CHEST

Using Trajectories of Bedside Vital Signs to Identify COVID-19 Subphenotypes

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BACKGROUND: Trajectories of bedside vital signs have been used to identify sepsis subphenotypes with distinct outcomes and treatment responses. The objective of this study was to validate the vitals trajectory model in a multicenter cohort of patients hospitalized with COVID-19 and to evaluate the clinical characteristics and outcomes of the resulting subphenotypes.

RESEARCH QUESTION: Can the trajectory of routine bedside vital signs identify COVID-19 subphenotypes with distinct clinical characteristics and outcomes?

STUDY DESIGN AND METHODS: The study included adult patients admitted with COVID-19 to four academic hospitals in the Emory Healthcare system between March 1, 2020, and May 31, 2022. Using a validated group-based trajectory model, we classified patients into previously defined vital sign trajectories using oral temperature, heart rate, respiratory rate, and systolic and diastolic BP measured in the first 8 h of hospitalization. Clinical characteristics, biomarkers, and outcomes were compared between subphenotypes. Heterogeneity of treatment effect to tocilizumab was evaluated.

RESULTS: The 7,065 patients with hospitalized COVID-19 were classified into four subphenotypes: group A (n = 1,429, 20%)—high temperature, heart rate, respiratory rate, and hypotensive; group B (1,454, 21%)—high temperature, heart rate, respiratory rate, and hypertensive; group C (2,996, 42%)—low temperature, heart rate, respiratory rate, and normotensive; and group D (1,186, 17%)—low temperature, heart rate, respiratory rate, and hypotensive. Groups A and D had higher ORs of mechanical ventilation, vasopressors, and 30-day inpatient mortality ($P < .001$). On comparing patients receiving tocilizumab (n = 55) with those who met criteria for tocilizumab but were admitted before its use (n = 461), there was significant heterogeneity of treatment effect across subphenotypes in the association of tocilizumab with 30-day mortality ($P = .001$).

INTERPRETATION: By using bedside vital signs available in even low-resource settings, we found novel subphenotypes associated with distinct manifestations of COVID-19, which could lead to preemptive and targeted treatments. CHEST 2024; 165(3):529-539

KEY WORDS: COVID-19; phenotypes; subphenotypes; trajectory; vital signs

ABBREVIATIONS: CRP = C-reactive protein; CVA = cerebrovascular accident; HTE = heterogeneity of treatment effect; ICD-10 = International Classification of Diseases,10th Edition; IQR = interquartile range; MSE = mean squared error

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Take-home Points

Study Question: Can the trajectory of the first 8 h of vital signs identify distinct COVID-19 subphenotypes with different manifestations of the disease and different outcomes?

Results: The study identified four distinct COVID-19 subphenotypes from the vital signs of 7,065 hospitalized patients, with groups A and D showing increased rates of mechanical ventilation, vasopressor use, and 30-day inpatient mortality, as well as group A displaying the highest rate of bacteremia and bacterial pneumonia.

Interpretation: The vital signs trajectory model uses bedside data available in most low-resource settings and reveals unique COVID-19 subphenotypes that can guide targeted treatments.

SARS-CoV-2 continues to be a major cause of morbidity and mortality worldwide. SARS-CoV-2 infection leads to COVID-19, which can result in heterogeneous organ dysfunction, including respiratory failure, acute kidney injury, VTE, shock, and death.[1-3] Discovery of COVID-19 subphenotypes could lead to preemptive and targeted treatments for these diverse manifestations of infection.[4]

Traditionally, studies identifying COVID-19 subphenotypes have used static measurements of vital signs and biomarkers.[5-11] However, the host response to infections, including SARS-CoV-2, is dynamic with physiologic and biological markers that evolve over the course of the hospitalization.[12-15] Clustering patients into a subphenotype based on a one-time measurement via laboratory tests or vital signs may result in subphenotypes with temporal instability. Recent work has shown that the first 8 h of vital signs can identify dynamic sepsis subphenotypes (ie, vitals trajectory subphenotypes) representing distinct manifestations of the heterogenous sepsis syndrome.[16] Similarly, the vitals trajectory subphenotypes may represent varying manifestations of COVID-19 such as respiratory failure and shock. Further, bacterial coinfections have been described in approximately 6% of patients with COVID-19, and vitals trajectory subphenotypes may be associated with different risks of bacteremia and bacterial pneumonia.[17] Importantly, in a secondary analysis of the Balanced Crystalloids Versus Saline in Critically Ill Adults trial, the vitals trajectory subphenotypes demonstrated significantly different treatment responses to balanced crystalloids vs normal saline.[16,18] Similarly, the vitals trajectory subphenotypes may respond differently to COVID-19-specific treatments such as tocilizumab.

The objectives of this current study were as follows: (1) to validate the vitals trajectory model in a multicenter cohort of patients hospitalized with COVID-19; (2) to evaluate the laboratory profiles of the COVID-19 subphenotypes; (3) to evaluate the association of these subphenotypes with adverse outcomes such as VTEs, cerebrovascular accidents (CVAs), shock, respiratory failure, and 30-day inpatient mortality; (4) to investigate the association of subphenotypes with bacterial coinfection; and (5) to evaluate for heterogeneity of treatment responses to tocilizumab therapy.

