Plasma Thrombomodulin Predicts Thrombotic Events and Mortality in Hospitalized COVID-19 patients

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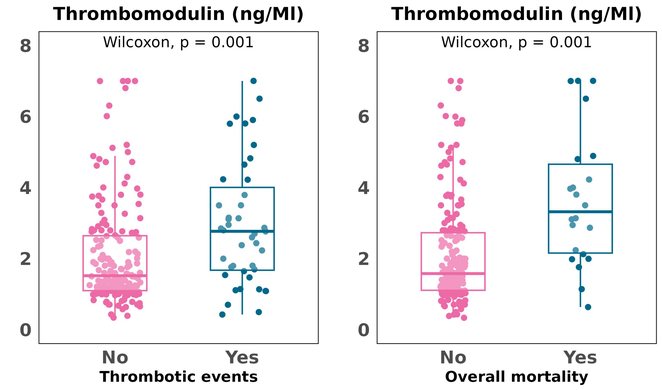
BACKGROUND

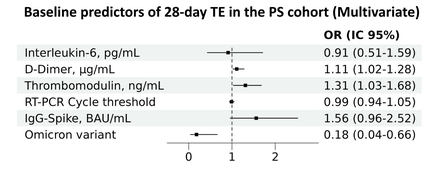
Plasma concentration of soluble thrombomodulin (sTM) is a marker of endothelial damage, and its elevation has been linked to cardiovascular diseases. The study aims to evaluate the predictive potential of sTM for thrombotic events, one of the most serious complications of COVID-19.

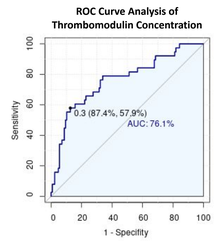
METHODS

Nested case-control study within a large cohort of hospitalized COVID-19 patients throughout the pandemic. Cases involved serious venous and arterial thrombotic events (TE) up to 28 days following hospital admission and they were compared with controls matched by sex, age, Charlson comorbidity index, and WHO-COVID-19 severity scale by propensity scores (PS) in a 1:3 ratio. We determined the plasma concentration of sTM in all available frozen samples collected prior to the TE using an automated immunoassay technique.

Elevated **soluble thrombomodulin** levels were significantly associated with both **thrombotic events and mortality** in hospitalized COVID-19 patients. The measurements of thrombomodulin, along with D-dimer plasma levels, could enhance **thrombotic risk assessment** in this population.





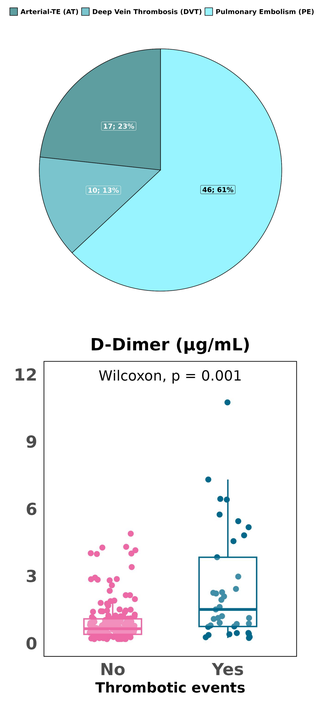


RESULTS

Between March 1st, 2020 and July 31st, 2022, a total of 2524 patients were hospitalized due to SARS-CoV-2 infection (22% Omicron variant). Forty-three percent of them were female and the median (Q1, Q3) age at admission was 67 (54, 80) years. There were 73 TE (56 venous-TE: 46 pulmonary embolism (PE) and 10 deep vein thrombosis (DVT); 17 arterial-TE (AT)) accounting for an incidence rate [95% CI] of 1.15 [0.90-1.44] per 1000 patient-days of follow-up. Frozen plasma samples were available in 43 cases (29 PE, 6 DVT, 8 AT) and in 176 PS-matched controls. There was no significant correlation between sTM and D-dimer (DD) (R [p-value] +0.01 [0.85]). Elevated plasma concentration of sTM was significantly associated with both mortality (median [Q1, Q3], 3.32 [2.16, 4.65] vs. 1.58 [1.11, 2.73] ng/mL; p=0.001) and TE (2.77 [1.67, 4.01] vs. 1.52 [1.1, 2.65] ng/mL; p=0.001), while DD showed a specific association with TE (2.1 [0.83, 5.6] vs. 0.66 [0.4, 1.12] mcg/mL; p=0.001). The association with thrombotic events remained in adjusted models (OR [95%CI] per unit increase, 1.31 [1.03-1.68] for sTM; 1.11 [1.02-1.28] for DD). The adjusted regression model that included both variables (sTM and DD) improved significatively the predictive capacity of the same model without sTM (p-value=0.011; sensitivity 84% and specificity 32% for TE diagnosis).

