CHEST Online Supplement

Identification of Distinct Clinical Subphenotypes in Critically Ill Patients With COVID-19

Charles R. Vasquez, MD, MSCE; Shruti Gupta, MD, MPH; Todd A. Miano, PharmD, PhD; Meaghan Roche, MD, MSCE; Jesse Hsu, PhD; Wei Yang, PhD; Daniel N. Holena, MD, MSCE; John P. Reilly, MD, MSCE; Sarah J. Schrauben, MD, MSCE; David E. Leaf, MD, MMSC; and Michael G.S. Shashaty, MD, MSCE; for the STOP-COVID Investigators

CHEST 2021; 160(3):929-943

 DOI: 10.1016/j.chest.2021.04.062

e-Appendix 1.

Patient Population

We included consecutive adults (≥18 years old) with laboratory-confirmed SARS-CoV-2, detected by polymerase chain reaction of nasopharyngeal or oropharyngeal samples. STOP-COVID was approved using a waiver of informed consent by the Institutional Review Board at each participating study site[1]. Data included demographics, comorbidities, pre-admission medications, symptoms at presentation, and hospital location. Longitudinal data were recorded for the 14 days following ICU admission for physiologic and laboratory variables, medications, and organ support. All patients who remained hospitalized at the time of analysis had a minimum of 28 days of follow-up. Those discharged alive before day 28 were assumed to be alive and free of new complications at 28 days. The accuracy of other collected data was validated using a series of automated and manual verifications, described below.

Data Collection and Validation

Study personnel at each site performed manual chart review and entered data into a secure online database using a standardized case report form. Data were collected using REDCap, a secure, HIPAA-compliant, web-based application. Wherever possible, data were captured using checkboxes rather manual entry to minimize keystroke errors. For data that required keystroke entry (e.g., laboratory values), we implemented validation ranges to flag potential errors in real-time. We also implemented automated data validation rules to flag errors in dates (e.g., if the date of death was entered as being before the date of ICU admission). Finally, all data were manually reviewed, and values that appeared incongruent or out of range were manually validated by confirming the accuracy of the data with the collaborator who entered it.

Definition of an ICU Patient

Patients were considered to have been admitted to an ICU if they were either admitted to a regular ICU room or if they were in a non-ICU room that was functioning as an ICU room for surge capacity. Non-ICU rooms were considered to be functioning as an ICU room under any of the following conditions: 1) the patient was being treated by an ICU team; 2) the patient was receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 3) the patient was receiving continuous renal replacement therapy; or 4) the patient was

receiving vasopressors/inotropes or mechanical cardiac support (e.g., ventricular assist device) in a room where this would traditionally not be permitted.

Sensitivity Analysis of 28-day mortality in patients discharged from the hospital prior to 28 days

In a subset of patients consisting of those who had been admitted to one of six hospitals in Boston, MA, and who had been discharged from the hospital prior to 28 days, we manually reviewed their charts or called them to ascertain their 28-day survival status. Among 50 patients reviewed, all 50 remained alive at 28 days.

Additional details of statistical methods

Latent class analysis

In LCA, there is a distinction between endogenous variables, those that result from and define latent classes, and exogenous variables, patient characteristics that may be associated with but do not define classes.[2,3] We considered demographics, comorbidities, and pre-admission medications to be exogenous, non-class-defining, variables, though their associations with latent classes were subsequently tested (see below). ICU day one variables were used for model fitting. ICU day one was defined as the 24-hour period (spanning from midnight to midnight) on the day of ICU admission. Selection by center, rather than by patient, was performed to facilitate external replication of subphenotypes.

Prior to model fitting, potential class-defining variables were examined by two study investigators (CRV, MGGS) to exclude variables with high-missingness. Several variables with missingness between 30-50% (e.g. D-dimer, ferritin) were included if previously reported to be of interest in COVID-19, those with very high missingness were excluded (e.g., IL-6 and fibrinogen, missing in >80% of patients).[4,5] In addition, all continuous variables were log-transformed to satisfy normality assumptions. Pairwise correlations between all potential class-defining variables were calculated. No variables included in the model had a correlation coefficient >0.80 and only a single pair (AST, ALT) had a correlation coefficient between 0.50 and 0.80.

The general structural equation modelling (gsem) program in Stata/IC 15.1 was used to generate latent class models. This command procedure produces full information maximum likelihood estimates for model parameters using the expectation-maximization (EM) algorithm. Missing data are handled within the EM algorithm using equation-wide deletion, which allows for all available information for a given individual to contribute to model creation. This method assumes data to be missing at random. To further verify the accuracy of this assumption, we compared standardized mean differences across three variables with the highest degree of missingness. To avoid a local maximum solution, we utilized 10 random starting values, each optimized over across 10 iterations, prior to model fitting. For each latent class model, we generated the average probability of being assigned to each class. Each patient was then assigned to the class with the highest probability.

We assessed model fit using several statistical methods, including the Akaike information criteria (AIC), Bayesian information criteria (BIC), and the Vuong-Lo-Mendell-Rubin (VLMR) likelihood ratio test, which compares the fit of a model with k classes to the fit of one with k - 1 classes[6,7]. The VLMR test was performed using tidyLPA package in the R statistical computing environment (version 4.0.1). A second aspect of model fit relates to the ability to generate high probability of subphenotype assignment, while minimizing the number of poor-fitting patients (i.e. patients with marginal probability of class assignment). Model entropy was also calculated and is normalized to range from 0 to 1, with values closer to one indicating less class uncertainty.[8] Class prevalence was also reported and considered in model determination, favoring a model with classes containing >10% of patients. Finally, clinical interpretability and subject matter knowledge contributed to selection of the most appropriate latent class model.[8,9] A separate sensitivity analysis was performed in which a four subphenotype model was derived within the Discovery cohort including only those patients that were receiving invasive mechanical ventilation on ICU Day 1. Using the results of the latent class analysis as the reference, we also compared the predictive accuracy of a limited variable multinomial logistic regression model, within the Discovery cohort.

Baseline characteristics across the two cohorts and across subphenotypes were compared using descriptive statistics, using median and interquartile ranges for continuous variables and count and percentages for categorical variables, with differences assessed using the Kruskal-Wallis test and χ^2 test, as appropriate. Prior to generation of heatmaps, to facilitate

comparison across variables with different measurement scales, we standardized all variables to a mean of 0 and a standard deviation of 1.[10]

Description of adjusted mortality and outcomes analysis

Analysis of the association of subphenotype with 28-day mortality was performed without inclusion of additional variables (unadjusted). Adjusted models included the following demographic and comorbidities previously associated with mortality in COVID-19– age, sex, race and ethnicity, hypertension, diabetes, chronic obstructive pulmonary disease, active malignancy, end-stage kidney disease and chronic liver disease; and physiologic measures of illness severity and organ dysfunction – respiratory support and oxygenation, platelet count, creatinine, altered mental status.[11] In addition, given the substantial regional variation in COVID-19 cases during the study enrollment period and to account for hospital-level variation, we adjusted for U.S. region and hospital ICU bed capacity.

All clinical outcomes were assessed daily up to 14 days following ICU admission. ARDS models were adjusted for age, BMI, blood type A, coinfection at ICU admission.[12] AKI models were adjusted for age, BMI, baseline eGFR, diabetes, hypertension, coinfection at ICU admission.[13] Thrombosis models were adjusted for age, BMI, CAD, COPD, CHF, eGFR, active malignancy, coinfection at ICU admission.[14] Infection models were adjusted for age, diabetes, immunosuppression medication, coinfection at ICU admission.[15] New onset CHF models were adjusted for age, BMI, diabetes, hypertension, CHF, CAD, coinfection at ICU admission.[16] The PH assumption was assessed for each outcome using the Grambsch and Therneau test based on Schoenfeld residuals.[17]

References

1. Gupta S, Hayek SS, Wang W, et al. Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US. *JAMA Intern Med.* 2020.
2. Hagenaars JA, McCutcheon AL. *Applied latent class analysis.* Cambridge ; New York: Cambridge University Press; 2002.
3. Lanza ST, Savage JS, Birch LL. Identification and prediction of latent classes of weight-loss strategies among women. *Obesity (Silver Spring).* 2010;18(4):833-840.
4. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* 2020;368:m1091.
5. Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. *JCI Insight.* 2020;5(10).
6. Nylund KL, Asparouhov T, Muthén BO. Deciding on the Number of Classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo Simulation Study. *Structural Equation Modeling: A Multidisciplinary Journal.* 2007;14(4):535-569.
7. Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. *Biometrika.* 2001;88(3):767-778.
8. Zhang Z, Abarda A, Contractor AA, Wang J, Dayton CM. Exploring heterogeneity in clinical trials with latent class analysis. *Annals of Translational Medicine.* 2018;6(7):9.
9. Mori M, Krumholz HM, Allore HG. Using Latent Class Analysis to Identify Hidden Clinical Phenotypes. *JAMA.* 2020;324(7):700-701.
10. Bhatraju PK, Zelnick LR, Herting J, et al. Identification of Acute Kidney Injury Subphenotypes with Differing Molecular Signatures and Responses to Vasopressin Therapy. *Am J Respir Crit Care Med.* 2019;199(7):863-872.
11. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020;584(7821):430-436.
12. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med.* 2017;377(6):562-572.
13. Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol.* 2018;14(10):607-625.
14. Wolberg AS, Rosendaal FR, Weitz JI, et al. Venous thrombosis. *Nat Rev Dis Primers.* 2015;1:15006.
15. Rodriguez-Acelas AL, de Abreu Almeida M, Engelman B, Canon-Montanez W. Risk factors for health care-associated infection in hospitalized adults: Systematic review and meta-analysis. *Am J Infect Control.* 2017;45(12):e149-e156.
16. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol.* 2011;8(1):30-41.
17. GRAMBSCH PM, THERNEAU TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81(3):515-526.

e-Table 1: List of participating sites

Northeast
Beth Israel Deaconess Medical Center
Brigham and Women's Faulkner Hospital
Brigham and Women's Hospital
Cooper University Health Care
Hackensack Mountainside Hospital
Hackensack University Medical Center
Johns Hopkins Hospital
Lowell General Hospital
Massachusetts General Hospital
MedStar Georgetown University Hospital
Montefiore Medical Center
Mount Sinai Medical Center
Newton Wellesley Hospital
New York-Presbyterian/Weill Cornell Medical Center
New York University Langone Hospital
Rutgers/New Jersey Medical School
Rutgers/Robert Wood Johnson Medical School
Temple University Hospital
Tufts Medical Center
University of Pennsylvania Health System
University of Pittsburgh Medical Center
Yale University Medical Center
South
Baylor College of Medicine, Houston
Baylor University Medical Center/Baylor Scott White and Health
Duke University Medical Center
Mayo Clinic, Florida
Memphis VA Medical Center
Methodist University Hospital
Ochsner Medical Center
Tulane Medical Center
University of Alabama-Birmingham Hospital
University of Florida Health-Gainesville
University of Florida Health-Jacksonville
University of Miami Health System
University of North Carolina Medical Center
University of Texas Southwestern Medical Center

