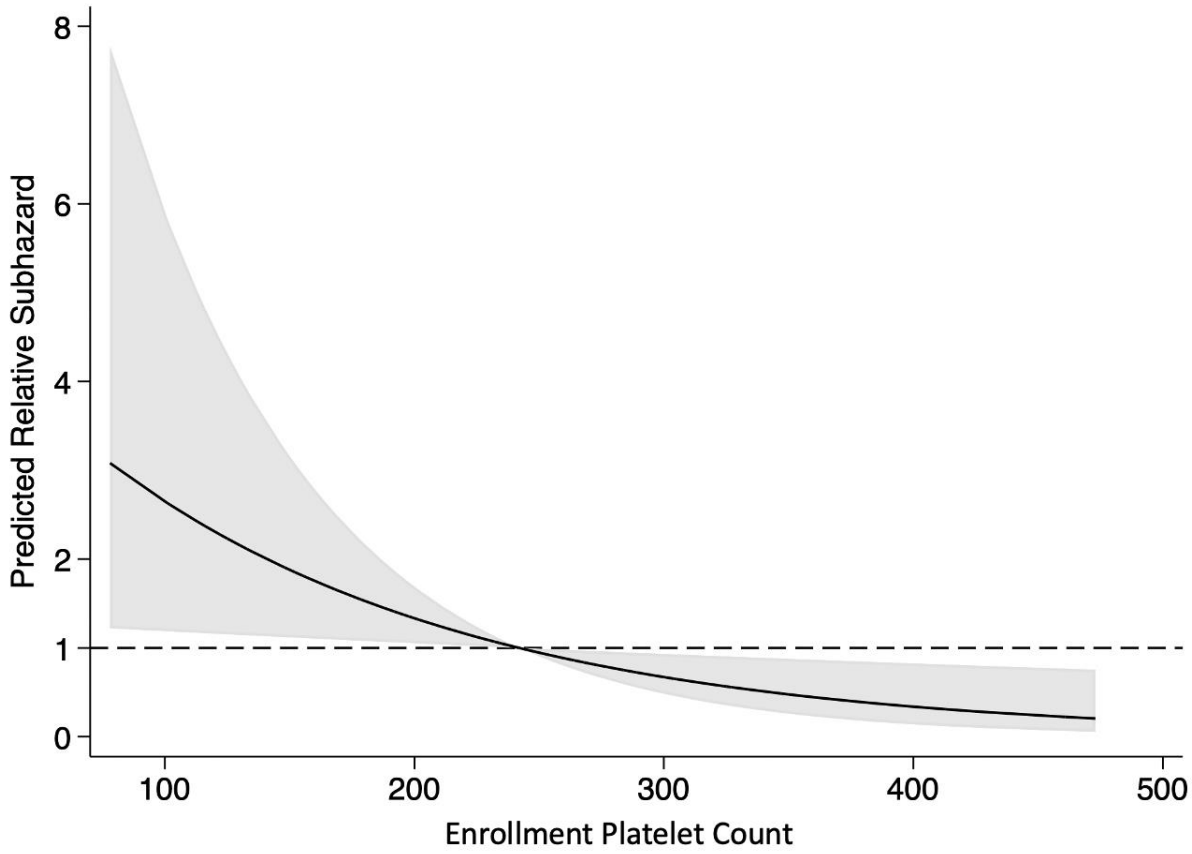
Panel A: MA: maximum amplitude (mm), Panel B: α: alpha angle (degrees), Panel C: G: shear elastic modulus (dynes/cm^2), and Panel D: clotting index. Patients who developed venous thromboembolism (VTE) during the index hospitalization are represented by larger circles. The color of circles represents thromboelastography measurement results as shown on the panels to the right of each plot.



Panel A demonstrates that low platelet count (toward the left on the x axis) was associated with low fibrinogen level (toward the bottom side of y axis), and that both low platelet count and low fibrinogen were associated with low MA (darker color of circles). Patients who developed VTE (large circles) tended to cluster to the bottom left of the plot and have a darker color, indicating that patients who developed VTE tended to have lower platelet count, lower fibrinogen, and lower MA

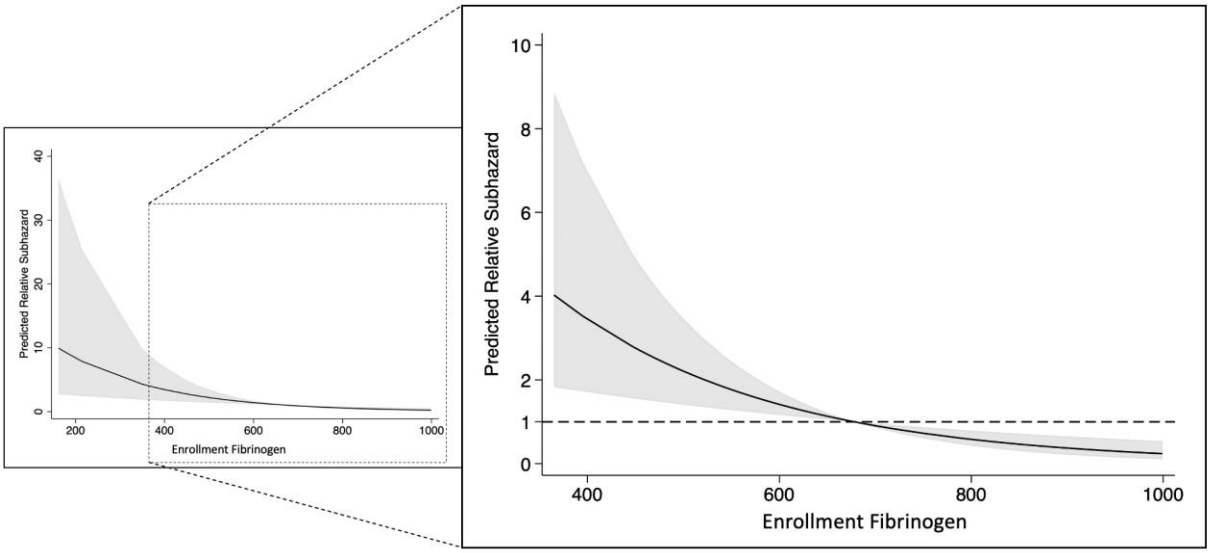
Supplemental Figure S3: Predicted Relative Subhazard for Fibrinogen

