Subclinical Hypercoagulable Viscoelastic Characteristics Associate With Post-Acute Sequelae of SARS-CoV-2 Physical Symptoms in COVID Acute Lung Injury/Acute Respiratory Distress Syndrome Survivors

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Rationale: COVID-19 acute lung injury and acute respiratory distress syndrome (ALI/ARDS) are associated with hypercoagulability and reduced fibrinolysis. Emerging evidence suggests that thrombo-inflammation may underly post-acute sequelae of SARS CoV-2 (PASC). Rotational Thromboelastometry (ROTEM) is a sensitive and comprehensive measure of dysregulated coagulation; potentially useful in characterizing subclinical dysregulated coagulation in COVID ALI/ARDS survivors. We hypothesized that COVID ALI/ARDS survivors with PASC phenotypes would have subclinical evidence of persistent hypercoagulability.
Methods: We conducted a single-center New York City-based prospective cohort study of 93 adults who survived COVID-19 ALI/ARDS hospitalization in 2020. Participants were not receiving treatment with dual antiplatelet or anticoagulation and denied genetic disorders of coagulation at 15-month follow-up when they underwent assessment of fresh whole-blood samples using ROTEM. We concurrently measured the severity and frequency of 43 symptoms via questionnaires. The primary ROTEM parameter exposures of interest were maximum clot firmness (MCF) in EXTEM, INTEM, and FIBTEM assays. The primary outcome of interest was PASC positivity based on the NIH Recover definition of a PASC score ≥ 12. We tested cross-sectional associations of ROTEM measures with the predicted risk of PASC phenotypes using generalized additive models with covariable balanced propensity scores to adjust for demographics, comorbidities, and single antiplatelet medication use. In sensitivity analyses, we tested associations with severe symptom phenotypes, defined as patient-reported moderate or greater post-exertional malaise (PEM), fatigue, or brain fog.
Results: COVID ALI/ARDS survivors had a mean (SD) age of 55 (11) and 40% were women. Fifty (54%) received invasive mechanical ventilation, 17 (18%) received non-rebreather mask or non-invasive mechanical ventilation, and 26 (28%) received only nasal cannula oxygen. In adjusted analyses, we found that greater clot strength (MCF) in the INTEM and FIBTEM assays were directly and linearly associated with a higher predicted risk of PASC positivity. We observed similar direct linear associations of greater clot strength with predicted risk of PEM and fatigue, but not brain fog (Figure 1). Similar significant relationships were not identified in EXTEM assays.
Conclusion: At 15 months follow-up, PASC positivity, PEM, and fatigue, but not brain fog, are associated with a subclinical hypercoagulable profile that appears to be driven by fibrinogen dysregulation in COVID ALI/ARDS survivors. Further work is needed to externally validate these findings and to investigate mechanistic drivers of these associations that may elucidate novel diagnostic and treatment approaches for physical symptoms of long COVID.

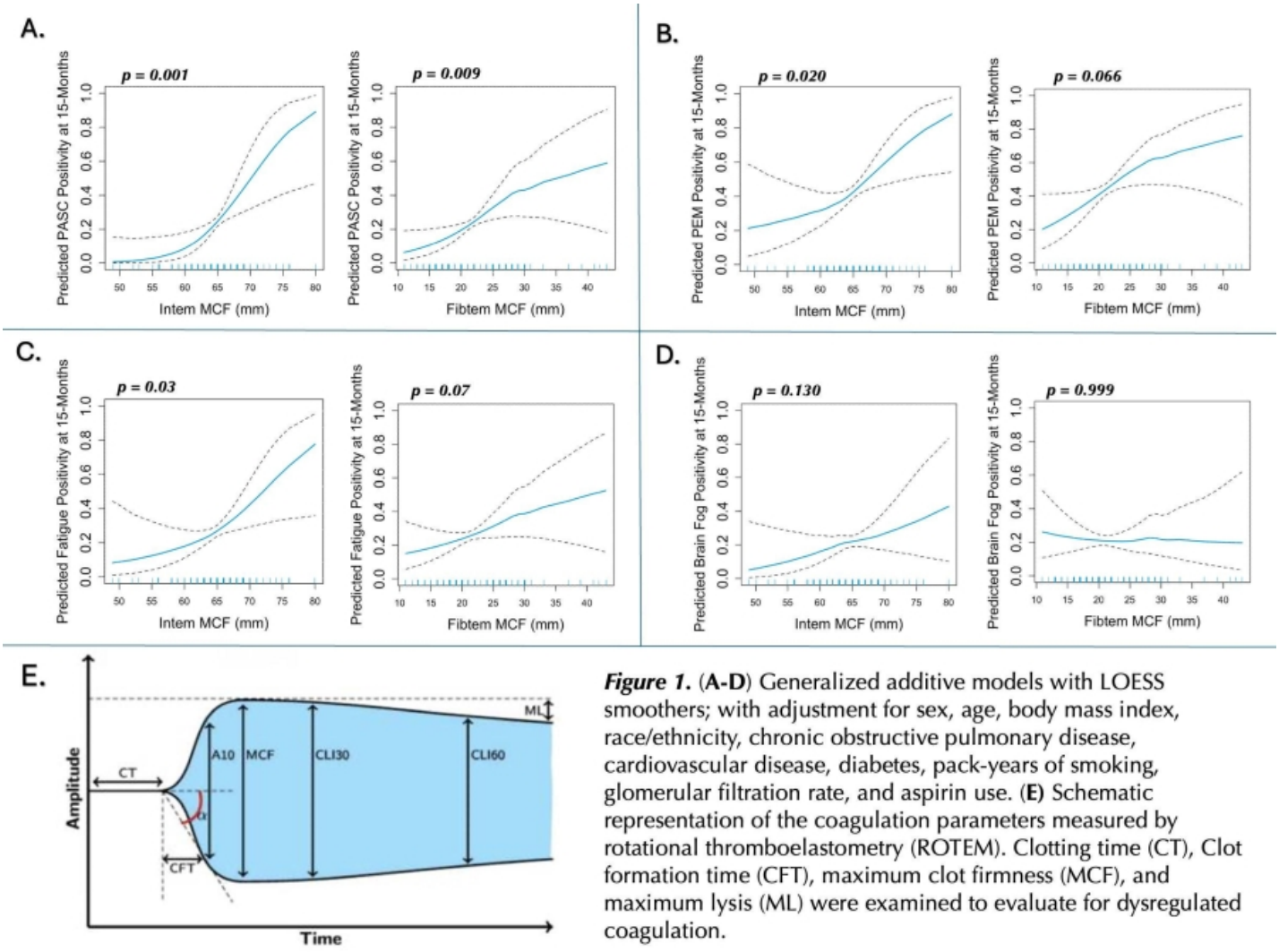

Figure 1. (**A-D**) Generalized additive models with LOESS smoothers; with adjustment for sex, age, body mass index, race/ethnicity, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, pack-years of smoking, glomerular filtration rate, and aspirin use. (**E**) Schematic representation of the coagulation parameters measured by rotational thromboelastometry (ROTEM). Clotting time (CT), Clot formation time (CFT), maximum clot firmness (MCF), and maximum lysis (ML) were examined to evaluate for dysregulated coagulation.

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