Midwest
Barnes-Jewish Hospital
Cook County Health
Froedtert Hospital
Indiana University Health Methodist Hospital
Mayo Clinic, Rochester
Medical College of Wisconsin
Northwestern Memorial Hospital
Rush University Medical Center
University Hospitals Cleveland Medical Center
University of Chicago Medical Center
University of Illinois Hospital and Health Sciences System
University of Kentucky Hospital
University of Michigan Hospital
University of Oklahoma Health Sciences Center
West
Loma Linda University Medical Center
Mayo Clinic, Arizona
Oregon Health and Science University Hospital
Renown Health
Stanford Healthcare
University of California-Davis Medical Center
University of California-Los Angeles Medical Center
University of California-San Diego Medical Center
University of California-San Francisco Medical Center
UCHealth University of Colorado
University Medical Center of Southern Nevada
University of Washington Medical Center

e-Table 2. Definitions of baseline characteristics, comorbidities, treatments, and outcomes

Baseline Characteristics	
Baseline serum creatinine	Lowest value (mg/dl) within 365 to 7 days prior to hospital admission. If not available, serum creatinine on hospital admission
Home medications	Medications that the patient was taking at home prior to admission. Does not include those started at an outside hospital if the patient was transferred
Anticoagulation	Therapeutic anticoagulants, not including anti-platelet agents such as aspirin or clopidogrel
Immunosuppressant drugs	Chemotherapy (in the 30 days prior to admission), corticosteroids >10 mg prednisone/day (or equivalent), calcineurin inhibitors (systemic, not topical), mycophenolate mofetil, azathioprine, rituximab, other
ACEI/ARB	ACEI include lisinopril, fosinopril, captopril, and others; ARB include losartan, valsartan, irbesartan, and others.
Altered mental status	Per chart review
Coinfection	Confirmed or suspected infection(s) on ICU day 1 other than COVID-19
Respiratory failure severity	Per chart review. Non-mechanically ventilated patients categorized as none vs. BiPAP, CPAP or HFNC. Patients on mechanical ventilation were additionally stratified by P:F ratio. Patients on ECMO were included as a separate category.
Kidney Function	eGFR was defined using the CKD-EPI equation. Baseline creatinine was determined as described above.
Comorbidities	
Asthma	Per chart review
Atrial fibrillation	Per chart review
Blood type	Per chart review. Blood Type A or other
Bone marrow transplant	Per chart review
Cancer	Per chart review (lung, breast, colorectal, prostate, gastric, pancreatic, melanoma, ovarian, brain, or other)
Chronic kidney disease	Baseline eGFR<60 on at least two consecutive values at least 12 weeks apart prior to hospital admission. If not available, defined as per chart review.
Chronic liver disease	Cirrhosis, alcohol-related liver disease, nonalcoholic fatty liver disease, autoimmune hepatitis, hepatitis B or hepatitis C, primary biliary cirrhosis, or other
Chronic obstructive pulmonary disease	Per chart review
Congestive heart failure	Per chart review; heart failure with preserved versus reduced ejection fraction
Coronary artery disease	Per chart review; any history of angina, myocardial infarction, or coronary artery bypass graft surgery

Diabetes mellitus	Per chart review; insulin or non-insulin dependent
HIV/AIDS	Per chart review
Hypertension	Per chart review
Solid organ transplant	Per chart review (kidney, liver, heart, lung, other)
Active malignancy	Per chart review; any malignancy (other than non-melanoma skin cancer) that was treated in the prior year
Longitudinal Treatments*	
PaO2†	Lowest PaO2 available on ICU day 1
FiO2†	FiO2 corresponding to lowest PaO2
Vasopressors	Maximum number of vasopressors and/or inotropes required on ICU day 1, irrespective of specific medication dose.
Outcomes*	
Acute kidney Injury‡	Defined as ≥ 0.3mg/dl increase from baseline creatinine, corresponding with stage 1 of the Kidney Disease: Improving Global Outcomes Criteria[1]. Baseline creatinine was defined as the lowest value (mg/dl) within 365 to 7 days prior to hospital admission. If not available, serum creatinine on hospital admission.
Acute respiratory distress syndrome	Modified Berlin criteria[2] (all three of the following were required): PaO2:FiO2 ratio < 300 mmHg and mechanically ventilated and a diagnosis of ARDS per chart review.
Congestive heart failure (new onset)	Per chart review; includes both heart failure with preserved and reduced ejection fraction
Infection	Per chart review; suspected or confirmed new infection other than COVID-19 that developed after admission to the ICU. Pneumonia (including ventilator-associated), urosepsis, biliary sepsis, bacteremia, other
Thromboembolic event	Per chart review; DVT, PE, stroke, heparin-induced thrombocytopenia, other

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker, ARDS, acute respiratory distress syndrome; BiPAP, bilevel positive airway pressure; COVID-19, coronavirus disease 2019; CPAP; continuous positive airway pressure; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FiO2, fraction of inspired oxygen; HFNC, high-flow nasal canula; HIV/AIDs, human immunodeficiency syndrome/acquired immunodeficiency virus; ICU, intensive care unit; PaO2, partial pressure of oxygen; P:F, ratio of partial pressure of oxygen to fraction of inspired oxygen; PE, pulmonary embolism.

* Longitudinal treatments and outcomes were recorded as occurring in the first 14 days following admission to the ICU
† Only applies to patients on mechanical ventilation with arterial blood gas available
‡ Excludes patients with end stage renal disease

References:

1. Kidney Disease; Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl 2*, 2012: 1-138.
2. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome. The Berlin Definition. *JAMA*, 2012; 307(23): 2526-2533.

e-Table 3: List of class-defining variables included in latent class models

ICU Day 1 Vital Signs*
Highest Temperature
Highest Heart Rate
Highest Respiratory Rate
Lowest Systolic Blood Pressure
ICU Admission Diagnosis
Co-infection†
Respiratory Support & Oxygenation Status‡
Altered Mental Status†
ICU Day 1 Laboratory Data
White Blood Cell Count
Lymphocyte %
Hemoglobin
Platelet Count
Creatinine
Sodium*
Albumin
AST
ALT
Bilirubin
Lactate
Procalcitonin*
C-Reactive Protein
D-Dimer
Ferritin
Creatine Kinase*
Arterial pH
Other Clinical Variables
Vasopressor Use§

*Available on ICU day 1 only
† Defined per chart review, categorized: No, Yes (present)
‡ Categorized: Neither HFNC, NIPPV or MV, BiPAP/CPAP/NFNC, Mechanical ventilation stratified by P:F Ratio > 300, P:F Ratio > 200 to ≤ 300, P:F Ratio > 100 to ≤ 200, P:F Ratio ≤ 100, and ECMO
§ Defined per chart review. Number of unique vasopressor and inotrope medications, irrespective of medication dose

Abbreviations: ICU, intensive care unit; AST; aspartate aminotransferase; ALT, alanine aminotransferase; UOP, urine output; HFNC, high-flow nasal cannula; NIPPV, non-invasive positive pressure ventilation; MV, mechanical ventilation; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; P:F, partial pressure of arterial oxygenation to fraction of inspired oxygenation; ECMO, extra-corporeal membrane oxygenation

e-Table 4: STROBE Statement

Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **See Abstract.**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **See Abstract.**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **See Introduction paragraph 1 and 2.**
Objectives	3	State specific objectives, including any prespecified hypotheses **See Introduction paragraph 3.**
Methods		
Study design	4	Present key elements of study design early in the paper **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **Not applicable.**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

		See Methods section, "Additional detail of statistical methods" in the online data supplement and supplemental e-Table 2
Bias	9	Describe any efforts to address potential sources of bias **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
Study size	10	Explain how the study size was arrived at **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
		(*b*) Describe any methods used to examine subgroups and interactions **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
		(*c*) Explain how missing data were addressed **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
		(*d*) If applicable, explain how loss to follow-up was addressed **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
		(*e*) Describe any sensitivity analyses **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement.**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **See Methods section, as well as "Additional detail of statistical methods" in the online data supplement, Table 1, and supplemental e-Figure 1**
		(b) Give reasons for non-participation at each stage

		See Methods section, as well as "Additional detail of statistical methods" in the online data supplement, supplemental e-Figure 1
		(c) Consider use of a flow diagram **See supplemental e-Figure 1.**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **See "Discovery and Replication" subheading of results and Table 1.**
		(b) Indicate number of participants with missing data for each variable of interest **See Table 1.**
		(c) Summarise follow-up time (eg, average and total amount) **Described in Methods section. Mortality assessed at 28 days from ICU admission. Clinical outcomes assessed at 14 days from ICU admission.**
Outcome data	15*	Report numbers of outcome events or summary measures over time **See "Association of COVID-19 subphenotypes with 28-day mortality" and "Association of COVID-19 subphenotypes with 14-day clinical outcomes" subheadings of the Results section, Figure 3, and Table 4.**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **See "Association of COVID-19 subphenotypes with 28-day mortality" and "Association of COVID-19 subphenotypes with 14-day clinical outcomes" subheadings of the Results section, Table 2, and Table E9.**
		(*b*) Report category boundaries when continuous variables were categorized **See e-Table 2.**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Multivariable associations of subphenotype with mortality and clinical outcomes are presented as relative risks and hazard ratios, respectively.**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **See "Identification of COVID-19 critical illness subphenotypes" and "Characteristics distinguishing COVID-19 subphenotypes" subheadings of the Results section, Figure 1, and supplementary tables and figures.**

Discussion		
Key results	18	Summarise key results with reference to study objectives **See Abstract and Discussion paragraph 1.**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **See Discussion paragraph 8-9.**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **See Discussion paragraph 10.**
Generalisability	21	Discuss the generalisability (external validity) of the study results **See Discussion paragraph 7**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **See Funding and Funding Acknowledgement statement at the bottom of the title page.**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

e-Table 5: Comparison of standardized mean differences in class-defining and baseline characteristics in three representative variables with high levels of missing data

Ferritin, D-dimer and creatine kinase (CK) represent the three class-defining variables with the highest rate of missing data across the combined study population. Ferritin was missing in 44% of patients, D-dimer was missing in 50% of patients, and CK was missing in 54% of patients.

