Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eCollaborators and acknowledgments

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ProCESS trial

The members of the ProCESS Trial are as follows: **Coordinating Center:** Derek C. Angus, Amber E. Barnato, Tammy L. Eaton, Elizabeth Gimbel, David T. Huang, Christopher Keener, John A. Kellum, Kyle Landis, Francis Pike, Diana K. Stapleton, Lisa A. Weissfeld, Michael Willochell, Kourtney A. Wofford, Donald M. Yealy.

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Data Safety Monitoring Board

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ACCESS trial

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PROWESS trial

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GenIMS cohort study

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eMethods

A. Summary and sepsis criteria in cohort and randomized clinical trials

- SENECA validation cohort: This is a retrospective cohort study in an integrated health system of 12 hospitals in Southwestern Pennsylvania from 2010-2012. We studied 20,189 encounters (16,552 unique) who met Sepsis-3 criteria within the first 6 hours of arrival to the emergency department.[1] These patients all had received antibiotics, a body fluid culture, and had 2 or more sequential organ failure assessment (SOFA) points within 6 hours.[2] The primary outcome in this cohort was in-hospital mortality.

- SENECA derivation cohort: This is a retrospective cohort study in an integrated health system of 12 hospitals in Southwestern Pennsylvania from 2013-2014. We studied 43,086 encounters (31,160 unique) who met Sepsis-3 criteria within the first 6 hours of arrival to the emergency department. These patients all had received antibiotics, a body fluid culture, and had 2 or more sequential organ failure assessment (SOFA) points within 6 hours. The primary outcome in this cohort was in-hospital mortality.

- GenIMS cohort study: The Genetic and Inflammatory Markers in Sepsis Study was a cohort study conducted in the emergency departments of 28 hospitals in the United States from 2001-2003.[3] The study investigated systemic cytokine response to pneumonia to determine if specific patterns were associated with development of severe sepsis and death. The study enrolled 2,320 patients, of which 1886 were included in the final analysis cohort. Among those 1886, 583 met clinical criteria for severe sepsis. The 583 severe sepsis patients were used in the analyses for this paper. The inclusion criteria were hospitalized for community-acquired pneumonia and the primary outcomes were development of severe sepsis and 90-day mortality. That study defined severe sepsis according to Sepsis-2,[4] with 3 or more SOFA points, which was present in approximately 1/3 of the cohort. This definition would correspond to the current term “sepsis” in Sepsis-3.[1] The study found statistically significant elevation of IL-6, IL-10, and TNF-alpha between patients that developed early severe sepsis versus those who did not, and found an increased risk of death in patients with both moderate & severely elevated IL-6 and IL-10.

- ProCESS trial: The Protocol-Based Care for Early Septic Shock Trial was a 1:1:1 randomized controlled trial conducted in 31 emergency departments in the United States from 2008-2013.[5] The trial investigated protocol-based early goal-directed therapy against protocol-based standard therapy and usual care. The study had a final cohort of 1,341 patients with severe sepsis or septic shock, defined as 2 or more SIRS criteria and either serum lactate greater than 4 mmol/L or refractory hypotension. The primary outcome was 60-day in-hospital mortality and the study found no statistically significant differences between the groups, nor differences in 90-day mortality, 1-year mortality, or need for organ support.

- ACCESS trial: The Controlled Comparison of Eritoran in Severe Sepsis Trial was a 2:1 randomized controlled trial conducted in 197 intensive care units across 6 continents from 2006-2010.[6] This phase 3 clinical trial investigated safety and efficacy of Eritoran, a MD2-TLR4 agonist, in treating patients with severe sepsis. The study had a final cohort size of 1,961 adult patients with severe sepsis and septic shock, though data for only 1,706 was available for analysis in this study. Severe sepsis and septic shock was defined as 3 or more SIRS criteria and at least one organ dysfunction, as well as an APACHE II score of 21 to 37. The primary outcome was 28-day mortality and the study found no significant difference between treatment and control groups.

