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Identifying Novel Subphenotypes in COVID-19 Using Protein Biomarkers

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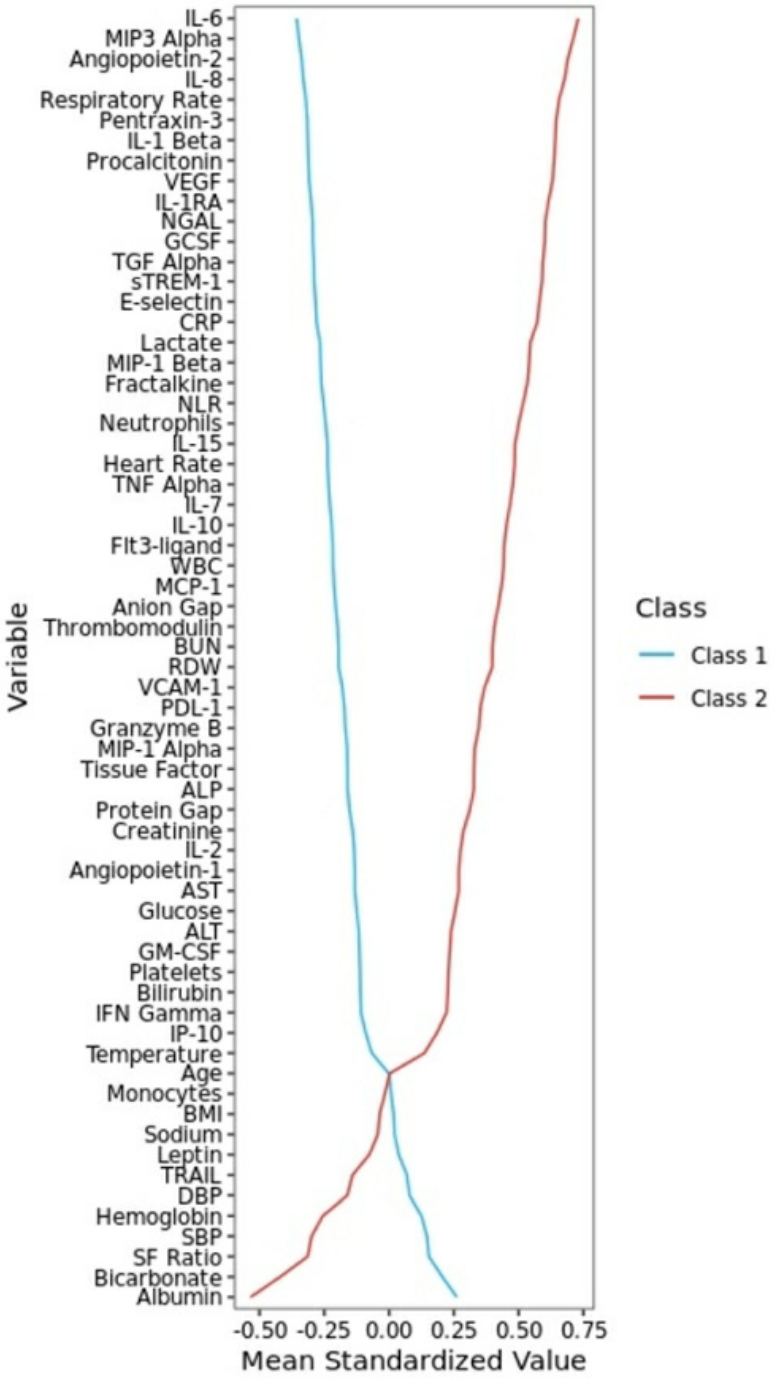
RATIONALE: COVID-19 is widely heterogeneous in presentation, even across patients with similar demographics and medical history. Identification of subphenotypes based on host immune responses that are biologically discrete and predict outcomes may enable personalized COVID-19 therapies. Accordingly, using a composite of electronic health record (EHR) data and 36 research biomarkers, we sought to compare COVID-19 immune responses across patients of varying disease severity, identify subphenotypes within hospitalized COVID-19 patients, and test for heterogeneity of treatment effect (HTE) to intravenous corticosteroids across these subphenotypes. METHODS: In this multicenter retrospective analysis of prospectively collected data, patients presenting to three medical centers from March, 2020 to May, 2021 were eligible if they had a positive PCR test or ICD-10 code indicative of COVID-19. Plasma protein biomarkers were measured from specimens acquired during routine clinical care, and values were compared across outpatients, inpatients not requiring intensive care (non-ICU), and inpatients requiring intensive care (ICU). Latent Profile Analysis (LPA), using both EHR data and biomarkers, was used to identify subphenotypes of COVID-19 inpatients. HTE for corticosteroid use among LPA classes was evaluated using an adjusted logistic regression model for in-hospital mortality. RESULTS: For most biomarkers, significantly different levels were observed between COVID-19 outpatients (n= 153), non-ICU (n = 229), and ICU patients (n = 170) with an increasing trend following severity of illness. Variables with the greatest observed differences included sTREM-1, IL-6, procalcitonin, and IL-8. TRAIL was a notable exception with outpatients showing higher values. LPA identified two classes with 270 patients in Class 1 and 129 in Class 2. Class 2 had higher circulating inflammatory markers, such as IL-6, MIP-3α, angiopoietin-2, and IL-8 (Figure). In contrast, higher levels of albumin and bicarbonate characterized Class 1. Class 2 had significantly longer median length of stay (8.6 days [IQR 4.9, 16.1] vs 4.7 days [IQR 2.5, 7.7] $p<0.001$) and significantly higher in-hospital mortality than Class 1 (29.5% vs 6.3%; $p<0.001$). HTE was observed, with corticosteroid treatment associated with decreased risk for mortality in Class 2 and increased risk for mortality Class 1 (OR 0.69 vs 4.6; p-value for HTE 0.03). CONCLUSIONS: Plasma protein biomarkers varied significantly by disease severity in COVID-19 patients, with higher levels observed in the sickest patients. LPA identified two distinct classes of COVID-19 with divergent clinical outcomes. Notably, differential treatment responses were observed with corticosteroid therapy in the classes, suggesting this algorithm has the potential to personalize COVID-19 interventions.

Figure: Mean Standardized Value Plot for COVID-19 Subphenotypes. Displays separation between the mean value of protein biomarkers, laboratory measurements, and vitals between the clusters. Biomarker measurements are within -1 to 6 hours of the first recorded vital sign. Labs and vitals are before biomarker collection or within 2 hours after.



Abbreviations: IL = Interleukin; MIP = Macrophage inflammatory protein; VEGF = Vascular endothelial growth factor; RA = Receptor antagonist, NGAL = Neutrophil gelatinase-associated lipocalin; GCSF = Granulocyte colony-stimulating factor; TGF = Transforming growth factor; TREM = Triggering receptor expressed on myeloid cells, CRP = C-reactive protein; NLR = Neutrophil-lymphocyte ratio; TNF = Tumour necrosis factor; WBC = White blood cell count; MCP = Monocyte chemoattractant protein; BUN = Blood urea nitrogen; RDW = Red cell distribution width; VCAM = Vascular cell adhesion molecule; PDL = Programmed death-ligand; ALP = Alkaline phosphatase; AST = Aspartate Aminotransferase; ALT = Alanine aminotransferase; GM-CSF = Granulocyte-macrophage colony-stimulating factor; INF = Interferon; IP = Interferon gamma-induced protein; BMI = Body mass index; TRAIL = TNF-related apoptosis-inducing ligand; DBP = Diastolic blood pressure; SBP = Systolic blood pressure; SF = Spo2/Fio2.

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