Ferritin	Non-missing	Missing	Standardized Mean Difference
n (%)	1849 (56·0)	1451 (44·0)	
Baseline Characteristics			
Age (years)	61 (14·4)	62 (14·4)	0·064
Male	1190 (64·4)	930 (64·1)	0·006
Race			
White	670 (36·2)	551 (38·0)	0·036
Black	564 (30·5)	479 (33·0)	0·054
Other	145 (7·8)	110 (7·6)	0·010
Unknown	470 (25·4)	311 (21·4)	0·094
Hispanic Ethnicity	412 (22·3)	266 (18·3)	0·098
BMI (kg/m²)	32 (9)	32 (8)	0·054
Diabetes	771 (41·7)	587 (40·5)	0·025
Hypertension	1128 (61·0)	908 (62·6)	0·032
CKD stage			
Normal – eGFR ≥ 90	608 (32·9)	441 (30·4)	0·054
Stage 1 – eGFR 60 to < 90	646 (34·9)	531 (36·6)	0·035
Stage 2 – eGFR 30 < 60	385 (20·8)	298 (20·5)	0·007
Stage 3-4 – eGFR 15 < 30	86 (4·7)	74 (5·1)	0·021
Stage 5 – eGFR <15 or HD	124 (6·7)	107 (7·4)	0·026
Coronary Artery Disease	253 (13·7)	204 (14·1)	0·011
Congestive Heart Failure	171 (9·2)	157 (10·8)	0·052
Atrial Fibrillation or Flutter	115 (6·2)	121 (8·3)	0·082
Chronic Obstructive Pulmonary Disease	153 (8·3)	125 (8·6)	0·012
Asthma	188 (10·2)	159 (11·0)	0·026
Chronic Liver Disease	59 (3·2)	53 (3·7)	0·025
HIV/AIDS	27 (1·5)	21 (1·4)	0·001
Active Malignancy	78 (4·2)	84 (5·8)	0·072
Solid Organ Transplant	62 (3·4)	44 (3·0)	0·018
Bone Marrow Transplant	2 (0·1)	6 (0·4)	0·060
Blood Type A	385 (20·8)	298 (20·5)	0·007
Smoking Status			
Non-smoker	1069 (57·8)	786 (54·2)	0·073
Current/Former	519 (28·1)	465 (32·0)	0·087
Unknown	261 (14·1)	200 (13·8)	0·010
Pre-admission ACEI or ARB	628 (34·0)	495 (34·1)	0·003
Pre-admission Anticoagulation	170 (9·2)	153 (10·5)	0·045
Pre-admission Immunosuppressive Medication	194 (10·5)	148 (10·2)	0·009

Class-Defining Variables			
Coinfection on ICU Day 1	357 (19·3)	369 (25·4)	0·148
Altered Mental Status on ICU Day 1	399 (21·6)	358 (24·7)	0·071
T_{max} ICU Day 1 (°F)	100·5 (1·8)	100·5 (1·9)	0·008
HR_{max} ICU Day 1	106 (22)	106 (21)	0·017
SBP_{min} ICU Day 1 (mmHg)	98 (20)	99 (21)	0·034
RR_{max} ICU Day 1	33 (10)	32 (9)	0·128
Respiratory Support & Oxygenation on ICU Day 1			0·145
Neither HFNC, NIPPV or MV*	190 (10·3)	231 (15·9)	
BiPAP, CPAP, HFNC or NRB	410 (22·2)	310 (21·4)	
Vent P/F > 300	268 (14·5)	254 (17·5)	
Vent P/F > 200 to ≤ 300	187 (10·1)	104 (7·2)	
Vent P/F > 100 to ≤ 200	433 (23·4)	295 (20·3)	
Vent P/F ≤ 100	349 (18·9)	251 (17·3)	
ECMO	12 (0·6)	6 (0·4)	
# Vasoactive Infusions on ICU Day 1	1 (1)	1 (1)	0·071
White Blood Cell Count (K/mm3)	9·6 (6·0)	9·5 (10·5)	0·014
Lymphocyte %	11·1 (7·5)	12·6 (8·7)	0·175
Hemoglobin (g/dl)	12·5 (2·2)	12·4 (2·3)	0·059
Platelet Count (K/mm3)	231 (96)	216 (88)	0·166
Creatinine (mg/dl)	1·81 (2·32)	1·82 (2·31)	0·005
Albumin (g/dl)	3·2 (0·6)	3·2 (0·6)	0·012
AST (U/L)	94 (296)	100 (308)	0·020
ALT (U/L)	60 (109)	62 (145)	0·018
Total Bilirubin (mg/dl)	0·8 (1·7)	0·7 (1·0)	0·018
Lactate (mmol/L)	2·0 (1·8)	2·1 (2·2)	0·047
CRP (mg/L)	175 (105)	157 (104)	0·168
Arterial pH	7·35 (0·11)	7·36 (0·13)	0·038
D-dimer (ng/ml)	4485 (10454)	4075 (8241)	0·044
Ferritin (ng/ml)	2009 (4275)	· (·)	n/a
Procalcitonin (ng/ml)	3·97 (16·10)	2·30 (9·47)	0·126
CK (U/L)	759 (3639)	912 (3395)	0·044

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (via CKD-EPI equation); HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate; HFNC, high-flow nasal cannula; MV, mechanical ventilation; NIPPV, non-invasive positive pressure ventilation; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; NRB, non-rebreather mask; P:F, partial pressure of arterial oxygenation to fraction of inspired oxygenation; ECMO, extra-corporeal membrane oxygenation; UOP, urine output; AST; aspartate aminotransferase; ALT, alanine aminotransferase; CRP, c-reactive protein; CK, creatine kinase

* Includes patients that received supplemental oxygen by nasal cannula administration

D-dimer	Non-missing	Missing	Standardized Mean Difference
n (%)	1654 (50·1)	1646 (49·9)	
Baseline Characteristics			
Age (years)	61 (14)	61 (14)	0·043
Male	1066 (64·4)	1054 (64·0)	0·009
Race			
White	594 (35·9)	627 (38·1)	0·045
Black	519 (31·4)	524 (31·8)	0·010
Other	126 (7·6)	129 (7·8)	0·008
Unknown	415 (25·1)	366 (22·2)	0·067
Hispanic Ethnicity	368 (22·2)	310 (18·8)	0·085
BMI (kg/m^2)	32 (9)	32 (8)	0·003
Diabetes	679 (41·1)	679 (41·3)	0·004
Hypertension	1009 (61·0)	1027 (62·4)	0·029
CKD stage			
Normal – eGFR ≥ 90	541 (32·7)	508 (30·9)	0·040
Stage 1 – eGFR 60 to <90	595 (36·0)	582 (35·4)	0·013
Stage 2 – eGFR 30 to <60	331 (20·0)	352 (21·4)	0·034
Stage 3-4 – eGFR 15 to <30	80 (4·8)	80 (4·9)	0·001
Stage 5 – eGFR <15 or HD	107 (6·5)	124 (7·5)	0·042
Coronary Artery Disease	218 (13·2)	239 (14·5)	0·039
Congestive Heart Failure	150 (9·1)	178 (10·8)	0·058
Atrial Fibrillation or Flutter	97 (5·9)	139 (8·4)	0·100
Chronic Obstructive Pulmonary Disease	130 (7·9)	148 (9·0)	0·041
Asthma	182 (11·0)	165 (10·0)	0·032
Chronic Liver Disease	50 (3·0)	62 (3·8)	0·041
HIV/AIDS	21 (1·3)	27 (1·6)	0·031
Active Malignancy	66 (4·0)	96 (5·8)	0·085
Solid Organ Transplant	58 (3·5)	48 (2·9)	0·033
Bone Marrow Transplant	3 (0·2)	5 (0·3)	0·025
Blood Type A	341 (20·6)	342 (20·8)	0·004
Smoking Status			
Non-smoker	945 (57·1)	910 (55·3)	0·037
Current/Former	464 (28·1)	520 (31·6)	0·077
Unknown	245 (14·8)	216 (13·1)	0·049
Pre-admission ACEI or ARB	576 (34·8)	547 (33·2)	0·034
Pre-admission Anticoagulation	150 (9·1)	173 (10·5)	0·049
Pre-admission Immunosuppressive Medication	178 (10·8)	164 (10·0)	0·026
Class-Defining Variables			
Coinfection on ICU Day 1	326 (19·7)	400 (24·3)	0·112
Altered Mental Status on ICU Day 1	333 (20·1)	424 (25·8)	0·133
T_{max} ICU Day 1 (°F)	100·5 (1·8)	100·5 (1·8)	0·013
HR_{max} ICU Day 1	107 (23)	105 (21)	0·052
SBP_{min} ICU Day 1 (mmHg)	98 (20)	99 (21)	0·066
RR_{max} ICU Day 1	33 (10)	32 (9)	0·145
Respiratory Support & Oxygenation on ICU Day 1			0·118
Neither HFNC, NIPPV or MV*	183 (11·1)	238 (14·5)	
BiPAP, CPAP, HFNC or NRB	352 (21·3)	368 (22·4)	
Vent P/F > 300	246 (14·9)	276 (16·8)	
Vent P/F > 200 to ≤ 300	155 (9·4)	136 (8·3)	

Vent P/F > 100 to ≤ 200	404 (24·4)	324 (19·7)	
Vent P/F ≤ 100	300 (18·1)	300 (18·2)	
ECMO	14 (0·8)	4 (0·2)	
# Vasoactive Infusions on ICU Day 1	1 (1)	1 (1)	0·134
White Blood Cell Count (K/mm3)	9·6 (5·2)	9·5 (10·5)	0·004
Lymphocyte %	11·1 (7·3)	12·4 (8·7)	0·167
Hemoglobin (g/dl)	12·6 (2·2)	12·4 (2·3)	0·096
Platelet Count (K/mm3)	231 (95)	217 (90)	0·15
Creatinine (mg/dl)	1·80 (2·29)	1·83 (2·34)	0·012
Albumin (g/dl)	3·2 (0·6)	3·2 (0·6)	0·042
AST (U/L)	98 (328)	95 (263)	0·010
ALT (U/L)	60 (112)	61 (137)	0·011
Total Bilirubin (mg/dl)	0·8 (1·3)	0·8 (1·6)	0·013
Lactate (mmol/L)	2·0 (1·8)	2·1 (2·2)	0·041
CRP (mg/L)	175 (106)	163 (103)	0·111
Arterial pH	7·35 (0·11)	7·36 (0·13)	0·026
D-dimer (ng/ml)	4407 (10069)	· (·)	n/a
Ferritin (ng/ml)	1947 (4146)	2171 (4597)	0·051
Procalcitonin (ng/ml)	4·28 (17·32)	2·11 (7·55)	0·162
CK (U/L)	676 (1557)	1002 (5092)	0·087