- PROWESS trial: The Activated Protein C Worldwide Evaluation in Severe Sepsis Trial was a 1:1 randomized controlled trial conducted in 164 centers across 11 counties from 1998-2000.[7] This phase 3 clinical trial investigated the safety and efficacy of Drotrecogin alfa (DrotAA; recombinant human activated protein c) in treating patients with severe sepsis. The study had a final cohort size of 1,690 patients and included patients with severe sepsis and septic shock, defined as 3 or more SIRS criteria and at least one organ dysfunction. The primary outcome was 28-day mortality and the study found a statistically significant reduction in mortality, 19.4% reduction in risk relative to placebo and 6.1% absolute reduction (P=0.005). However, DrotAA was withdrawn after negative findings in other trials.[8]

B. Approach to missing data

Missing data was present in our cohort studies and randomized trials (**eTable 4** in the Supplement). Prior to clustering algorithms, we assumed that missing data was conditional on observed covariates, and was "missing at random". We used a flexible multivariable imputation procedure of multiple chained regression equations (multiple imputation by chained equations, i.e. MICE) which generated values for all missing data using the observed data for all patients.[9] We included all covariates and our primary outcome in the imputation procedure. We modeled variables using logistic, multinomial, or ordinal regression as appropriate. We evaluated distributions of clustering variables before and after imputation (**eTable 4** in the Supplement). MICE may still lead to bias in the setting of missingness > 50%, but this bias is generally less than that resulting from complete case analysis (which assumes missing completely at random).[10,11] The imputation procedure created 11 independent datasets. For continuous, non-normal variables with upper and lower bounds (e.g. Glasgow coma scale score), we used predictive mean matching. For graphical depictions of clustering variables or descriptive output from clustered models on imputed data, we randomly chose representative imputation datasets to share results.

C. Determination of optimal clustering methodology using OPTICS

A variety of techniques exist for both clustering and partitioning data, and we sought to determine the optimal approach to apply to our data. In general, data can arrange into discrete natural groupings or clusters (e.g. apples and oranges), while others tend to contain a single mass of data that can be partitioned (e.g. cutting a pizza into slices). To determine which technique was most appropriate for our data, we applied a density-based clustering algorithm called ordering points to identify the clustering structure (OPTICS).[12] OPTICS is able to detect natural clusters with various densities and is not overly sensitive about use-selected tuning parameters. It generates a reachability plot that can provide an overall visualization of data structure and help guide towards appropriate clustering methods. In general, an OPTICS plot that is smooth is more suitable for partitioning, whereas a plot that is jagged and stepped is more suitable for clustering.

The reason this distinction is possible lies in the nature of the plot itself. The vertical axis of the reachability plot is reachability distance, so lower values represents closer distances. Therefore, each "valley" represents a group of subjects that are close to each other, but far away from the others, namely a potential phenotype. If we observe valleys in a reachability plot, it indicates that we have relatively clear natural cluster structure in the data and we can apply a clustering approach, such as partition clustering or hierarchical clustering. However, if we encounter a smooth reachability plot without obvious "valleys", this implies that all of the subjects are clustered together. In this case, partition clustering is more appropriate.

To grasp the overall structure of our data, we employed the OPTICS algorithm and generated the associated reachability plot (**eFigure 4** in the Supplement) to check whether there existed natural distinct clustering of the training and validation data.

D. Consensus K clustering

Based on findings in the OPTICS plot, we applied a partitioning approach called "Consensus Clustering" to our data.[13] Consensus clustering is a partitioning approach in which the clustering framework incorporates results from multiple runs of an inner-loop clustering algorithm on sub-sampled subjects.[14] It generates a "consensus value" for each pair of subjects, which is defined as the proportion of times the two subjects are assigned to the same cluster among times when they are both sampled. Consensus value ranges from 0 to 1, with larger values indicating stronger consensus. A value of 0 means that the pair has never been assigned to the same cluster among times they are both sampled, whereas a value of 1 means that this pair has always been assigned to the same cluster among times they are both sampled. Therefore, we can obtain a symmetric consensus matrix containing consensus value for each pair. Then, a hierarchical clustering algorithm is applied on consensus matrix to obtain final cluster assignment for each subject.