Study Design and Methods

Study Cohort

We included all adult patients admitted to four academic hospitals in the Emory Healthcare system. Patients who were admitted between March 1, 2020, and May 31, 2022, were included if they had laboratory-confirmed COVID-19 and/or had a primary or secondary International Classification of Diseases, 10th Edition (ICD-10) diagnosis of COVID-19 (U07.1). If a patient had multiple admissions for COVID-19 over the study period, only the first hospitalization was included in the analysis. We excluded patients who were discharged or died within 8 h of hospitalization, given the use of the first 8 h of vital signs for subphenotype classification. We excluded patients who were transferred to a different hospital at any point during their encounter given potential incomplete encounter data. We excluded patients who did not have at least one complete set of vital signs data in the first 8 h of presentation to the hospital (the minimum vitals data required to classify patients into subphenotypes). On the basis of general impracticability and minimal harm, the Emory University institutional review boards granted a waiver of consent for this study (STUDY00001627).

Measurement of Vital Signs

The study included oral temperature, heart rate, respiratory rate, and systolic and diastolic BP from the first 8 h of presentation to the hospital. The vital signs data were divided into eight 1-h blocks of time. No imputation process was used for missing vital signs. The mean

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measurement of a vital sign was used if multiple measurements were available in a 1-h period. The vital signs were standardized to the mean and SD of that vital sign in the originally published training cohort.[16] The rationale for standardization was to avoid weighing vital signs differently (eg, systolic BP weighing more than respiratory rate because it is on a larger scale). In addition, the rationale for standardization to a previous cohort was to ensure that the standardized values are based on a broader cohort rather than having to standardize within new cohorts, which may be smaller and less generalizable.

Application of Vitals Trajectory Algorithm

In the original vitals trajectory study, group-based trajectory modeling was applied to vital signs data in patients with sepsis to identify the vitals trajectory subphenotypes. Sepsis is defined as a dysregulated immune response to infection. In the context of this study and the sepsis subphenotyping strategy employed, we position COVID-19 infection within this broader framework of sepsis. In the sepsis study, we found that a four-group trajectory model fit best. The four vitals trajectory subphenotypes were as follows: group A—hyperthermic, tachycardic, tachypneic, and hypotensive; group B—hyperthermic, tachycardic, tachypneic (all less pronounced than in group A), and hypertensive; group C—lower temperature, heart rate, respiratory rate, and normotensive; group D—lower temperature, heart rate, respiratory, and the most hypotensive subphenotype.

The subphenotypes are defined by a set of five unique polynomial functions describing each vital sign as a function of time from presentation to the hospital (eg, temperature $= \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{time}^2$). The Euclidean distance between a patient's five vital sign measurements at hour 0 and the respective five vital sign measurements for each of the four subphenotypes at hour 0 are calculated and squared. This process is repeated for all available hours of measurement for the patient in relation to each subphenotype, and the resulting squared Euclidean distances over the 8-h period are summed. The patient is then assigned to the subphenotype with the lowest summed mean squared error (MSE) (ie, the subphenotype the patient is the smallest distance from).[19,20] Example cases of study patient vital signs are shown in relation to the reference subphenotype trajectories in Supplementary Methods in the online article.

After patients were classified into subphenotypes, the differences in demographics, comorbidities, and clinical characteristics between the subphenotypes were compared by analysis of variance or χ^2 tests, as appropriate.

Association of Subphenotypes With Laboratory Biomarkers

Laboratory biomarkers were selected a priori for comparison between subphenotypes: C-reactive protein (CRP), WBC count, procalcitonin, ferritin, IL-6, D-dimer, fibrinogen, platelets, creatinine, total bilirubin, troponin, B-natriuretic peptide, and lactic acid. If a patient had multiple measurements of a biomarker in the first 72 h of hospitalization, the maximum value of that biomarker was used (except for platelets, in which case the minimum value was used). For WBC count, the deviation from normal was measured by Acute Physiology and Chronic Health Evaluation II scoring to capture both leukocytosis and leukopenia as abnormal responses. No imputation process was used for patients with missing biomarkers. Nonnormally distributed biomarkers were log-transformed. Biomarker levels were compared between subphenotypes by analysis of variance. All tests of significance were corrected for multiple testing, using the Bonferroni correction.

Association of Subphenotypes With Outcomes

The subphenotypes were evaluated for association with the primary outcome of 30-day inpatient mortality. Logistic regression was performed to evaluate the association with the outcome, adjusting for age, sex, race, and comorbidities (congestive heart failure, chronic pulmonary disease, diabetes, hypertension, chronic kidney disease, liver disease, and metastatic cancer). Group C was used as the reference group based on our prior work, as this subphenotype has "normal" vital signs trajectories and a comparatively lower mortality rate. The subphenotypes were also evaluated for association with VTEs, CVAs, renal replacement therapy, vasopressors, and mechanical ventilation. Patients with VTEs were identified by using the following ICD-10 codes based on previously published work: (1) pulmonary embolism (I26) and (2) DVT (I80.1, I80.2, and I80.3).[21] Patients with CVAs were identified on the basis of the following ICD-10 codes: I61, I62, I63, I69, and I67.[22]

Association of Subphenotypes With Bacterial Coinfection

Incidence of bacteremia on admission and bacteremia ever during hospitalization were compared between the subphenotypes. Bacteremia on admission was defined as any positive noncontaminant blood culture obtained within 72 h of hospitalization. Incidence of bacterial pneumonia during hospitalization was also compared between the subphenotypes. Bacterial pneumonia was defined as any positive noncontaminant sputum, endotracheal, or bronchioalveolar culture. The association between bacterial coinfection and subphenotype was tested by χ^2 test.