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (via CKD-EPI equation); HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate; HFNC, high-flow nasal cannula; MV, mechanical ventilation; NIPPV, non-invasive positive pressure ventilation; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; NRB, non-rebreather mask; P:F, partial pressure of arterial oxygenation to fraction of inspired oxygenation; ECMO, extra-corporeal membrane oxygenation; UOP, urine output; AST; aspartate aminotransferase; ALT, alanine aminotransferase; CRP, c-reactive protein; CK, creatine kinase

* Includes patients that received supplemental oxygen by nasal cannula administration

Creatine Kinase	Non-missing	Missing	Standardized Mean Difference
n (%)	1505 (45·6)	1795 (54·4)	
Baseline Characteristics			
Age (years)	61 (14)	61 (15)	0·011
Male	968 (64·3)	1152 (64·2)	0·003
Race			
White	540 (35·9)	681 (37·9)	
Black	443 (29·4)	600 (33·4)	
Other	115 (7·6)	140 (7·8)	
Unknown	407 (27·0)	374 (20·8)	
Hispanic Ethnicity	319 (21·2)	359 (20·0)	0·03
BMI (kg/m^2)	32 (8)	32 (9)	0·007
Diabetes	597 (39·7)	761 (42·4)	0·055
Hypertension	918 (61·0)	1118 (62·3)	0·026
CKD stage			
Normal – eGFR ≥ 90	469 (31·2)	580 (32·3)	0·025
Stage 1 – eGFR 60 to < 90	572 (38·0)	605 (33·7)	0·090
Stage 2 – eGFR 30 to < 60	348 (23·1)	335 (18·7)	0·110
Stage 3-4 – eGFR 15 to < 30	80 (5·3)	80 (4·5)	0·040
Stage 5 – eGFR <15 or HD	36 (2·4)	195 (10·9)	0·346
Coronary Artery Disease	192 (12·8)	265 (14·8)	0·058
Congestive Heart Failure	123 (8·2)	205 (11·4)	0·109
Atrial Fibrillation or Flutter	92 (6·1)	144 (8·0)	0·075
Chronic Obstructive Pulmonary Disease	125 (8·3)	153 (8·5)	0·008
Asthma	170 (11·3)	177 (9·9)	0·047
Chronic Liver Disease	50 (3·3)	62 (3·5)	0·007
HIV/AIDS	17 (1·1)	31 (1·7)	0·050
Active Malignancy	73 (4·9)	89 (5·0)	0·005
Solid Organ Transplant	40 (2·7)	66 (3·7)	0·058
Bone Marrow Transplant	5 (0·3)	3 (0·2)	0·033
Blood Type A	341 (22·7)	342 (19·1)	0·089
Smoking Status			
Non-smoker	846 (56·2)	1009 (56·2)	<0·001
Current/Former	430 (28·6)	554 (30·9)	0·050
Unknown	229 (15·2)	232 (12·9)	0·066
Pre-admission ACEI or ARB	519 (34·5)	604 (33·6)	0·018
Pre-admission Anticoagulation	134 (8·9)	189 (10·5)	0·055
Pre-admission Immunosuppressive Medication	129 (8·6)	213 (11·9)	0·110
Class-Defining Variables			
Coinfection on ICU Day 1	288 (19·1)	438 (24·4)	0·127
Altered Mental Status on ICU Day 1	353 (23·5)	404 (22·5)	0·024
T_{max} ICU Day 1 (°F)	100·5 (1·8)	100·5 (1·8)	0·017
HR_{max} ICU Day 1	105 (22)	106 (22)	0·040
SBP_{min} ICU Day 1 (mmHg)	98 (20)	99 (21)	0·028
RR_{max} ICU Day 1	33 (9)	32 (9)	0·018

Respiratory Support & Oxygenation on ICU Day 1			0·193
Neither HFNC, NIPPV or MV*	150 (10·0)	271 (15·1)	
BiPAP, CPAP, HFNC or NRB	301 (20·0)	419 (23·3)	
Vent P/F > 300	230 (15·3)	292 (16·3)	
Vent P/F > 200 to ≤ 300	143 (9·5)	148 (8·2)	
Vent P/F > 100 to ≤ 200	381 (25·3)	347 (19·3)	
Vent P/F ≤ 100	292 (19·4)	308 (17·2)	
ECMO	8 (0·5)	10 (0·6)	
# Vasoactive Infusions on ICU Day 1	1 (1)	1 (1)	0·192
White Blood Cell Count (K/mm3)	9·8 (6·4)	9·4 (9·4)	0·046
Lymphocyte %	11·7 (8·2)	11·7 (7·9)	0·009
Hemoglobin (g/dl)	12·6 (2·1)	12·4 (2·3)	0·106
Platelet Count (K/mm3)	229 (95)	221 (91)	0·093
Creatinine (mg/dl)	1·54 (1·43)	2·05 (2·84)	0·229
Albumin (g/dl)	3·2 (0·6)	3·2 (0·6)	0·042
AST (U/L)	99 (322)	94 (279)	0·016
ALT (U/L)	61 (113)	60 (133)	0·014
Total Bilirubin (mg/dl)	0·8 (1·5)	0·8 (1·4)	0·014
Lactate (mmol/L)	2·1 (2·0)	2·0 (1·9)	0·023
CRP (mg/L)	176 (106)	166 (104)	0·103
Arterial pH	7·35 (0·11)	7·36 (0·13)	0·046
D-dimer (ng/ml)	4795 (10146)	3992 (9976)	0·080
Ferritin (ng/ml)	1843 (2884)	2179 (5335)	0·078
Procalcitonin (ng/ml)	4·43 (16·88)	2·20 (9·93)	0·161
CK (U/L)	817 (3549)	· (·)	n/a

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (via CKD-EPI equation); HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate; HFNC, high-flow nasal cannula; MV, mechanical ventilation; NIPPV, non-invasive positive pressure ventilation; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; NRB, non-rebreather mask; P:F, partial pressure of arterial oxygenation to fraction of inspired oxygenation; ECMO, extra-corporeal membrane oxygenation; UOP, urine output; AST; aspartate aminotransferase; ALT, alanine aminotransferase; CRP, c-reactive protein; CK, creatine kinase

* Includes patients that received supplemental oxygen by nasal cannula administration

e-Table 6: Comparison of baseline characteristics, stratified by subphenotype, in the Discovery cohort

	SP1	SP2	SP3	SP4	P-value
Patients, n (%)	244 (11·2)	600 (27·4)	475 (21·7)	869 (39·7)	
Baseline Characteristics					
Age (years)	67 (56; 75)	63 (52; 72)	65 (55; 74)	60 (49; 68)	<0·001
Male	166 (68·0)	435 (72·5)	242 (50·9)	575 (66·2)	
Race					
White	69 (28·3)	192 (32·0)	159 (33·5)	335 (38·6)	
Black	95 (38·9)	177 (29·5)	216 (45·5)	295 (33·9)	
Other	22 (9·0)	53 (8·8)	23 (4·8)	63 (7·2)	
Unknown	58 (23·8)	178 (29·7)	77 (16·2)	176 (20·3)	<0·001
Latino Ethnicity	33 (13·5)	116 (19·3)	61 (12·8)	150 (17·3)	0·018
BMI (kg/m^2)	29 (25; 35)	30 (27; 35)	30 (26; 37)	31 (27; 37)	0·002
Diabetes	126 (51·6)	218 (36·3)	253 (53·3)	316 (36·4)	<0·001
Hypertension	177 (72·5)	343 (57·2)	353 (74·3)	490 (56·4)	<0·001
Kidney Function (eGFR, ml/min/1·73 m^2)					<0·001
eGFR ≥ 90	50 (20·5)	183 (30·5)	110 (23·2)	341 (39·2)	
eGFR 60 to < 90	59 (24·2)	216 (36·0)	128 (26·9)	386 (44·4)	
eGFR 30 to < 60	60 (24·6)	166 (27·7)	97 (20·4)	131 (15·1)	
eGFR 15 to < 30	28 (11·5)	23 (3·8)	48 (10·1)	5 (0·6)	
eGFR <15 or HD	47 (19·3)	12 (2·0)	92 (19·4)	6 (0·7)	
Coronary Artery Disease	41 (16·8)	67 (11·2)	104 (21·9)	97 (11·2)	<0·001
Congestive Heart Failure	44 (18·0)	40 (6·7)	92 (19·4)	51 (5·9)	<0·001
Atrial Fibrillation or Flutter	18 (7·4)	39 (6·5)	58 (12·2)	49 (5·6)	<0·001
Chronic Obstructive Pulmonary Disease	22 (9·0)	35 (5·8)	60 (12·6)	58 (6·7)	<0·001