The advantages of consensus clustering are that it can help determine an optimal number of clusters and can be used to assess cluster stability. For each given number of clusters, a consensus matrix is created as a heatmap. By varying numbers of

clusters and comparing the heat maps, visual assessment can determine fit to the data. Ideally, clear separation on a heatmap indicating that discovered clusters are stable among multiple clustering runs, and that an optimal number of clusters has been selected. We also used consensus cumulative density function (CDF) plots and cluster-consensus plots to help choose a number of clusters and access cluster stability. Consensus CDF is a plot of cumulative density function for consensus values for each given number of clusters. The optimal number of clusters is represented by a CDF plot that has a first step close to 0, then a flat plateau until a second step close to 1. This indicates that the consensus values are dominated by numbers close to 0 and 1, which indicates good consensus across multiple inner-loop algorithm runs. Cluster-consensus plots demonstrate mean consensus value of all pairs within each cluster. A number of clusters with higher cluster consensus (above 0.8) for all clusters is preferred.

As explained under (C), the SENECA derivation data had no observed natural clustering structure. Therefore, partition clustering algorithms were more appropriate. We chose k-means as the inner-loop clustering algorithm. We standardized (minus mean and divided by standard deviation, giving a mean of 0 and standard deviation of 1.0) and normalized (transferred non-normally distributed variables) the data and then applied consensus k-means method to, i) determine an optimal number of clusters and ii) obtain cluster assignment for each subject. The results of the consensus k-means can be summarized into three different plots: consensus matrix heatmap, consensus CDF plot, and cluster-consensus plot. Based on the combination of these plots, class size, and the clinical characteristics, we determined an optimal number of clusters.

E. Latent class analysis

We applied latent class analysis (LCA) in a sensitivity analysis for deriving phenotypes in the SENECA derivation data. Similar to consensus *k* clustering, LCA can be used to (1) determine an optimal number of clusters and (2) obtain cluster assignment for each subject. For each subject-cluster combination, LCA produces a posterior probability describing the likelihood of a subject belonging to the cluster. Posterior probability ranges from 0 to 1. For a given subject and a given cluster, the larger the posterior probability is, the more likely this subject belongs to this cluster. Subjects are assigned to the cluster for which they have the highest posterior probability. We determined the optimal number of clusters (*k*) using a combination of criteria, i.) a smaller Bayesian information criterion, ii.) adequate sample size within cluster, iii.) higher median posterior probabilities of group membership, and clinical characteristics of the clusters.

F. Data visualization

- Chord plots

Chord plots were created to visualize patterns of abnormal variables by phenotype. For these plots, each of the 29 clustering variables were assigned to one of eight groups for illustration. Specifically:

  - Hepatic: Bilirubin, AST, ALT
  - Hematologic: Hemoglobin, INR, Platelets
  - Neurologic: GCS
  - Cardiovascular: Heart rate, Systolic blood pressure, Bicarbonate, Troponin, Lactate
  - Pulmonary: Respiratory rate, SaO_2, PaO_2
  - Inflammatory: Temperature, ESR, WBC count, Bands, C-Reactive protein
  - Renal: Serum creatinine
  - Other: Age, Gender, Elixhauser, Albumin, Chloride, Sodium, Glucose, BUN

For each phenotype, if the variable mean is greater than the grand mean for the SENECA derivation cohort, then a ribbon is connected between the phenotype and the group. Phenotypes are shown in separate colors. The more variables abnormal for that phenotype, the broader the ribbon. Plots were created in R using the Circlize package.

> Please see "Gu, Z., et al. Circlize Implements and Enhanced Circular Visualization in R. Bioinformatics. 2014;30(19):2811-2812" for more information.