Predicted relative subhazard for the risk of venous thromboembolism compared to the median baseline platelet count. The dotted line at a subhazard ratio of 1 represents the reference line.



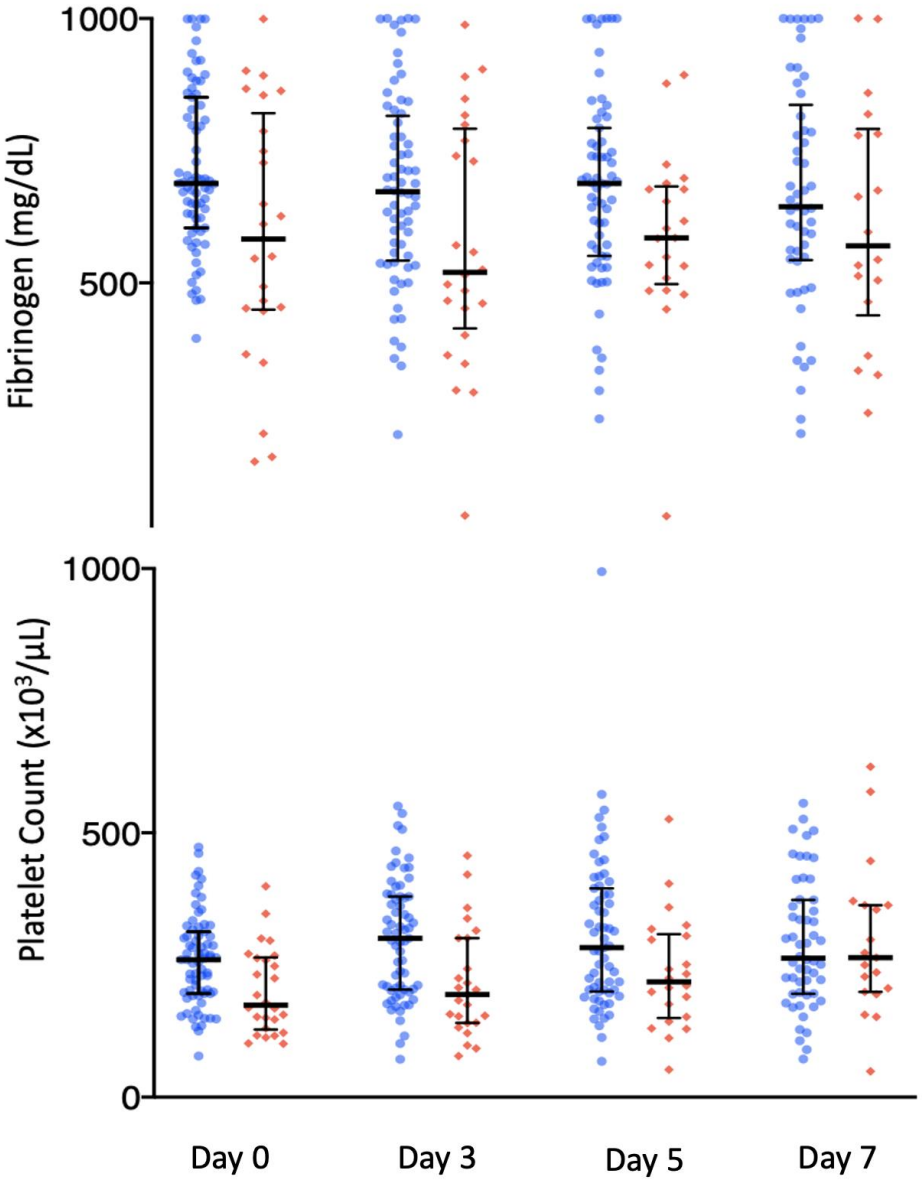
Supplemental Figure S4: Predicted Relative Subhazard for Platelet Counts

Left: Predicted relative subhazard for the risk of venous thromboembolism compared to the median intensive care unit (ICU) admission fibrinogen level. Right: Zoomed in image including 96% of ICU admission measures. The dotted line at a predicted subhazard ratio of 1 represents the reference line and intersects with the curve at the median ICU admission fibrinogen level.



Supplemental Figure S5: Trend of Platelet Counts and Fibrinogen Stratified by Venous Thromboembolism Status

Dot plot of platelet counts and fibrinogen levels on days 0, 3, 5, and 7 of enrollment grouped by patients who did not develop a venous thromboembolism (blue circles) and those who did develop a venous thromboembolism (red diamond) during the index hospitalization. Each dot represents a single measurement. The median (bolded center line) and interquartile range (brackets) are also denoted for measurements at each time point.



Supplemental Figure S6: Scatter Plot of Immature Platelet Fraction and Platelet Counts

Scatter plot of the immature platelet fraction (IPF) compared to the platelet count. As the platelet count declines even within the normal range, the IPF increases consistent with intact platelet production in the setting of a consumptive process.