Asthma	10 (4·1)	66 (11·0)	46 (9·7)	116 (13·3)	<0·001
Chronic Liver Disease	21 (8·6)	9 (1·5)	22 (4·6)	22 (2·5)	<0·001
HIV/AIDS	1 (0·4)	7 (1·2)	13 (2·7)	10 (1·2)	0·038
Active Malignancy	23 (9·4)	22 (3·7)	28 (5·9)	29 (3·3)	<0·001
Solid Organ Transplant	6 (2·5)	16 (2·7)	27 (5·7)	20 (2·3)	0·005
Bone Marrow Transplant	1 (0·4)	1 (0·2)	0 (0·0)	2 (0·2)	0·643
Blood Type A	55 (22·5)	117 (19·5)	108 (22·7)	153 (17·6)	0·094
Smoking Status					<0·001
Non-smoker	120 (49·2)	348 (58·0)	243 (51·2)	534 (61·4)	
Current/Former	77 (31·6)	146 (24·3)	176 (37·1)	249 (28·7)	
Unknown	47 (19·3)	106 (17·7)	56 (11·8)	86 (9·9)	
Pre-admission ACEI or ARB	91 (37·3)	211 (35·2)	148 (31·2)	279 (32·1)	0·237
Pre-admission Anticoagulation	29 (11·9)	47 (7·8)	77 (16·2)	72 (8·3)	<0·001
Pre-admission Immunosuppressive Medication	30 (12·3)	54 (9·0)	75 (15·8)	77 (8·9)	<0·001
Clinical & Laboratory Data					
Time from Symptom Onset to ICU Admission (days)	6 (2;9)	8 (5;11)	6 (3;9)	8 (5;10)	<0·001
Time from Hospital Admission to ICU Admission (days)	1 (0;4)	1 (0;3)	1 (0;3)	1 (0;2)	0·367
Antibiotic on ICU Day 1	215 (88·1)	498 (83·0)	387 (81·5)	675 (77·7)	0.001
Coinfection on ICU Day 1	87 (35·7)	118 (19·7)	154 (32·4)	154 (17·8)	<0·001
Altered Mental Status on ICU Day 1	104 (42·6)	132 (22·0)	129 (27·2)	72 (8·3)	<0·001
T_{max} ICU Day 1 (°F)	99·9 (98·5; 101·6)	100·6 (99·3; 102·0)	99·9 (98·8; 101·1)	101·0 (99·5; 102·4)	<0·001
HR_{max} ICU Day 1	109 (92; 129)	114 (99; 128)	100 (86; 114)	102 (90; 113)	<0·001
SBP_{min} ICU Day 1 (mmHg)	88 (75; 103)	90 (80; 104)	98 (87; 112)	101 (91; 115)	<0·001
RR_{max} ICU Day 1	30 (26; 38)	33 (28; 40)	30 (24; 36)	32 (27; 39)	<0·001

Respiratory Support & Oxygenation on ICU Day 1					<0·001
Neither HFNC, NIPPV or MV*	33 (13·5)	7 (1·2)	76 (16·0)	150 (17·3)	
BiPAP, CPAP, HFNC or NRB	28 (11·5)	54 (9·0)	137 (28·8)	275 (31·6)	
Vent P:F > 300	39 (16·0)	112 (18·7)	92 (19·4)	104 (12·0)	
Vent P:F > 200 to ≤ 300	34 (13·9)	56 (9·3)	37 (7·8)	60 (6·9)	
Vent P:F > 100 to ≤ 200	57 (23·4)	183 (30·5)	67 (14·1)	179 (20·6)	
Vent P:F ≤ 100	49 (20·1)	182 (30·3)	65 (13·7)	101 (11·6)	
ECMO	4 (1·6)	6 (1·0)	1 (0·2)	0 (0·0)	
# Vasoactive Infusions on ICU Day 1	1 (1; 2)	1 (0; 1)	1 (0; 1)	0 (0; 1)	<0·001
24-Hour UOP on ICU Day 1 (ml/day)	435 (123; 895)	621 (302; 1011)	698 (250; 1140)	878 (489; 1351)	<0·001
White Blood Cell Count (K/mm^3)	9·6 (6·0; 14·2)	11·6 (9·1; 15·1)	7·2 (5·3; 9·8)	6·6 (5·2; 8·5)	<0·001
Lymphocyte %	8·7 (6·0; 13·6)	6·9 (4·5; 10·4)	10·9 (6·1; 17·3)	13·1 (9·3; 18·2)	<0·001
Hemoglobin (g/dl)	11·4 (9·1; 13·3)	13·0 (11·8; 14·4)	10·7 (9·5; 12·0)	13·3 (12·2; 14·4)	<0·001
Platelet Count (K/mm^3)	185 (118; 254)	244 (199; 314)	199 (149; 270)	198 (155; 248)	<0·001
Creatinine (mg/dl)	2·38 (1·28; 4·59)	1·14 (0·82; 1·60)	1·55 (0·88; 3·01)	0·91 (0·75; 1·15)	<0·001
Sodium (mEq/L)	138 (134; 143)	137 (133; 141)	138 (135; 141)	136 (134; 139)	<0·001
Albumin (g/dl)	2·9 (2·4; 3·4)	3·0 (2·6; 3·4)	3·2 (2·8; 3·6)	3·4 (3·1; 3·7)	<0·001
AST (U/L)	117 (67; 247)	68 (47; 93)	31 (24; 44)	51 (38; 75)	<0·001
ALT (U/L)	59 (37; 142)	48 (32; 71)	19 (13; 25)	35 (25; 54)	<0·001
Total Bilirubin (mg/dl)	0·7 (0·4; 1·2)	0·7 (0·5; 1·0)	0·4 (0·3; 0·6)	0·5 (0·4; 0·8)	<0·001
Lactate (mmol/L)	2·3 (1·4; 4·0)	1·9 (1·3; 2·8)	1·4 (1·0; 1·8)	1·3 (1·0; 1·7)	<0·001

CRP (mg/L)	160 (73; 267)	240 (171; 300)	120 (65; 201)	134 (80; 189)	<0·001
Arterial pH	7·29 (7·20; 7·40)	7·33 (7·26; 7·40)	7·38 (7·32; 7·43)	7·41 (7·36; 7·45)	<0·001
D-dimer (ng/ml)	3115 (1100; 11575)	2237 (1130; 8235)	1300 (600; 2297)	778 (510; 1168)	<0·001
Ferritin (ng/ml)	2097 (694; 4717)	1404 (813; 2509)	543 (233; 1260)	862 (452; 1430)	<0·001
Procalcitonin (ng/ml)	1·72 (0·52; 7·98)	1·06 (0·45; 3·05)	0·40 (0·14; 1·06)	0·19 (0·11; 0·34)	<0·001
CK (U/L)	852 (262; 1760)	224 (119; 751)	126 (63; 323)	185 (98; 448)	<0·001

Data are shown as n (%) for categorical variables and median (IQR) for continuous variables. Differences between cohorts were compared using the Kruskal-Wallis test and chi-squared test, as appropriate.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (via CKD-EPI equation); HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate; HFNC, high-flow nasal cannula; MV, mechanical ventilation; NIPPV, non-invasive positive pressure ventilation; BiPAP, bilevel positive airway pressure; NRB, non-rebreather mask; CPAP, continuous positive airway pressure; P:F, partial pressure of arterial oxygenation to fraction of inspired oxygenation; ECMO, extra-corporeal membrane oxygenation; UOP, urine output; AST; aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

*Includes patients that received supplemental oxygen by nasal cannula administration.

e-Table 7: Comparison of baseline characteristics, stratified by subphenotype, in the Replication cohort

	SP1	SP2	SP3	SP4	P-value
Patients, n (%)	145 (13·0)	360 (32·4)	251 (22·6)	356 (32·0)	
Baseline Characteristics					
Age (years)	62 (52; 70)	62 (52; 72)	66 (56; 75)	60 (49; 68)	<0·001
Male	99 (68·3)	260 (72·2)	128 (51·0)	215 (60·4)	<0·001
Race					<0·001
White	48 (33·1)	148 (41·1)	113 (45·0)	157 (44·1)	
Black	44 (30·3)	62 (17·2)	82 (32·7)	72 (20·2)	
Other	14 (9·7)	35 (9·7)	10 (4·0)	35 (9·8)	
Unknown	39 (26·9)	115 (31·9)	46 (18·3)	92 (25·8)	
Latino Ethnicity	35 (24·1)	114 (31·7)	63 (25·1)	106 (29·8)	0·186
BMI (kg/m^2)	30 (26; 35)	30 (27; 35)	30 (26; 35)	31 (28; 36)	0·004
Diabetes	58 (40·0)	114 (31·7)	147 (58·6)	126 (35·4)	<0·001
Hypertension	89 (61·4)	198 (55·0)	194 (77·3)	192 (53·9)	<0·001
Kidney Function (eGFR, ml/min/1·73 m^2)					<0·001
eGFR ≥ 90	35 (24·1)	120 (33·3)	44 (17·5)	166 (46·6)	
eGFR 60 to < 90	40 (27·6)	151 (41·9)	62 (24·7)	135 (37·9)	
eGFR 30 to < 60	34 (23·4)	79 (21·9)	66 (26·3)	50 (14·0)	
eGFR 15 to < 30	17 (11·7)	9 (2·5)	27 (10·8)	3 (0·8)	
eGFR < 15 or HD	19 (13·1)	1 (0·3)	52 (20·7)	2 (0·6)	
Coronary Artery Disease	20 (13·8)	26 (7·2)	61 (24·3)	41 (11·5)	<0·001
Congestive Heart Failure	19 (13·1)	17 (4·7)	53 (21·1)	12 (3·4)	<0·001
Atrial Fibrillation or Flutter	12 (8·3)	21 (5·8)	26 (10·4)	13 (3·7)	0·008
Chronic Obstructive Pulmonary Disease	17 (11·7)	20 (5·6)	31 (12·4)	35 (9·8)	0·019

Asthma	14 (9·7)	36 (10·0)	21 (8·4)	38 (10·7)	0·823
Chronic Liver Disease	7 (4·8)	10 (2·8)	11 (4·4)	10 (2·8)	0·489
HIV/AIDS	2 (1·4)	6 (1·7)	3 (1·2)	6 (1·7)	0·958
Active Malignancy	12 (8·3)	13 (3·6)	18 (7·2)	17 (4·8)	0·093
Solid Organ Transplant	4 (2·8)	3 (0·8)	22 (8·8)	8 (2·2)	<0·001
Bone Marrow Transplant	0 (0·0)	2 (0·6)	0 (0·0)	2 (0·6)	0·528
Blood Type A	35 (24·1)	77 (21·4)	70 (27·9)	68 (19·1)	0·071
Smoking Status					<0·001
Non-smoker	64 (44·1)	204 (56·7)	140 (55·8)	202 (56·7)	
Current/Former	43 (29·7)	91 (25·3)	84 (33·5)	118 (33·1)	
Unknown	38 (26·2)	65 (18·1)	27 (10·8)	36 (10·1)	
Pre-admission ACEI or ARB	47 (32·4)	120 (33·3)	110 (43·8)	117 (32·9)	0·018
Pre-admission Anticoagulation	21 (14·5)	18 (5·0)	41 (16·3)	18 (5·1)	<0·001
Pre-admission Immunosuppressive Medication	15 (10·3)	21 (5·8)	38 (15·1)	32 (9·0)	0·002
Clinical & Laboratory Data					
Time from Symptom Onset to ICU Admission (days)	6 (3;10)	7 (5;10)	6 (2;10)	7 (5;10)	0.001
Time from Hospital Admission to ICU Admission (days)	1 (0;3)	1 (0;3)	1 (0;3)	1 (0;2)	0.292
Antibiotic on ICU Day 1	121 (83.5)	287 (79.7)	194 (77.3)	273 (76.7)	0.343
Coinfection on ICU Day 1	33 (22·8)	69 (19·2)	65 (25·9)	46 (12·9)	0·001
Altered Mental Status on ICU Day 1	65 (44·8)	121 (33·6)	97 (38·8)	37 (10·4)	<0·001
T_{max} ICU Day 1 (°F)	100·0 (98·8; 101·7)	101·0 (99·3; 102·3)	99·3 (98·4; 101·0)	100·6 (99·3; 101·9)	<0·001
HR_{max} ICU Day 1	116 (95; 136)	108 (96; 122)	99 (86; 117)	100 (87; 110)	<0·001
SBP_{min} ICU Day 1 (mmHg)	90 (78; 104)	93 (84; 104)	96 (85; 112)	105 (94; 115)	<0·001
RR_{max} ICU Day 1	30 (24; 34)	32 (26; 39)	28 (22; 35)	31 (26; 37)	<0·001