- Alluvial plots

Alluvial plots were created to visualize both SOFA Score and site of infection by phenotype. These plots were created using the Alluvial package in R. Phenotypes are grouped in the left most column and arranged by proportion. Patients were then grouped by SOFA score, and ribbons connect phenotype to SOFA category. A thicker ribbon indicates that a greater number of subjects fell into a particular phenotype or range. The alluvial plot for site of infection was created in the same fashion.

> Please see "Alluvial: R Package for Creating Alluvial Diagrams. Version: 0.1-2. Bojanowski M and Edwards R; 2016. https://github.com/mbojan/alluvial" for more information.

- t-SNE plots

t-Distributed Stochastic Neighbor Embedding (t-SNE) is a technique that utilizes non-parametric, non-linear dimension reduction allow visualization of high dimension datasets. The technique assigns a weigh to each of the modeling variables to create 2-dimension composite eigenvectors representing gradients within the data. t-SNE does this by identifying similar variable patterns between data points with multiple features. It then maximizes the gradient of data by the weighting of features to show similar data points nearby one another on the plot, while showing more different points further apart.

In our work, we created 2-dimensional t-SNE plots to represent the overall structure of our data. We colored patients by their membership in phenotypes. These plots were created in R using the tsne package.

G. Predicting cluster members in new datasets

In the GenIMS cohort study and 3 RCTs, we used a prospective approach to assign phenotype membership to subject based upon clinical characteristics of typical cluster members in the SENECA derivation data.

To accomplish this, we first standardized and normalized the variables in the new cohort/trial if necessary. Data was imputed using the procedure above (B). We then predicted phenotype assignments for new subjects by calculating the Euclidean distance from each subject to the centroid of each phenotype from the SENECA validation data, following the equation:

$$d_{i,\mu_k} = \sqrt{\sum_{j=1}^{p} (x_{ij} - \mu_{kj})^2}$$

Here, $d_{i,\mu k}$ represents the distance to the center, for the i^{th} subject to the mean, μ, of the k^{th} phenotype center, x_{ij} represents the value of variable j for subject i, and μ_{kj} represents the mean of variable j for the kth phenotype center. Distances to phenotype centroids were calculated for all subjects to all phenotype centroids, and subjects were assigned to the nearest phenotype.

H. Heterogeneity of treatment effects

In each of the 3 RCTs, we used logistic regression models to determine if treatment effects were differential in existing trial datasets by phenotype. The model included: covariates for treatment, indicator of phenotype, and their interaction. A likelihood ratio test of the interaction terms was used as a test of statistical significance of heterogeneous treatment effects between the 4 phenotypes. Interaction terms were considered significant if p-value was less than 0.05.

I. Simulation methods

We used simulation to explore the degree to which the distribution of disease phenotypes enrolled in each trial could affect the inference of the trial. For each trial, we derived a series of phenotype scenarios, where the baseline scenario maintains the same proportion of patients in each phenotype as was observed in the original trial. We then decreased the proportion of patients in phenotypes by 1% increments, increasing the proportion of patients in one or more of the other phenotypes to compensate. We also considered scenarios in which we increased the proportion of patients in a phenotype in 1% increments, thus decreasing the proportion of patients in one or more other phenotypes. The relative sizes of the other phenotypes were held constant.

