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## Thromboelastometry and D-Dimer Elevation in Coronavirus-2019



To the Editor:

SEVERE elevation of D-dimer is a hallmark of septic shock and a predictor of mortality in coronavirus-2019 (COVID-19) disease.<sup>1</sup> D-dimer reflects the extent of plasmin-mediated degradation of cross-linked fibrin, thereby causing intravascular coagulation. Use of thromboelastometry has gained popularity to assess systemic fibrinolysis in liver transplantation and major trauma,<sup>2</sup> but its utility has not been fully elaborated in the critical care setting.<sup>3</sup> We therefore analyzed the laboratory and thromboelastometry data from 11 critically ill patients receiving mechanical lung ventilation and intensive care support for COVID-19 at the R Adams Cowley Shock Trauma Center over a 2-day period. The Institutional Review Board approved the study. Patients were characterized as follows (data in median [25%-75% quartiles] or percentage); median age 53 years (45.5-65.5 y), body mass index 28.1 (27.1-34.6), 64% male, 54.5% hypertensive, and 45.5% diabetic. Patients were dichotomized into 2 groups on the basis of D-dimer levels 5 times the

upper limit of normal (649 ng/mL fibrinogen equivalent unit). Three of 6 patients in the high D-dimer group were on extracorporeal membrane oxygenation support. Despite highly significant C-reactive protein and D-dimer elevations in the latter group, systemic fibrinolysis was not detected either on EXTEM or FIBTEM (maximal lysis 0%). D-dimer has a half-life of about 8 hours and reflects in vivo thrombus formation.<sup>4</sup> On the other hand, thromboelastometry only measures the reserve hemostasis capacity in the collected blood using a high-dose coagulation trigger (eg, tissue factor). Tissue plasminogen activator is an important trigger of fibrinolysis in vivo, but its half-life is normally less than 3 minutes.<sup>5</sup> Circulating plasminogen activator inhibitor-1 levels are increased during Severe Acute Respiratory Syndrome (SARS) corona virus infection.<sup>6</sup> Systemic fibrinolysis thus is unlikely to occur in COVID-19 patients with cytokine storm (Table 1).

Raza et al. previously showed that only 5% of trauma patients had fibrinolysis on ROTEM, whereas 57% of patients had moderate fibrinolysis with a median D-dimer level of 38,687 ng/mL.<sup>7</sup> In our patients, a median D-dimer fibrinogen equivalent unit of 15,465 ng/mL and fibrinogen 734 mg/dL showed that only 0.21 % of fibrinogen was converted to D-dimer. In contrast, the data in the study by Raza et al showed that 1.84% of fibrinogen (median 210 mg/dL) was converted to D-dimer. Taken together, critically ill COVID-19 patients demonstrated significant elevations in D-dimer consistent with microvascular thromboses, but only small fractions of fibrin seem to be broken down locally and systemic fibrinolysis is rarely observed.

Table 1

Laboratory Data of Patients with Moderate versus Severe D-Dimer Elevations

	D-Dimer (ng/mL)	
	≤3,245	>3,245
Standard laboratory	n = 5	n = 6
CRP (mg/dL)	4.9 (3.8-26.1)	27.5 (13.0-32.7)
D-dimer (ng/mL)	2,410 (1,220-2,800)	15,465 (8,050-19,730)
Fibrinogen (mg/dL)	478 (351-1,057)	734 (567-1,016)
Hematocrit (%)	28.4 (24.4-30.3)	25.9 (22.1-28.7)
Platelet (× 10 <sup>9</sup> /mL)	211 (152-269)	144 (104-301)
PT (sec)	14.7 (13-14.7)	15.1 (14.9-15.4)
Thromboelastometry		
EXTEM-CT (s)	73 (69-74)	76.5 (73-91.5)
EXTEM-A10 (mm)	63 (60-70)	67 (61.5-68.9)
FIBTEM-A10 (mm)	30 (30-36)	36.5 (32.8-43.4)
EXTEM-ML (%)	0	0

NOTE. Thromboelastometry was performed on the ROTEM Delta (TEM Innovations, Munich, Germany). EXTEM and FIBTEM reagents contain hexadimethrine bromide, that neutralizes heparin. Five patients in the high D-dimer group were on intravenous heparin. Reference ranges: C-reactive protein <1 mg/dL; D-dimer <640 ng/mL fibrinogen equivalent unit; fibrinogen 216-438 mg/dL; hematocrit 37%-50%; platelet 153-367 × 10<sup>9</sup>/mL; prothrombin time 9.6-11.2 sec; EXTEM clotting time 43-82 seconds; EXTEM clot amplitude at 10 minutes 46-67 mm; FIBTEM clot amplitude at 10 minutes 7-24 mm; EXTEM maximal lysis <15%.

Abbreviations: A10, clot amplitude at 10 minutes; CRP, C-reactive protein; CT, clotting time; ML, maximal lysis; PT, prothrombin time.

## Conflict of Interest

None.

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