Respiratory Support & Oxygenation on ICU Day 1					<0·001
Neither HFNC, NIPPV or MV*	10 (6·9)	13 (3·6)	44 (17·5)	88 (24·7)	
BiPAP, CPAP, HFNC or NRB	14 (9·7)	39 (10·8)	42 (16·7)	131 (36·8)	
Vent P:F > 300	18 (12·4)	65 (18·1)	52 (20·7)	40 (11·2)	
Vent P:F > 200 to ≤ 300	15 (10·3)	44 (12·2)	30 (12·0)	15 (4·2)	
Vent P:F > 100 to ≤ 200	42 (29·0)	96 (26·7)	52 (20·7)	52 (14·6)	
Vent P:F ≤ 100	41 (28·3)	102 (28·3)	30 (12·0)	30 (8·4)	
ECMO	5 (3·4)	1 (0·3)	1 (0·4)	0 (0·0)	
# Vasoactive Infusions on ICU Day 1	1 (1; 2)	1 (0; 1)	1 (0; 1)	0 (0; 1)	<0·001
24-Hour UOP on ICU Day 1 (ml/day)	400 (150; 905)	715 (350; 1288)	675 (330; 1250)	960 (610; 1650)	<0·001
White Blood Cell Count (K/mm^3)	10·5 (7·4; 16·5)	10·5 (8·1; 13·6)	8·5 (6·0; 12·2)	6·3 (4·9; 7·7)	<0·001
Lymphocyte %	8·0 (5·0; 14·1)	6·8 (4·4; 10·0)	8·0 (4·7; 13·4)	14·1 (10·3; 19·7)	<0·001
Hemoglobin (g/dl)	11·5 (9·5; 13·4)	13·1 (11·9; 14·2)	10·5 (9·0; 12·3)	13·3 (12·2; 14·2)	<0·001
Platelet Count (K/mm^3)	200 (120; 268)	238 (187; 299)	217 (158; 283)	202 (161; 246)	<0·001
Creatinine (mg/dl)	2·20 (1·40; 3·73)	1·00 (0·81; 1·39)	1·81 (0·91; 4·06)	0·83 (0·72; 1·07)	<0·001
Sodium (mEq/L)	137 (133; 142)	136 (133; 139)	138 (134; 142)	136 (134; 138)	<0·001
Albumin (g/dl)	2·9 (2·4; 3·3)	3·2 (2·9; 3·5)	3·0 (2·7; 3·5)	3·4 (3·1; 3·7)	<0·001
AST (U/L)	119 (77; 252)	64 (47; 96)	35 (24; 48)	49 (35; 71)	<0·001
ALT (U/L)	80 (41; 163)	46 (32; 70)	21 (15; 29)	36 (23; 55)	<0·001
Total Bilirubin (mg/dl)	0·8 (0·4; 1·4)	0·7 (0·5; 1·0)	0·4 (0·3; 0·6)	0·5 (0·4; 0·7)	<0·001
Lactate (mmol/L)	2·7 (1·4; 4·2)	1·7 (1·2; 2·2)	1·5 (1·0; 2·2)	1·2 (1·0; 1·6)	<0·001

CRP (mg/L)	186 (99; 273)	195 (138; 260)	108 (43; 222)	96 (56; 143)	<0·001
Arterial pH	7·28 (7·18; 7·37)	7·36 (7·31; 7·42)	7·34 (7·26; 7·40)	7·43 (7·39; 7·46)	<0·001
D-dimer (ng/ml)	5610 (2164; 20000)	2073 (1048; 7726)	1973 (1095; 4880)	880 (565; 1290)	<0·001
Ferritin (ng/ml)	3107 (1843; 6273)	1377 (765; 2418)	744 (232; 1820)	821 (451; 1497)	<0·001
Procalcitonin (ng/ml)	6·78 (2·38; 40·67)	0·76 (0·30; 1·90)	0·54 (0·23; 2·01)	0·12 (0·07; 0·25)	<0·001
CK (U/L)	389 (160; 1324)	280 (123; 689)	140 (63; 378)	142 (78; 275)	<0·001

Data are shown as n (%) for categorical variables and median (IQR) for continuous variables· Differences between cohorts were compared using the Kruskal-Wallis test and chi-squared test, as appropriate.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (via CKD-EPI equation); HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate; HFNC, high-flow nasal cannula; MV, mechanical ventilation; NIPPV, non-invasive positive pressure ventilation; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; NRB, non-rebreather mask; P:F, partial pressure of arterial oxygenation to fraction of inspired oxygenation; ECMO, extra-corporeal membrane oxygenation; UOP, urine output; AST; aspartate aminotransferase; ALT, alanine aminotransferase; CRP, c-reactive protein.

* Includes patients that received supplemental oxygen by nasal cannula administration.

e-Table 8: Classification performance of a limited variable multinomial model using primary latent class analysis-assigned subphenotype as the outcome (Discovery cohort)

LCA-assigned subphenotypes	Model-predicted subphenotype*					
	SP1	SP2	SP3	SP4	Total	% Accuracy
SP1	161	38	24	21	244	66.0
SP2	149	346	22	83	600	57.8
SP3	150	24	242	59	475	50.9
SP4	253	63	32	521	869	60.0

* A multinomial logistic regression model was constructed by using a limited set of commonly available clinical and laboratory explanatory variables and considering latent class analysis (LCA)-assigned COVID-19 subphenotype as the model outcome. The following explanatory variables were included based on both limited missingness and ability to distinguish subphenotypes in the primary LCA: white blood cell count, hemoglobin, platelet count, serum creatinine, albumin, AST, total bilirubin, maximum temperature, minimum systolic blood pressure and maximum respiratory rate. Class-defining variables with >20% missingness were excluded from consideration for use in the multinomial model.

e-Table 9: Restricted mean survival time analysis in the Discovery and Replication cohort

The restricted mean survival time (RMST) is equivalent to the average duration of survival during the follow-up period. Graphically, RMST is equivalent to the area under the Kaplan-Meier curve from the start of follow-up to a specified time point (ex. 28 days). Similar to a risk calculation, RMST estimates of two groups can be compared by computing the absolute difference or the ratio. Here, all RMSTs were estimated at 28 days and corresponding 95% confidence intervals are reported.

Discovery Cohort				
	SP1	**SP2**	**SP3**	**SP4**
RMST (days)	17·3 (16·0-18·7)	21·3 (20·5-22·0)	22·4 (21·5-23·2)	24·7 (24·2-25·2)
RMST Difference (days)*	-7·4 (-8·9--6·0)	-3·5 (-4·4--2·6)	-2·4 (-3·4--1·4)	0 (ref)
RMST Ratio*	0·70 (0·65-0·76)	0·86 (0·83-0·90)	0·90 (0·87-0·94)	1 (ref)
*Compared to SP4				

Replication Cohort				
	SP1	**SP2**	**SP3**	**SP4**
RMST (days)	15·2 (13·5-16·9)	19·2 (18·3-20·2)	19·8 (18·7-20·9)	23·0 (22·3-23·7)
RMST Difference (days)*	-7·8 (-9·7--6·0)	-3·8 (-4·9--2·6)	-3·2 (-4·5--1·9)	0 (ref)
RMST Ratio*	0·66 (0·59-0·74)	0·84 (0·79-0·89)	0·86 (0·81-0·92)	1 (ref)
*Compared to SP4				

e-Table 10: Adjusted pairwise mortality comparison in the Discovery and Replication cohort

Pairwise Comparison		
	Discovery	**Replication**
SP1 vs· SP2	1·29 (1·08-1·53)	1·20 (0·96-1·49)
SP1 vs· SP3	1·19 (1·01-1·42)	1·10 (0·90-1·34)
SP1 vs· SP4	1·63 (1·28-2·09)	1·94 (1·40-2·68)
SP2 vs· SP3	1·00 (0·85-1·18)	0·92 (0·76-1·13)
SP2 vs· SP4	1·47 (1·20-1·79)	1·24 (0·95-1·60)
SP3 vs· SP4	1·28 (1·03-1·59)	1·32 (1·01-1·73)

*Adjusted for: age, sex, race and ethnicity, hypertension, diabetes, chronic obstructive pulmonary disease, end-stage kidney disease, active malignancy, chronic liver disease, illness severity and organ dysfunction on ICU day 1 (respiratory support and oxygenation, platelet count, altered mental status, and creatinine), hospital ICU bed capacity, and U.S. region.

e-Table 11: Unadjusted and adjusted hazard ratios for clinical outcomes in the Discovery and Replication cohort

Cox proportional hazards regression estimates with 95% confidence intervals. ARDS hazard adjusted for age, BMI, blood type A, coinfection at ICU admission. AKI hazard adjusted for age, BMI, baseline eGFR, diabetes, hypertension, coinfection at ICU admission. Thrombosis hazard adjusted for age, BMI, CAD, COPD, CHF, eGFR, active malignancy, coinfection at ICU admission. Infection hazard adjusted for age, diabetes, immunosuppression medication, coinfection at ICU admission. New onset CHF hazard adjusted for age, BMI, diabetes, hypertension, CHF, CAD, coinfection at ICU admission. For all models, SP4 was the reference group and patients were censored at time of death, ICU discharge or ICU day 14.