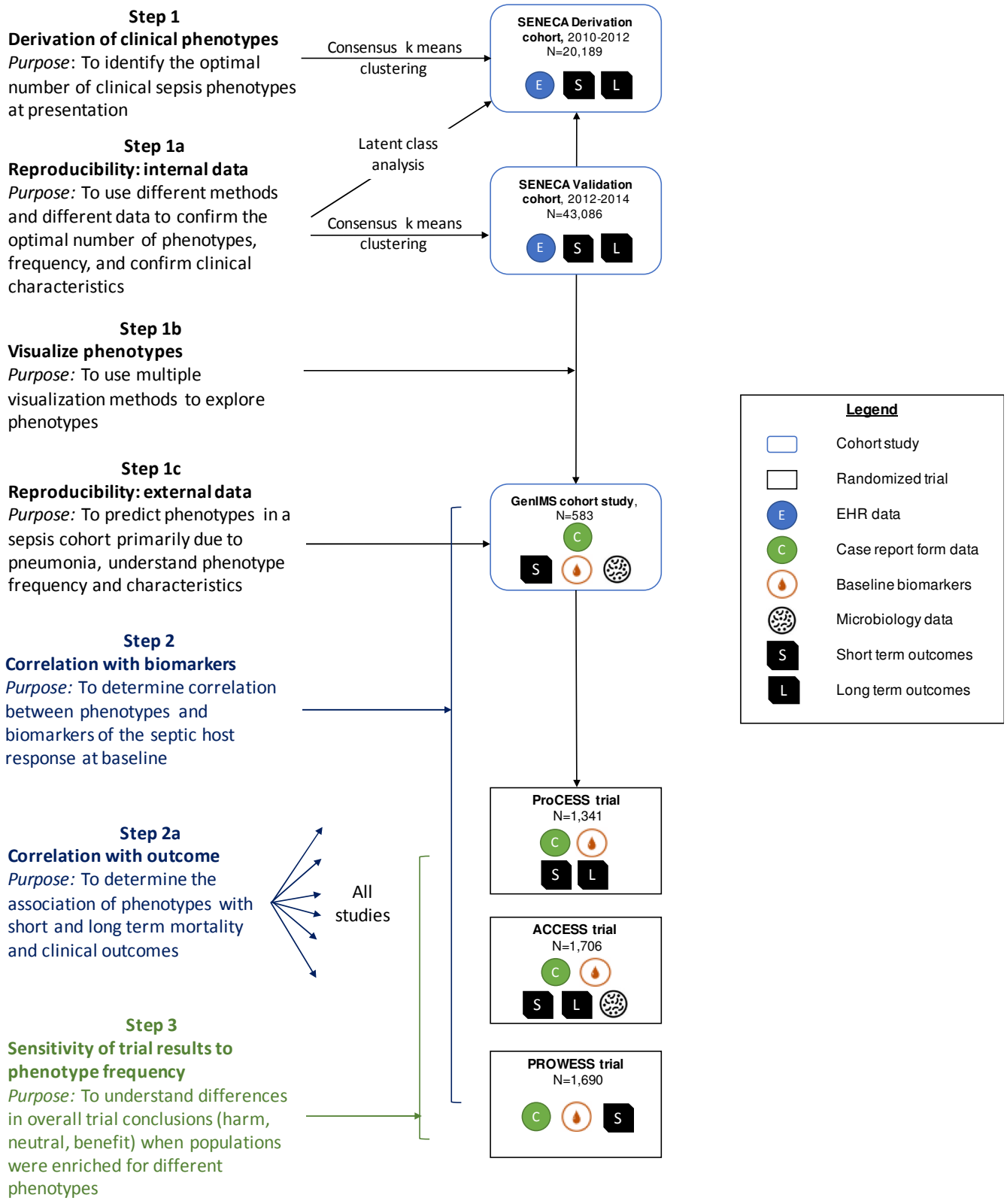
We chose the following scenarios with the accompanying changes to phenotypes:

Scenario	Phenotypes held constant	Phenotypes increased	Phenotypes decreased
1	ß, *y*	∂	α
2	*y*	ß, ∂	α
3	.	ß, *y*, ∂	α
4	ß, *y*	α	∂
5	*y*	α	ß, ∂
6	.	α	ß, *y*, ∂