Heterogeneity of Treatment Effect to Tocilizumab

Tocilizumab was tested for heterogeneity of treatment effect (HTE) across subphenotypes. The outcome of patients in each subphenotype receiving tocilizumab were compared with that of patients who met the criteria for tocilizumab but were admitted before use of tocilizumab in our healthcare system (before April 2021). Inclusion criteria based on the Randomized Embedded Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Randomised Evaluation of COVID-19 Therapy (RECOVERY) trials were as follows[23,24]: (1) receipt of respiratory or cardiovascular support (high-flow nasal cannula, mechanical ventilation, or vasopressors/inotropes) within 72 h of hospitalization, (2) CRP $\geq$ 75, and (3) receipt of dexamethasone therapy. Further, adapted from trial criteria, our health care system excluded patients with platelets $<$ 50,000, absolute neutrophil count $<$ 1,000, aspartate aminotransferase/alanine aminotransferase $>$ 10 times the upper limit of normal, or active malignancy. The association between tocilizumab and 30-day mortality was evaluated in the overall cohort, adjusting for age, sex, race, ethnicity, comorbidities (congestive heart failure, chronic pulmonary disease, hypertension, diabetes, chronic kidney disease), and the 4C mortality score. HTE across subphenotypes was tested in a "full" model including the baseline covariates, subphenotypes, treatment, and interaction terms between the subphenotype and treatment. *P* values for HTE were calculated by means of a likelihood ratio test between a "nested" model without interaction terms and the "full" model with interaction terms. The following sensitivity analyses were performed: (1) limited to control subjects admitted in the 3-month period immediately preceding tocilizumab use in our system, (2) limited to the cohort of patients who required mechanical ventilation in the first 72 h, and (3) limited to the cohort of patients who required respiratory or cardiovascular support within 24 h of hospital presentation.

Subgroup Analysis by Oxygen Strata and Epoch of Pandemic

Subgroup analyses were performed to evaluate the association of subphenotypes with clinical characteristics and outcomes in patients stratified by oxygen requirements in the first 8 h of hospitalization (supplemental oxygen, high-flow nasal cannula/noninvasive

ventilation, or mechanical ventilation) and stratified by epoch of admission (Alpha-predominant, Delta-predominant, or Omicron-predominant). The epochs were defined on the basis of prior work that "defined the Alpha-predominant period…to 3 July 2021, the Delta-predominant period as 4 July 2021, to 25 December 2021, and the Omicron-predominant period as 26 December 2021 through the last date of enrollment."[25] All analyses were performed with R version 3.6.1.

Results

Of the 9,342 patients hospitalized for COVID-19 (e-Fig 1), 176 patients were excluded for death or discharge within 8 h of presentation, 285 were excluded for transfer to other hospitals, and 1,816 patients were excluded for incomplete vital signs, defined as no data for one or more vital signs in the first 8 h. The cohort with incomplete vital signs had an overall mortality rate of 11.2%.

Of the 7,065 patients included in the study, the median age was 60 years (46-73 years), with 7.0% incidence of VTEs and 3.5% incidence of CVAs during hospitalization. Further, 11% of patients required mechanical ventilation, 11% required vasopressors, and the 30-day inpatient mortality rate was 5.9% (Table 1). The vitals trajectory model was applied to the study cohort, and the distribution of subphenotype membership was group A (n = 1,429; 20%), group B (1,454; 21%), group C (2,996; 42%), and group D (1,186; 17%) (Fig 1). Group A subjects had high temperature, heart rate, and respiratory rate, and were relatively hypotensive. Group B subjects also had high temperature, heart rate, and respiratory rate, and were hypertensive. Group C subjects had lower temperature, heart rate and respiratory rate, and were normotensive.

TABLE 1] Clinical Characteristics and Outcomes of Vitals Trajectory Subphenotypes

Characteristic	Overall	Group A	Group B	Group C	Group D	*P* Value
No.	7,065	1,429	1,454	2,996	1,186	…
Age, y	60 (46-73)	52 (38-64)	58 (48-70)	64 (51-76)	61 (43-73)	< .001
Sex, female	3,663 (51.8)	790 (55.3)	638 (43.9)	1,504 (50.2)	731 (61.6)	< .001
Race						< .001
Black	4,019 (56.9)	863 (60.4)	975 (67.1)	1,568 (52.3)	613 (51.7)	
White	2,182 (30.9)	349 (24.4)	341 (23.5)	1,069 (35.7)	423 (35.7)	
Other	864 (12.2)	217 (15.2)	138 (9.5)	359 (12)	150 (12.6)	
Hispanic ethnicity	511 (7.2)	133 (9.3)	85 (5.8)	198 (6.6)	95 (8)	.001
Comorbidities						
CHF	1,242 (17.6)	188 (13.2)	280 (19.3)	553 (18.5)	221 (18.6)	< .001
Pulmonary disease	1,247 (17.7)	275 (19.2)	266 (18.3)	492 (16.4)	214 (18)	.1
Hypertension	4,333 (61.3)	698 (48.8)	1,099 (75.6)	1,945 (64.9)	591 (49.8)	< .001
Diabetes	2,316 (32.8)	458 (32.1)	593 (40.8)	970 (32.4)	295 (24.9)	< .001
Renal disease	1,689 (23.9)	204 (14.3)	420 (28.9)	793 (26.5)	272 (22.9)	< .001
Liver disease	322 (4.6)	73 (5.1)	58 (4)	126 (4.2)	65 (5.5)	.2
Hospital outcomes						
VTE	494 (7)	128 (9)	115 (7.9)	178 (5.9)	73 (6.2)	.001
CVA	246 (3.5)	27 (1.9)	59 (4.1)	125 (4.2)	35 (3)	.001
Dialysis	517 (7.3)	67 (4.7)	162 (11.1)	213 (7.1)	75 (6.3)	< .001
Mechanical ventilation	746 (10.6)	210 (14.7)	164 (11.3)	236 (7.9)	136 (11.5)	< .001
Vasopressors	791 (11.2)	211 (14.8)	143 (9.8)	273 (9.1)	164 (13.8)	< .001
Inotropes	97 (1.4)	34 (2.4)	10 (0.7)	30 (1)	23 (1.9)	< .001
LOS, d	5 (3-10)	6 (4-11)	6 (3-11)	5 (3-10)	5 (3-10)	.003
Mortality	414 (5.9)	88 (6.2)	71 (4.9)	157 (5.2)	98 (8.3)	.001