ARDS*								
	SP1		**SP2**		**SP3**		**SP4**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Discovery	1·03 (0·90-1·20)	1·07 (0·91-1·26)	1·63 (1·50-1·77)	1·63 (1·49-1·78)	0·99 (0·88-1·10)	1·00 (0·88-1·13)	1 (ref)	1 (ref)
Replication	1·42 (1·19-1·69)	1·41 (1·17-1·69)	1·55 (1·37-1·77)	1·53 (1·35-1·75)	1·11 (0·95-1·30)	1·06 (0·90-1·26)	1 (ref)	1 (ref)
*Adjusted for: age, BMI, blood type A, coinfection at ICU admission								

Thrombosis†								
	SP1		**SP2**		**SP3**		**SP4**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Discovery	2·12 (1·36-3·29)	2·02 (1·23-3·32)	2·03 (1·47-2·81)	1·96 (1·40-2·73)	0·93 (0·60-1·43)	0·77 (0·46-1·29)	1 (ref)	1 (ref)
Replication	1·76 (0·99-3·13)	2·10 (1·13-3·88)	2·06 (1·37-3·11)	2·12 (1·39-3·23)	1·43 (0·88-2·32)	1·69 (0·97-2·94)	1 (ref)	1 (ref)
†Adjusted for: age, BMI, CAD, COPD, CHF, CKD, active malignancy, coinfection at ICU admission								

AKI‡								
	SP1		**SP2**		**SP3**		**SP4**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Discovery§	3·00 (2·48-3·63)	2·99 (2·44-3·68)	1·89 (1·65-2·16)	2·03 (1·76-2·34)	1·56 (1·33-1·83)	1·43 (1·20-1·70)	1 (ref)	1 (ref)
Replication‖	3·88 (3·01-5·00)	4·20 (3·19-5·52)	2·05 (1·67-2·51)	2·21 (1·80-2·71)	2·50 (1·99-3·15)	2·25 (1·76-2·87)	1 (ref)	1 (ref)
‡Adjusted for: age, BMI, CKD, diabetes, hypertension, coinfection at ICU admission								
§N=117 with baseline ESRD excluded from Disocvery Cohort analysis								
‖N=50 with baseline ESRD excluded from Replication Cohort analysis								

New Infection**								
	SP1		SP2		SP3		SP4	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Discovery	1·50 (1·16-1·94)	1·25 (0·96-1·63)	1·41 (1·18-1·68)	1·39 (1·16-1·67)	1·14 (0·93-1·40)	0·98 (0·79-1·21)	1 (ref)	1 (ref)
Replication	2·02 (1·43-2·85)	1·98 (1·40-2·79)	1·51 (1·16-1·96)	1·42 (1·09-1·86)	1·38 (1·02-1·86)	1·23 (0·90-1·67)	1 (ref)	1 (ref)
**Adjusted for: age, diabetes, pre-admission immunosuppressive medication, coinfection present at ICU admission								

New Onset CHF††								
	SP1		SP2		SP3		SP4	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Discovery‡‡	2·96 (1·47-5·92)	2·33 (1·01-5·39)	2·47 (1·42-4·32)	2·32 (1·28-4·22)	0·62 (0·25-1·54)	0·71 (0·28-1·81)	1 (ref)	1 (ref)
Replication§§	4·25 (1·65-11·00)	2·98 (1·07-8·26)	2·54 (1·06-6·09)	2·40 (1·02-5·68)	2·35 (0·90-6·11)	1·47 (0·53-4·11)	1 (ref)	1 (ref)
††Adjusted for: age, BMI, diabetes, hypertension, CHF, CAD, coinfection at ICU admission								
‡‡N=192 with baseline CHF excluded from Discovery Cohort analysis								
§§N=60 with baseline CHF excluded from Replication Cohort analysis								

e-Table 12: Treatment Exposure Across Subphenotypes

Treatment Exposure (%)					
	SP1	**SP2**	**SP3**	**SP4**	**P-value**
Corticosteroids*					
Discovery	39.8	45.3	30.5	32.5	<0.001
Replication	49.0	49.2	46.2	28.9	<0.001
Anti-IL6 Therapy*					
Discovery	9.4	22.2	12.4	18.1	<0.001
Replication	11.7	20.3	12.8	19.4	0.017

* Defined as received treatment at any time from ICU day 1-14

e-Table 13: Interaction between subphenotype and common COVID-19 therapies, in the Discovery and Replication cohorts

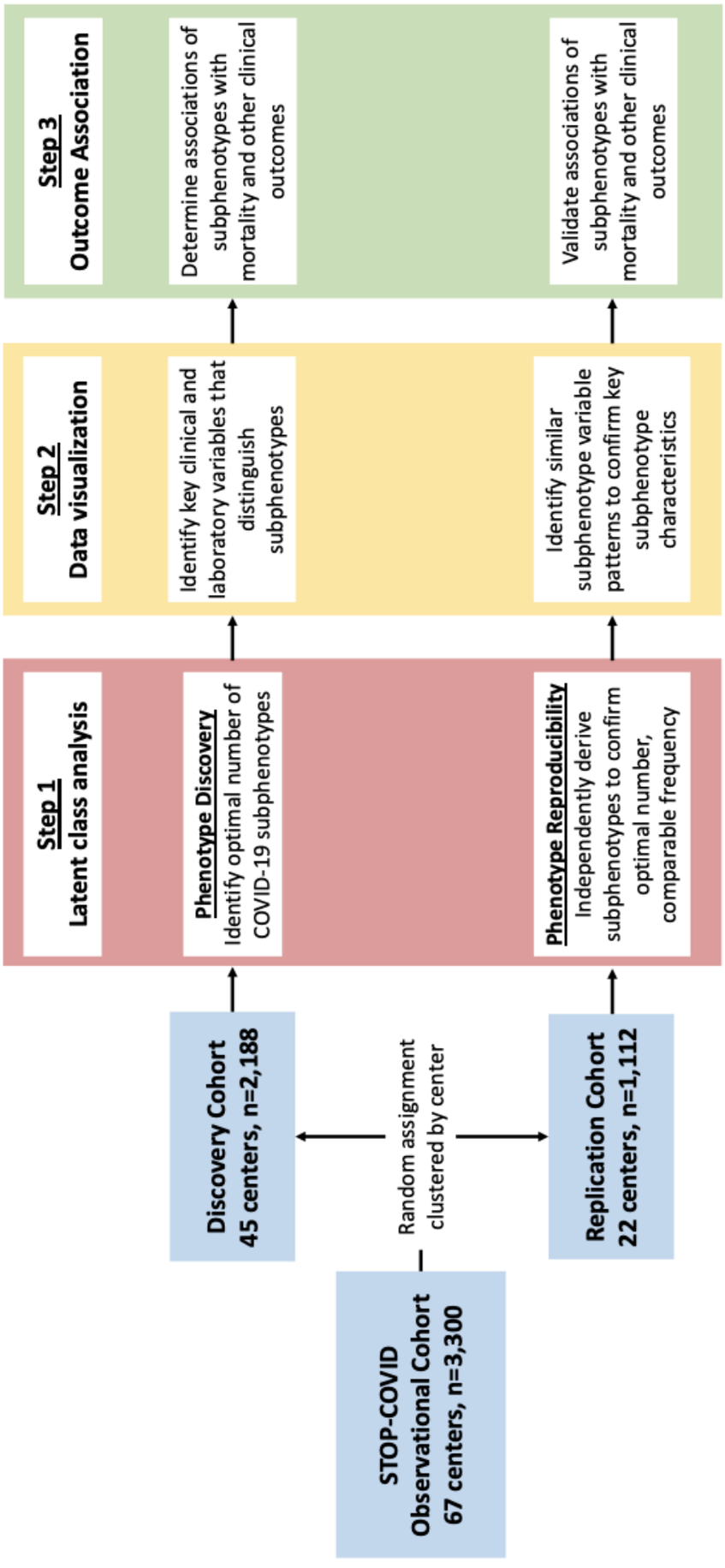
Adjusted Relative Risk of Mortality					
	SP1	**SP2**	**SP3**	**SP4**	**P-value for Interaction**
Corticosteroids*					
Discovery	1.21 (0.97-1.51)	1.24 (1.01-1.52)	1.55 (1.20-2.02)	1.72 (1.27-2.32)	0.376
Replication	1.13 (0.79-1.62)	0.81 (0.62-1.05)	1.16 (0.86-1.56)	1.40 (0.90-2.18)	0.452
Anti-IL6 Therapy*					
Discovery	0.92 (0.66-1.28)	0.90 (0.68-1.19)	0.90 (0.49-1.62)	1.41 (0.98-2.01)	0.745
Replication	1.04 (0.63-171)	0.71 (0.47-1.09)	0.80 (0.48-1.33)	1.35 (0.88-2.08)	0.965
Antimicrobial Therapy†					
Discovery	1.16 (0.78-1.74)	0.93 (0.72-1.22)	1.43 (0.94-2.16)	1.36 (0.94-1.98)	0.436
Replication	0.85 (0.62-1.17)	0.90 (0.69-1.17)	0.99 (1.01-1.03)	0.80 (0.51-1.24)	0.999

Wthin subphenotype associations with mortality are shown as relative risks (95% confidence intervals) with the non-treated group serving as control. Models adjusted for: age, sex, race and ethnicity, hypertension, diabetes, chronic obstructive pulmonary disease, end-stage kidney disease, active malignancy, chronic liver disease, illness severity and organ dysfunction on ICU day 1 (respiratory support and oxygenation, platelet count, altered mental status, and creatinine), hospital ICU bed capacity, and U.S. region. P-value determined using likelihood ratio test comparing a multivariable model including the treatment (ex. corticosteroids) with a multivariable model including the treatment with an interaction term.