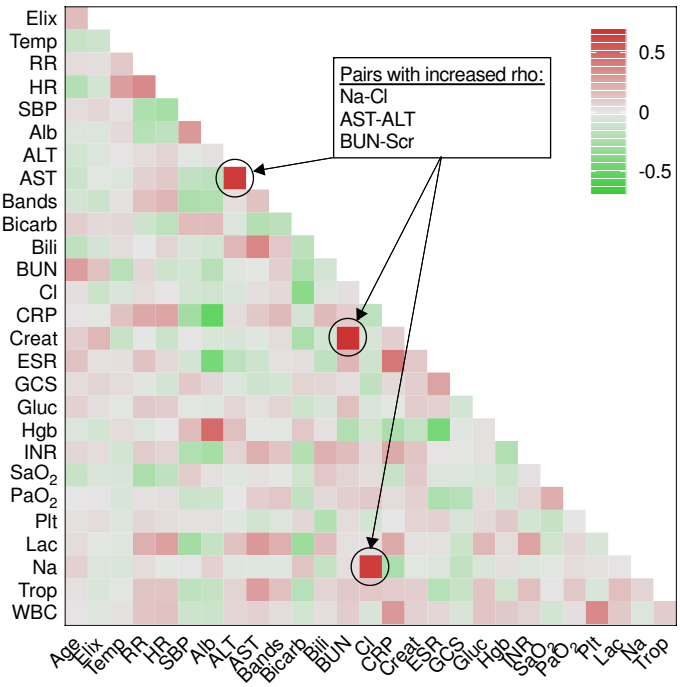
Under each scenario, we simulated 10,000 trials. We assumed the same sample size and randomization ratio as the original trial. In each simulated trial, a given patient experienced a mortality outcome according to the mortality rate observed in the original trial for his or her arm and phenotype. Across the 10,000 simulated trials, we calculated the proportion of trials on which Arm 1 performed superior to or inferior to the other arm according to a chi-square test between the two arms. If the chi-square test was significant at the 0.05 level, then the superiority or inferiority of Arm 1 was determined by the direction of the treatment benefit. If the chi-square test was not significant at the 0.05 level, we concluded no benefit between the two arms.

We also conducted a simulation similar to above using a severity of illness measure—the Acute Physiology and Chronic Health Evaluation 3 (APACHE3) score. This was measured at baseline in the PROCESS trial. We created APACHE3 quartiles and performed the same re-allocation of patients in 6 scenarios as above. We compared the conclusions of trials as no difference, harm, or benefit, similar to the primary simulations.

eFigure 1. Schematic of study



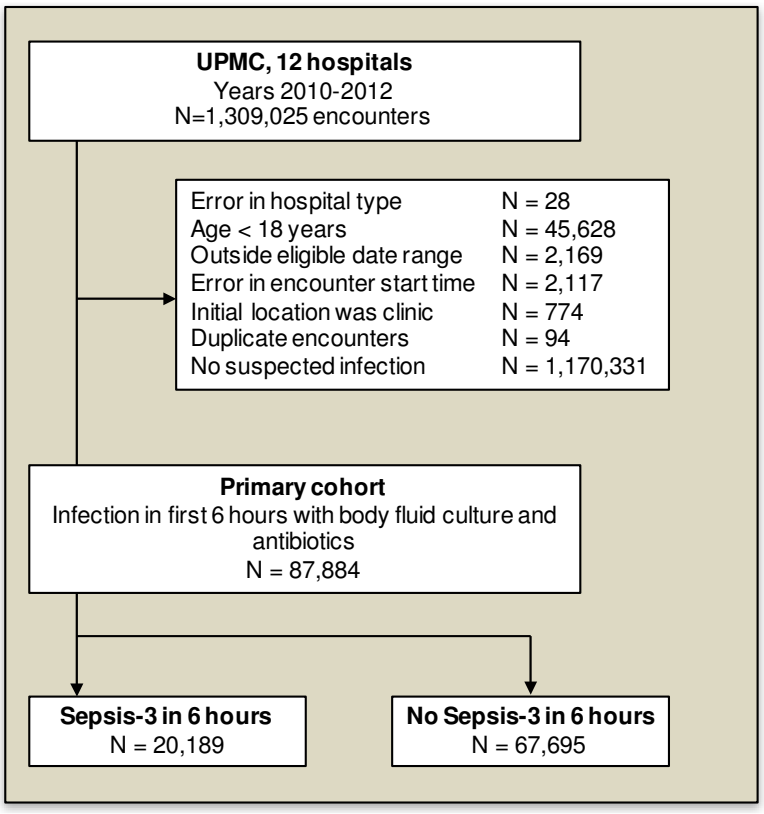
eFigure 2. Heatmap of correlation between clinical variables for phenotyping