Presented is the comparison of demographics, comorbidities, and outcomes between the subphenotypes. Age is presented as medians, and all other values are presented as percentages. Inotropes are defined as dobutamine and milrinone. Mortality represents 30-day hospital mortality. *P* values signify the results of comparisons between subphenotypes through χ^2 or analysis of variance testing, as appropriate. CHF = congestive heart failure; CVA = cerebrovascular accident; LOS = length of stay.

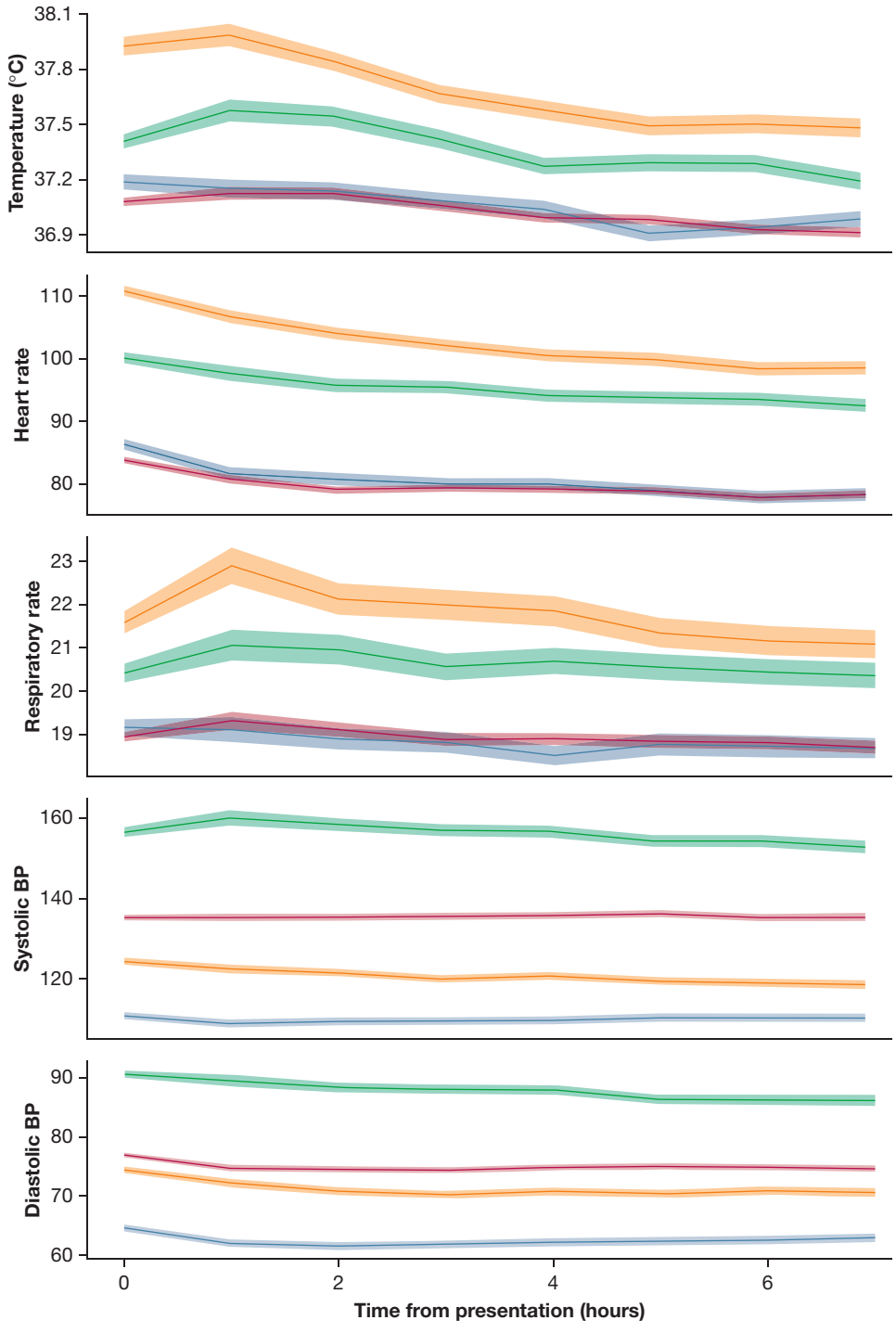

Figure 1 – *Vitals trajectory subphenotypes in patients with COVID-19. By applying a validated algorithm to vital signs (temperature, heart rate, respiratory rate, systolic and diastolic BP) from the first 8 h of hospitalization, four vitals trajectory subphenotypes were identified in a multicenter cohort of 7,065 patients hospitalized with COVID-19: group A (orange [n = 1,429, 20%]), group B (green [1,454, 21%]), group C (red [2,996, 42%]), and group D (blue [1,186, 17%]). Presented are the mean and 95% CI for each vital sign at each hour for the four subphenotypes.*

Group D subjects had lower temperature, heart rate, and respiratory rate, and were hypotensive. Compared with the full 8-h trajectory model, the accuracy of admission vital signs alone in classifying patients was only 70% (e-Table 1), suggesting admission vitals were inadequate for subphenotype classification.