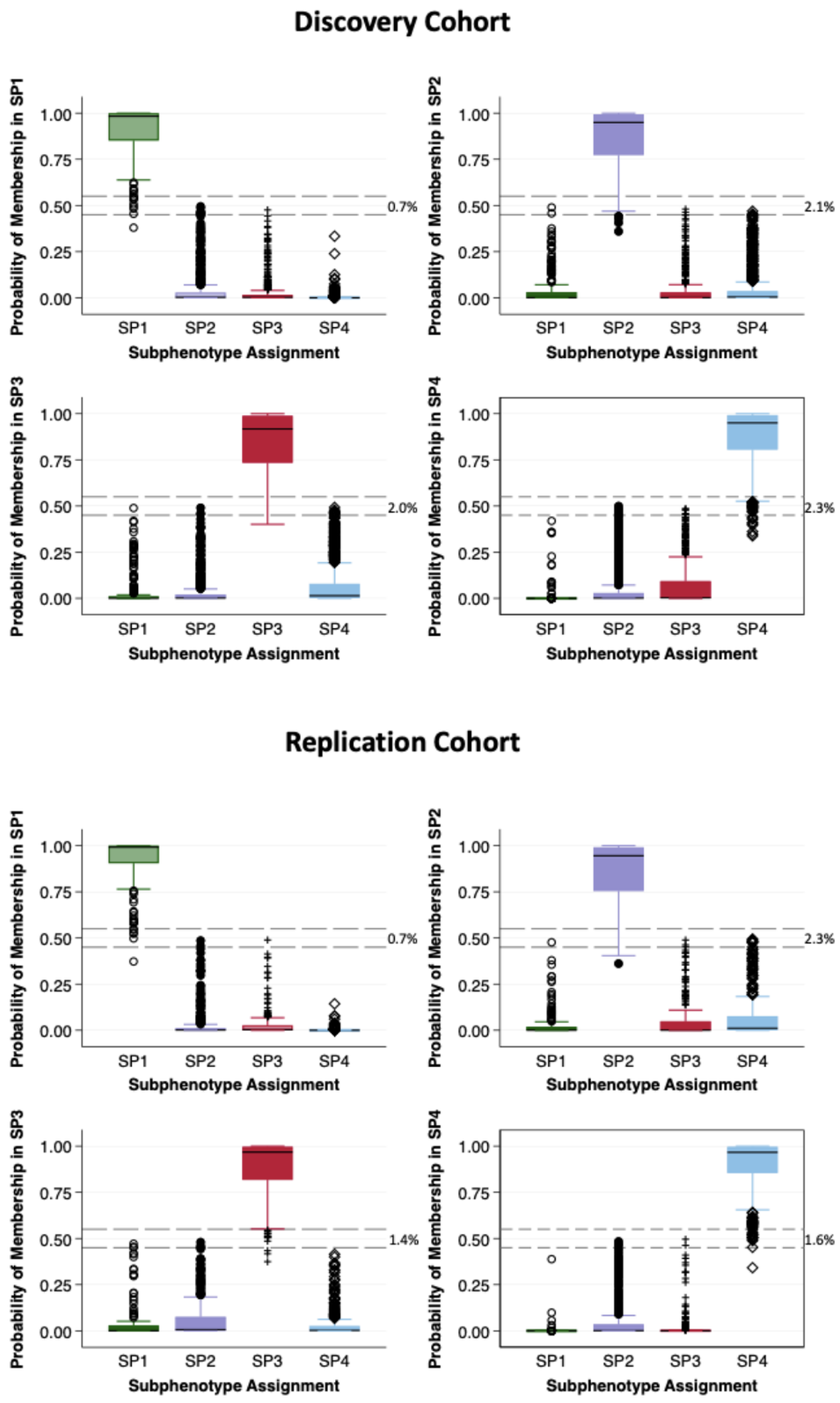
* Defined as received treatment at any time from ICU day 1-14

† Defined as received treatment on ICU day 1

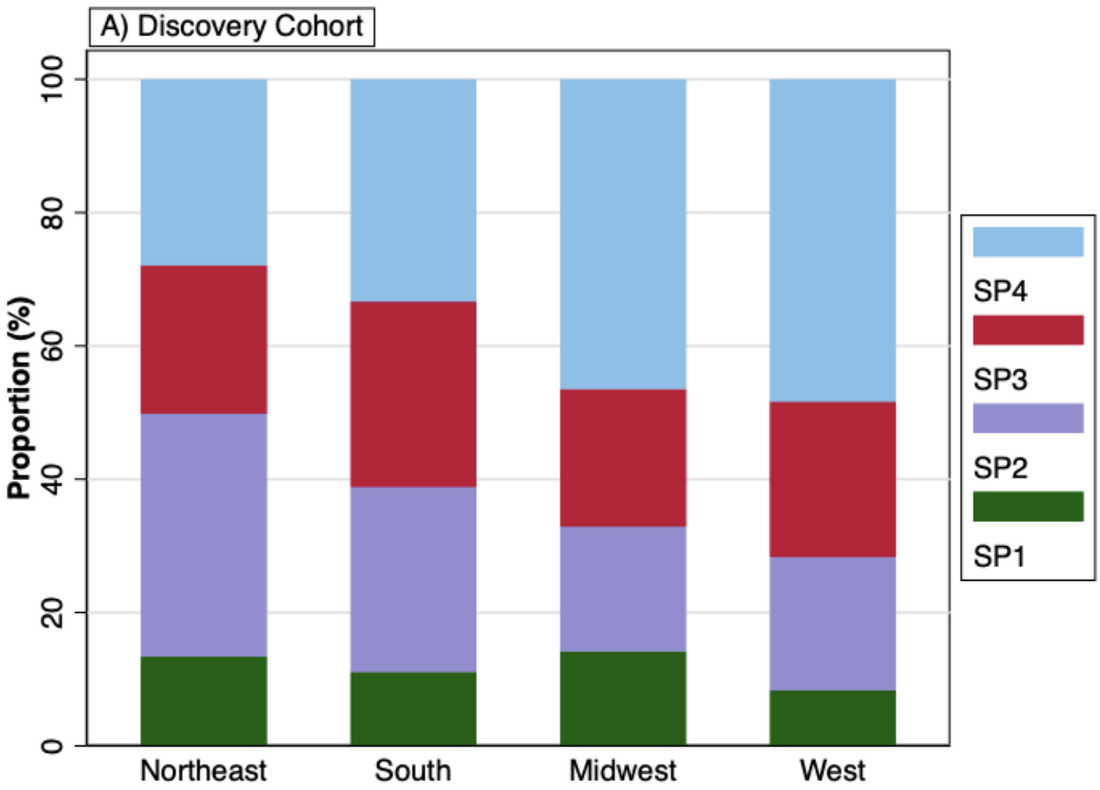
e-Figure 1: Study population flow diagram
A total of 80 U.S. centers were approached to participate in the initial STOP-COVID study. 11 centers declined to participate or did not respond to the inquiry. Of the remaining 69 centers, two centers were unable to obtain Institutional Review Board protocol prior to initiation of our study.

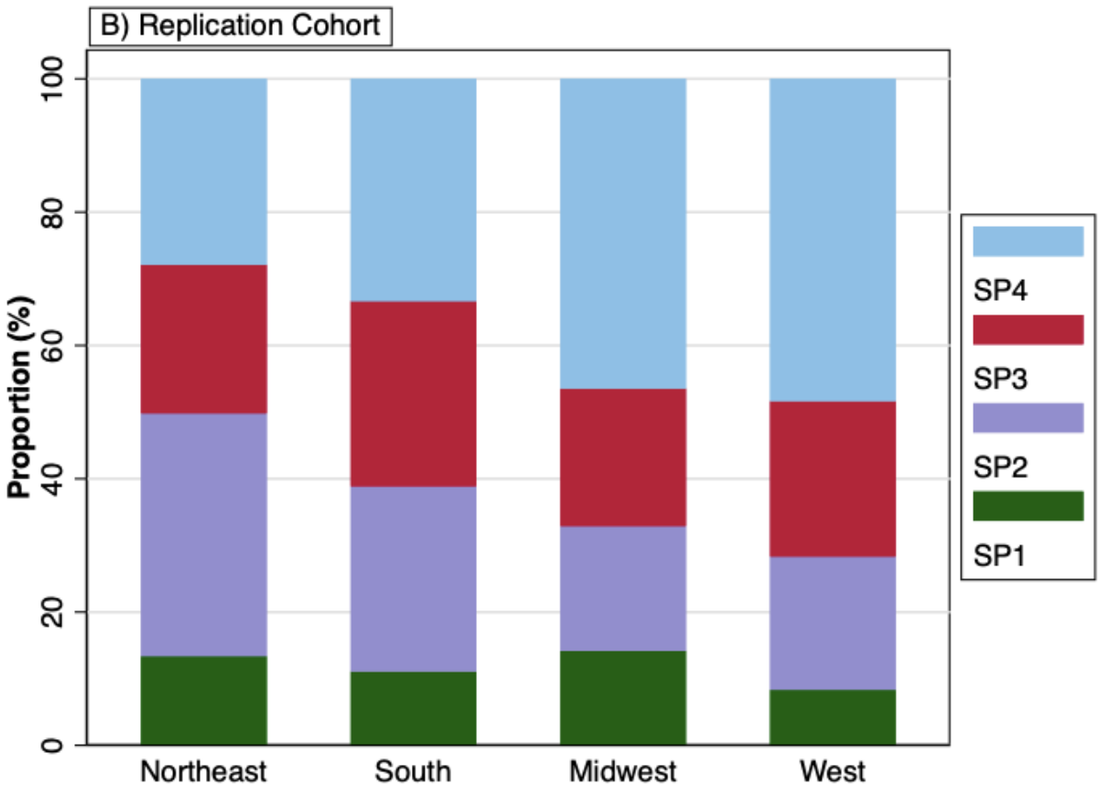


e-Figure 2: Probabilities of assignment to each subphenotype grouped by actual phenotype assignment.
Latent class analysis models in both Discovery and Replication cohorts generated probabilities of membership in each subphenotype for each patient. Each patient was then assigned to the subphenotype for which they had the highest probability of membership. Each panel (A-H) displays box plots summarizing model-determined probabilities of membership in a given phenotype grouped by actual subphenotype assignment. Boxes show interquartile range of probabilities, with median designated by the center line and outliers shown as individual data points. The gray *dashed lines* delineate patients with 45-55% probability of subphenotype membership, a range that implies greater uncertainty about membership versus non-membership. Total percent of patients in this uncertain probability range is noted in the right margin of each graph.



e-Figure 3: Distribution of subphenotypes by U.S. region
Regions composed of the following U.S. states (only states that contributed to the STOP-COVID database are listed). *Northeast:* Connecticut, Washington D.C., Massachusetts, Maryland, New Jersey, New York, Pennsylvania; *South:* Alabama, Florida, Louisiana, North Caroline, Tennessee, Texas, Virginia; *Midwest:* Illinois, Indiana, Kentucky, Michigan, Minnesota, Missouri, Ohio, Oklahoma, Wisconsin; *West:* Arizona, California, Colorado, Nevada, Oregon, Washington.





e-Figure 4: Heatmap displaying the standardized values for each variable across each COVID-19 subphenotype in the Discovery cohort, restricted to only those patients receiving invasive mechanical ventilation on ICU Day 1

The heatmap is divided into two sections: Latent class-defining variables (top), and baseline characteristics that were not used to define class membership (bottom). Within each section, variables are ordered by standardized mean values, lowest to highest, among Discovery cohort patients assigned to subphenotype 1 (SP1). Variables were standardized by scaling to a mean = 0 and a standard deviation = 1 and represented graphically using a continuous color scale. A variable with value +1 represents a mean value for that subphenotype which is 1 SD above the mean value for the entire cohort population.