Baseline Characteristics of all patients and in the PS cohort

	All Patients				Propensity Matched cohort		
		Thrombotic events			Thrombotic events		
	All	No	Yes	P-value	No	Yes	P-value
N	2524	2451	73	-	299	73	-
Female sex	1092 (43)	1060 (43)	32 (44)	0.999	127 (42)	32 (44)	0.949
Age, years	67 (54, 80)	67 (54, 80)	72 (61, 79)	0.121	72 (61, 79)	72 (61, 79)	0.902
Charlson Comorbidity Index	3 (1, 5)	3 (1, 5)	4 (2, 5)	0.021	4 (2, 5)	4 (2, 5)	0.961
Any comorbidity	1892 (75)	1831 (67)	61 (84)	0.139	253 (85)	61 (84)	0.939
Cardiovascular disease	849 (34)	821 (33)	28 (38)	0.490	112 (37)	28 (38)	0.969
Hypertension	1169 (46)	1133 (46)	36 (49)	0.735	167 (56)	36 (49)	0.462
Diabetes	622 (25)	606 (25)	16 (22)	0.653	95 (32)	16 (22)	0.097
WHO COVID-19 severity score (5-6-7)	96 (4)	84 (3)	12 (16)	0.001	54 (18)	12 (16)	0.999
FiO2, %	28 (24, 32)	28 (24, 32)	28 (28, 36)	0.083	28 (28, 35)	28 (28, 36)	0.592
eGFR, mL/min/1.73 m²	91.8 (65.8, 105)	91.8 (65.8, 105)	89.5 (64.5, 98)	0.045	87 (63, 99)	89.5 (64.5, 98)	0.808
C-reactive protein, mg/dL	44 (16.6, 93.4)	44 (16.7, 93)	44 (9.9, 113)	0.821	59 (25, 120)	44 (9.9, 113)	0.405
IL-6, pg/mL	33 (9.6, 118.7)	33 (9.4, 117)	35.5 (18.5, 222)	0.058	51 (14.6, 159)	35.5 (18.5, 222)	0.525
Ferritin, ng/dL	269 (124, 556)	269 (123, 555)	291 (134, 586)	0.606	333 (149, 664)	291 (134, 586)	0.552
Lactate Dehydrogenase, U/L	246 (201, 315)	246 (201, 313)	275 (229, 426)	0.001	254 (204, 322)	275 (229, 426)	0.017
NLR	4.5 (2.8, 7.9)	4.4 (2.8, 7.8)	6.1 (4, 12.4)	0.001	5 (3, 9.5)	6.1 (4, 12.4)	0.054
D-Dimer, µg/mL	0.7 (0.4, 1.4)	0.7 (0.4, 1.4)	2.3 (0.8, 7.4)	0.001	0.75 (0.4, 1.46)	2.3 (0.8, 7.4)	0.001
INR	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1, 1.2)	0.968	1.1 (1, 1.2)	1.1 (1, 1.2)	0.982
Platelets, x 10^3/µL	186 (146, 238)	186 (146, 238)	214 (169, 289)	0.002	175 (141, 226)	214 (169, 289)	0.001
RT-PCR Cycle threshold	25 (19, 31)	25 (19, 31)	29 (22, 33)	0.012	24 (19, 30)	29 (22, 33)	0.007
SARS-CoV-2 vaccination	576 (23)	563 (23)	13 (18)	0.371	52 (17)	13 (18)	0.999
SARS-CoV-2 IgG immunity							
IgG-N, positive	623 (25)	595 (24)	28 (38)	0.003	48 (16)	28 (38)	0.022
IgG-S, positive	974 (39)	938 (38)	36 (49)	0.020	70 (23)	36 (49)	0.059
IgG-S, BAU/mL	21.2 (4.8, 314)	20.6 (4.8, 307)	78 (4.8, 476)	0.097	9.8 (4.8, 125)	78 (4.8, 476)	0.041
Assumed Variant				0.001			0.001
pre-alfa	1224 (48.5)	1195 (49)	29 (39)		168 (56)	29 (39)	
alfa	511 (20.2)	483 (19)	28 (38)		58 (19)	28 (38)	
delta	219 (8.7)	209 (9)	10 (14)		15 (5)	10 (14)	
omicron	552 (21.9)	546 (22)	6 (8)		54 (18)	6 (8)	
Clinical events at 28 days							
Overall mortality	237 (9)	226 (9)	11 (15)	0.138	30 (10)	11 (15)	0.357
Mechanical ventilation	148 (6)	133 (5)	15 (21)	0.001	45 (15)	15 (21)	0.165
NIV or HFO	211 (8)	192 (8)	19 (26)	0.001	42 (14)	19 (26)	0.030
ICU admission	207 (8)	181 (7)	26 (36)	0.001	51 (17)	26 (36)	0.001



CONCLUSIONS

Elevated soluble thrombomodulin levels were significantly associated with both thrombotic events and mortality in hospitalized COVID-19 patients. The measurements of thrombomodulin, along with D-dimer plasma levels, could enhance thrombotic risk assessment in this population.

ADDITIONAL KEY INFORMATION

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