Age was significantly different between subphenotypes ($P < .001$): Group A subjects were the youngest (median age, 52 years; interquartile range [IQR], 38-64 years), followed by group B (58; IQR, 48-70), group D (61; IQR, 43-73), and group C (64; IQR, 51-76). Comorbidities were significantly different, with group A having the lowest burden of congestive heart failure and chronic kidney disease ($P < .001$). Group B had the highest burden of congestive heart failure, hypertension, diabetes, and chronic kidney disease ($P < .001$). There was a significant association between subphenotype and processes of care within the 8-h classification window (e-Table 2). Of the 7,065 patients, 1,210 had positive COVID-19 test results before presentation, with no significant association between subphenotype and time from test to hospital presentation.

In terms of outcomes, group A had the highest rates of requiring mechanical ventilation and vasopressors ($P < .001$), and the highest incidence of VTEs ($P = .001$). Groups B and C had the highest rates of CVAs ($P = .001$). Group B also had the highest requirement for renal replacement therapy ($P < .001$). The inpatient 30-day mortality rate was significantly different between subphenotypes ($P = .001$): 6.2% mortality rate for group A, 4.9% for group B, 5.2% for group C, and 8.3% for group D (Table 1). The distributions of subphenotype membership, outcomes, and demographics stratified by hospital are provided in e-Tables 3 and 4.

Association of Subphenotypes With Laboratory Markers

There were significant differences in levels of inflammatory markers between subphenotypes. Group A had the highest CRP level, with a mean of 135 mg/L (95% CI, 130-141 mg/L), followed by group B (107; 95% CI, 102-113), group D (103; 95% CI, 98-109), and group C (91; 95% CI, 88-94) ($P < .001$). Group A also had the highest WBC and IL-6 levels ($P < .001$) (Fig 2, e-Table 5). Fibrinogen and platelet counts were lowest in group D ($P < .001$). Creatinine and B-natriuretic peptide levels were highest in group B ($P < .001$). The missingness of the laboratory markers is presented in e-Table 6, and missingness was found to be associated with subphenotype membership.

Association of Subphenotypes With Outcomes

Group A had an increased OR of several poor outcomes, when controlling for demographics and comorbidities, with group C serving as the reference group (Fig 3, e-Table 7). Group A had a higher OR of VTE (OR, 1.74; 95% CI, 1.36-2.22; $P < .001$), mechanical ventilation (OR, 2.54; 95% CI, 2.05-3.13; $P < .001$), and vasopressors (OR, 2.28; 95% CI, 1.86-2.80; $P < .001$). Group B had a higher OR of VTE (OR, 1.45; 95% CI, 1.13-1.86; $P = .003$) and mechanical ventilation (OR, 1.42; 95% CI, 1.15-1.77; $P = .001$). Group D had a higher OR of mechanical ventilation (OR, 1.79; 95% CI, 1.42-2.25; $P < .001$) and vasopressors (OR, 1.86; 95% CI, 1.50-2.30; $P < .001$). For the primary outcome, group A and group D had higher ORs of 30-day inpatient mortality (group A: OR, 2.20; 95% CI, 1.65-2.93; group D: OR, 2.00; 95% CI, 1.52-2.63; $P < .001$ for both). Kaplan-Meier survival curves are presented in e-Figure 2. Median time of death was 11 days after hospital presentation in groups A and D, and 12 days for groups B and C.

Using likelihood ratio testing, the addition of subphenotypes was compared with a model adjusted for Sequential Organ Failure Assessment score without the use of subphenotypes. The addition of subphenotypes significantly improved predictive performance for predicting mechanical ventilation, renal replacement therapy, CVAs, and VTEs, but not vasopressor requirement and mortality.

Bacterial Coinfection

The overall incidence of bacteremia on admission was 1.6%. Bacteremia was significantly associated with subphenotype ($P < .001$). Group A had the highest incidence of bacteremia on admission (4.0%), with 1.9% gram-positive and 2.1% gram-negative. Group B had 1.4% bacteremia, group C had 0.8% bacteremia, and group D had 1.7% bacteremia. Bacteremia ever during hospitalization followed the same trend, with the highest rate in group A (6.4%). Bacterial pneumonia during hospitalization also followed the same trend, with the highest rates in group A (7.7%), and with 6.4% in group B, 4.6% in group C, and 5.7% in group D (e-Tables 8-10). Bacterial pneumonia culture results by site of collection are presented in e-Table 11.

Heterogeneity of Treatment Effect to Tocilizumab

The outcome of patients in each subphenotype receiving tocilizumab were compared with patients who met the criteria for tocilizumab but were admitted before use of tocilizumab in our health care system. In the overall cohort, the mortality rate was 27% for patients who did not receive tocilizumab (n = 461) and 31% for patients who received tocilizumab (n = 55).