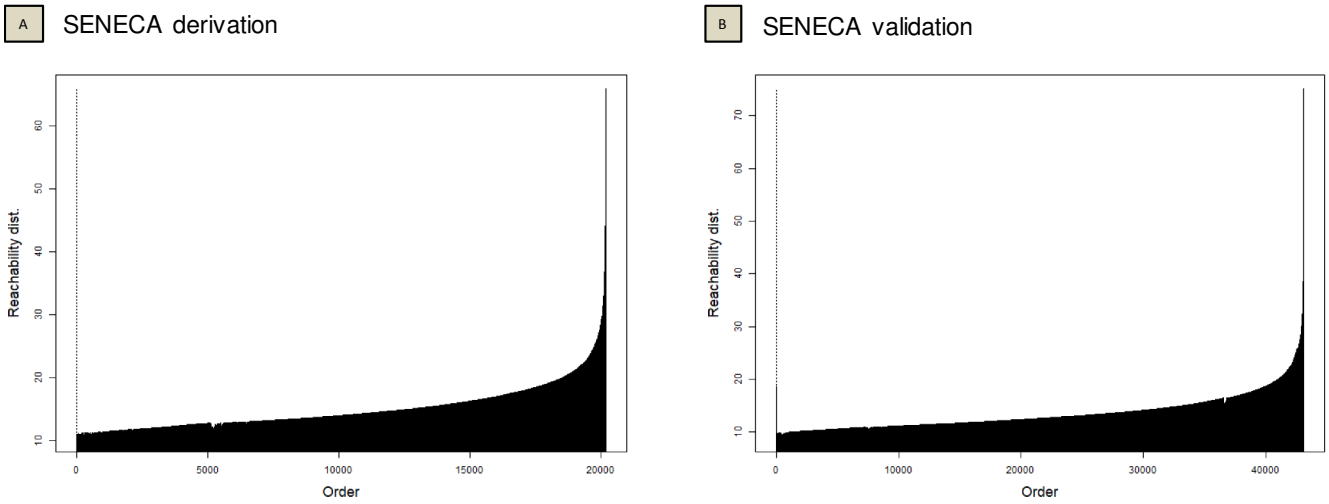
Heatmap shows greater color (red or green) when the Spearman rank order correlation coefficient is greater in positive or negative direction. The call out box identifies pairs of variables with correlation (rho>0.4).

Abbreviations in order: Elix: elixhauser comorbidity; Temp: temperature; RR: respiratory rate; HR: heart rate; SBP: systolic blood pressure; Alb: albumin; ALT: alanine transaminase; AST: aspartate transaminase; Bicarb: bicarbonate; Bili: bilirubin; BUN: blood urea nitrogen; Cl: chloride; CRP: C-reactive protein; Creat: serum creatinine; ESR: erythrocyte sedimentation rate; GCS: Glasgow coma scale score; Gluc: glucose; Hgb: hemoglobin; INR: international normalized ratio; SaO_2: oxygen saturation; PaO_2: arterial oxygen pressure; Plt: platelet count; Lac: serum lactate; Na: sodium; Trop: troponin; WBC: white blood cell count