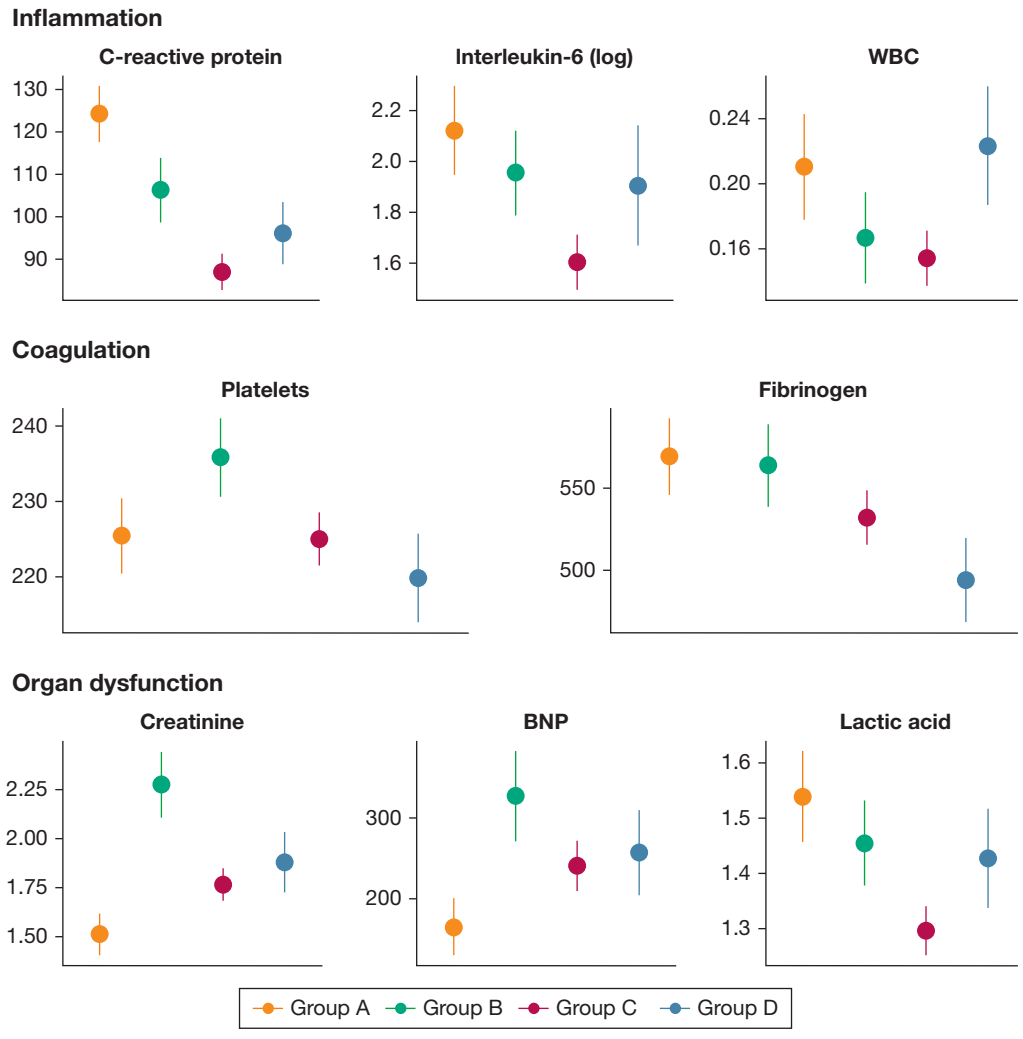

Figure 2 – *Laboratory values compared between vitals trajectory subphenotypes. Laboratory values (most abnormal values in the first 72 h of hospitalization) were compared between the subphenotypes, using analysis of variance testing. Presented are the mean and 95% SD for the values. For WBC, presented is the deviation from the central value as determined by the APACHE II score to capture both leukopenia and leukocytosis. All biomarkers that remained significant after Bonferroni correction for multiple testing (P < .004) are presented. Group A had the highest levels of inflammatory markers including WBC, C-reactive protein, and IL-6. Group D had the lowest platelet count and fibrinogen. Group B had the highest creatinine and BNP. APACHE = Acute Physiology and Chronic Health Evaluation; BNP = B-natriuretic protein.*

Stratified outcomes by subphenotype are presented in Figure 4. In group A, the mortality rate was 25% (35 of 139 patients) in the control cohort compared with 43% (6 of 14 patients) in the tocilizumab cohort. In group B, the mortality rate was 18% (17 of 96 patients) in the control cohort compared with 45% (5 of 11 patients) in the tocilizumab cohort. In group C, the mortality rate was 28% (42 of 150 patients) in the control cohort compared with 5.9% (1 of 17 patients) in the tocilizumab cohort. In group D, the mortality rate was 38% (29 of 76 patients) in the control cohort compared with 38% (5 of 13 patients) in the tocilizumab cohort. The median time to tocilizumab administration was 1.8 days (IQR, 0.8-3.0 days).

In the overall cohort, there was no significant association between tocilizumab and mortality ($P = .3$). Within subphenotypes, there was significant HTE with tocilizumab in predicting 30-day mortality ($P = .001$). In a sensitivity analysis limiting the control group to patients admitted in the 3-month period immediately preceding tocilizumab use in our system, we found similar results, with significant HTE ($P = .002$). In a sensitivity analysis limiting the cohort to patients who required mechanical ventilation, we also found significant HTE ($P = .01$). Finally, in a sensitivity analysis limiting the cohort to patients who required respiratory or cardiovascular support within 24 h of hospital presentation, we found significant HTE ($P = .003$).

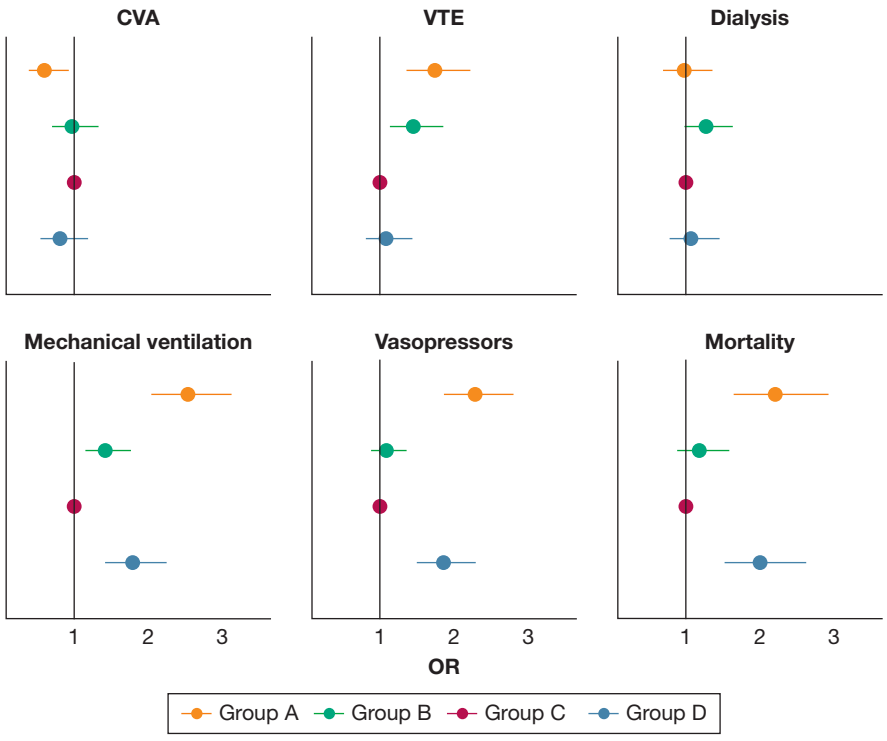

Figure 3 – *OR for hospital outcomes compared between vitals trajectory subphenotypes. Presented are the point estimates of the OR and the 95% CIs. Group A had an increased OR of most poor outcomes, when controlling for demographics and comorbidities with group C serving as the reference group. Both group A and group D had higher OR of 30-day inpatient mortality (group A: OR, 2.20; 95% CI, 1.65-2.93; group D: OR, 2.00; 95% CI, 1.52-2.63; P < .001 for both).*

Subgroup Analysis by Oxygen Strata and Epoch of Pandemic

Patient characteristics and outcomes by subphenotype in subgroups of patients requiring supplemental oxygen, patients requiring high-flow nasal cannula/noninvasive ventilation, and patients requiring mechanical ventilation are presented in e-Tables 12 through 14. In patients requiring supplemental oxygen and patients requiring high-flow nasal cannula/noninvasive ventilation, rates of mechanical ventilation and mortality were significantly different by subphenotype, with group D having the highest mortality rate. When evaluating subphenotype membership distribution in different epochs of the pandemic (Alpha-predominant, Delta-predominant, and Omicron-predominant), we found significant association between group membership and epoch ($P < .001$) (e-Table 15). The distribution of clinical

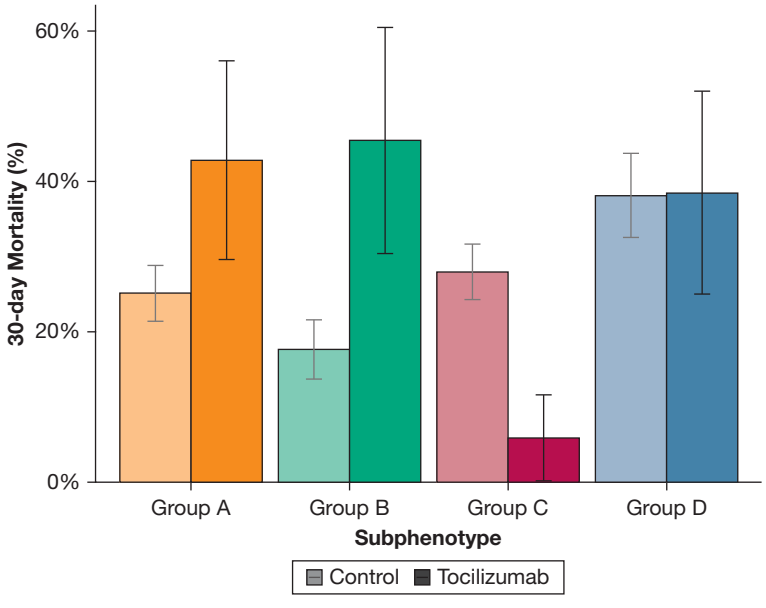

Figure 4 – *Thirty-day mortality for each subphenotype receiving tocilizumab vs control. Presented are the 30-day mortality rates with SE for patients in each subphenotype receiving tocilizumab compared with patients who met the criteria for tocilizumab but were admitted before use of tocilizumab in our health care system (before April 2021). Inclusion and exclusion criteria for tocilizumab were based on RECOVERY and REMAP-CAP trials. There was significant heterogeneity of treatment effect of tocilizumab across the subphenotypes (P = .001). RECOVERY = Randomised Evaluation of COVID-19 Therapy; REMAP-CAP = Randomized Embedded Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia.*

characteristics and outcomes by subphenotype in the different epochs are presented in e-Tables 16 through 18. Changes in trajectory membership, mortality, and bacteremia rates over the course of the pandemic are presented in e-Figure 3 and e-Table 19.

Model Sensitivity Analyses

The goodness of fit for patients to their respective subphenotype was assessed by using the MSE of patients from their assigned subphenotype. The MSE mean, median, and IQR for the subphenotypes are presented in e-Table 20. The distribution of MSE was consistent with prior work on vitals trajectory subphenotypes in sepsis, suggesting that the fit of patients into each subphenotype was similar to prior work (e-Fig 4).

The number of vital signs was different by subphenotype, with a median of five sets of vital signs in groups A and B, and a median of four sets of vital signs in groups C and D. To evaluate whether missingness of vital signs affects group classification, carry-forward imputation was used to equalize the number of vital signs across study patients, and there was found to be significant agreement in classification (91.4%) between both imputed and nonimputed models.

Discussion

We present the validation of an established sepsis subphenotyping algorithm using routinely measured bedside vital signs in patients with COVID-19. We found a similar distribution of clinical characteristics and outcomes in the COVID-19 subphenotypes compared with the sepsis subphenotypes. Similar to the sepsis subphenotypes, group A and group D had the highest 30-day mortality. The subphenotypes were also associated with varying manifestations of severe COVID-19, including VTEs, CVAs, the need for vasopressors and mechanical ventilation, and rates of bacterial coinfections. Finally, the COVID-19 subphenotypes had significant heterogeneity in responses to tocilizumab therapy.

Although multiple sepsis and COVID-19 subphenotypes exist in the literature, few have been validated across multiple cohorts, and there have been no published use-cases of these subphenotypes in precision enrollment in clinical trials.[26] The generalizability, reproducibility, physiologic plausibility, and routine availability of vitals data make the vitals trajectory model a candidate model for precision enrollment in COVID-19 and sepsis clinical trials. The vitals trajectory model is as follows: (1) generalizable: it has been validated across time (2014-2019 in the original study and 2020-2022 in the current study) and health care systems (Emory Healthcare and Vanderbilt University in the original study); (2) reproducible: the model has resulted in consistent subphenotypes with similar distribution of clinical characteristics and outcomes in varying cohorts including all patients with suspected infection, patients with sepsis, and now patients with COVID-19; (3) physiologic plausibility: the model uses objective vital signs measurements with clear physiologic significance; (4) routinely available data: the model uses bedside data that are available in most low-resource settings, although reliability and accuracy of measurement devices may vary.

In the vitals trajectory model, group A was characterized by high temperature, heart rate, and respiratory rate, and relatively lower BP. Consistent with group A in the sepsis subphenotypes, group A patients with COVID-19 were younger and had fewer comorbidities on admission. Group A had the highest OR of 30-day mortality, as well as the highest OR of requiring mechanical ventilation and vasopressors. In addition, this subphenotype had a hyperinflammatory profile, with elevated WBC count and CRP and IL-6 levels. This subphenotype may be analogous to the hyperinflammatory subphenotype identified in prior ARDS research.[27,28]

Group D was an older subphenotype, characterized by low temperature, heart rate, and respiratory rate, and the lowest BP. Group D also had higher odds of 30-day mortality and requirements for mechanical ventilation and vasopressors. However, these patients did not exhibit the same hyperinflammatory profile as group A. In the original sepsis study, group D had a lower risk of death when given balanced crystalloids compared with normal saline (20% mortality compared with 35%).[16] Whether this same treatment benefit exists in group D patients with COVID-19 requires further research.

Although the COVID-19 subphenotypes were found to have similar distribution of clinical characteristics as the sepsis subphenotypes, there were notable differences. The patients in the COVID-19 cohort had higher incidence of respiratory failure requiring mechanical ventilation and higher 30-day mortality compared with the original study of patients with all-cause infection. Also, the prevalence of group B and group C was higher in the COVID-19 cohort (21% and 42%, respectively)

compared with group B and group C in the original study (13% and 32%, respectively). The differences in overall outcomes and prevalence of subphenotypes may reflect differences in the host responses to COVID-19 compared with other causes of infection.

Finally, in the evaluation of tocilizumab in patients with COVID-19, there was significant heterogeneity of treatment effect across subphenotypes. Despite no significant association between treatment and mortality rate in the overall study cohort, we found varying mortality rates between treatment and control within the subphenotypes. Notably, mortality benefit was not observed in group A, the subphenotype with the highest CRP in the overall study cohort. However, all patients included in the tocilizumab vs control analysis had a CRP $\geq$ 75 based on RECOVERY study criteria, which may have reduced the effect of the CRP variability between subphenotypes on tocilizumab response. This exploratory analysis was limited by the retrospective nature and small sample size. However, the analysis illustrates a potential use-case for these physiologic trajectories in precision enrichment of COVID-19 clinical trials.

The study has several limitations. First, this was a retrospective study, and vital signs were measured as clinically indicated. Prospective measurement of vital signs is necessary to ensure equal frequency of vital sign measurements for all patients. Second, the study took place within a single health care system, which may limit generalizability. Third, the laboratory markers were collected as clinically indicated, and the missingness was associated with subphenotypes. Fourth, temporal subphenotypes may be modified by processes of care within the subphenotyping window. Fifth, there was no time to event data for VTEs and CVAs, and death may be a competing risk. Finally, it is unknown how this subphenotyping model compares with other existing subphenotyping models, and this represents an important area for future research.

Interpretation

We validated a sepsis subphenotyping algorithm based on routinely measured vital signs in patients with COVID-19. We found four COVID-19 subphenotypes with distinct manifestations of the disease and outcomes. Future work should investigate whether vitals trajectory subphenotypes have differential responses to targeted treatments, and how these subphenotypes compare in prognostic and predictive usefulness with other subphenotyping methods.

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Algorithm availability statement: The polynomial functions and implementation code for the vitals trajectory algorithm are available on request for research purposes. Please contact the corresponding author for any research requests.

Additional information: The e-Figures and e-Tables are available online under "Supplementary Data."

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