eFigure 3. Encounters in the SENECA derivation cohort

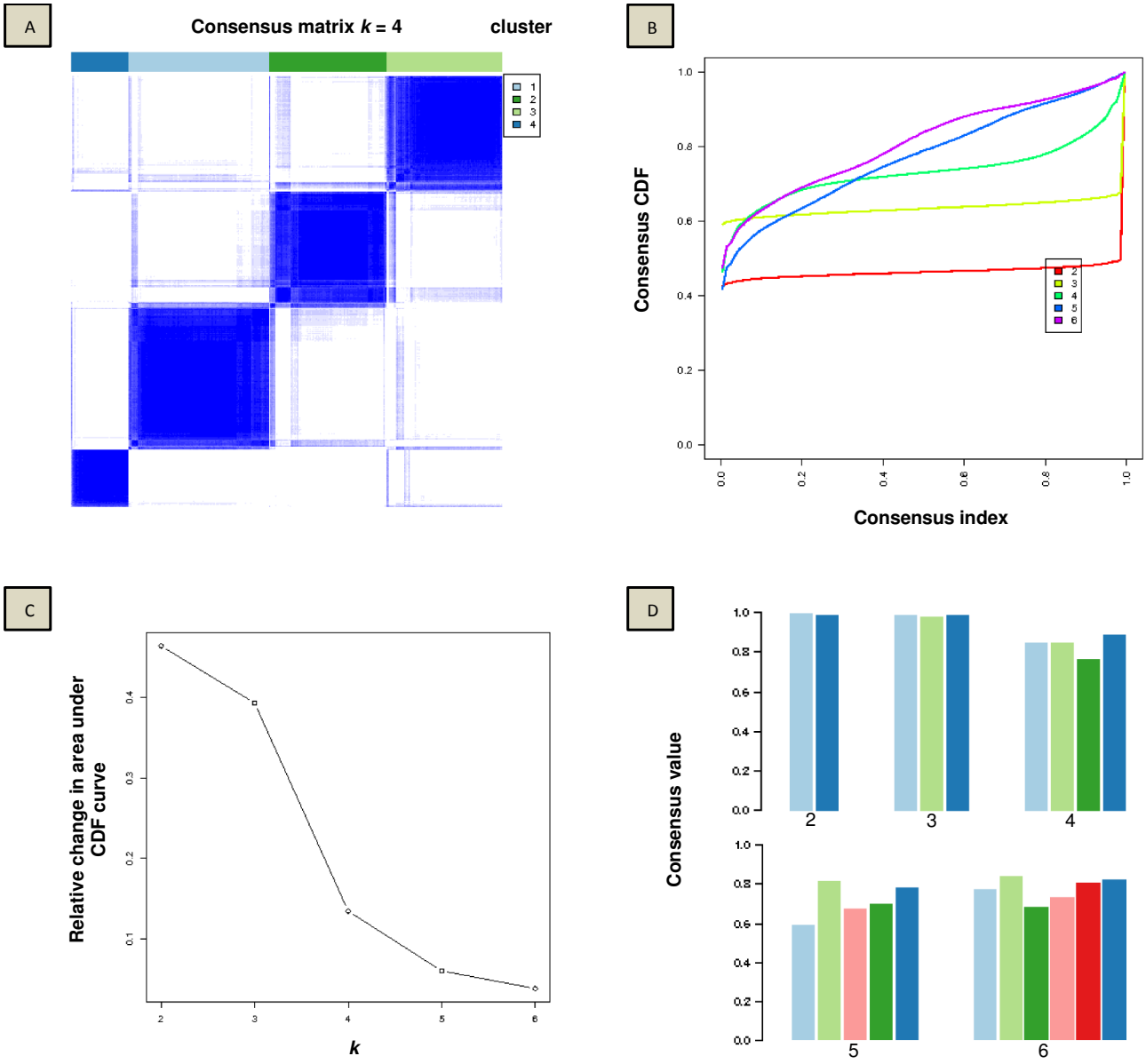


eFigure 4. OPTICS plots for SENECA derivation (A, N=20,189) and validation cohorts (B, N=43,086).



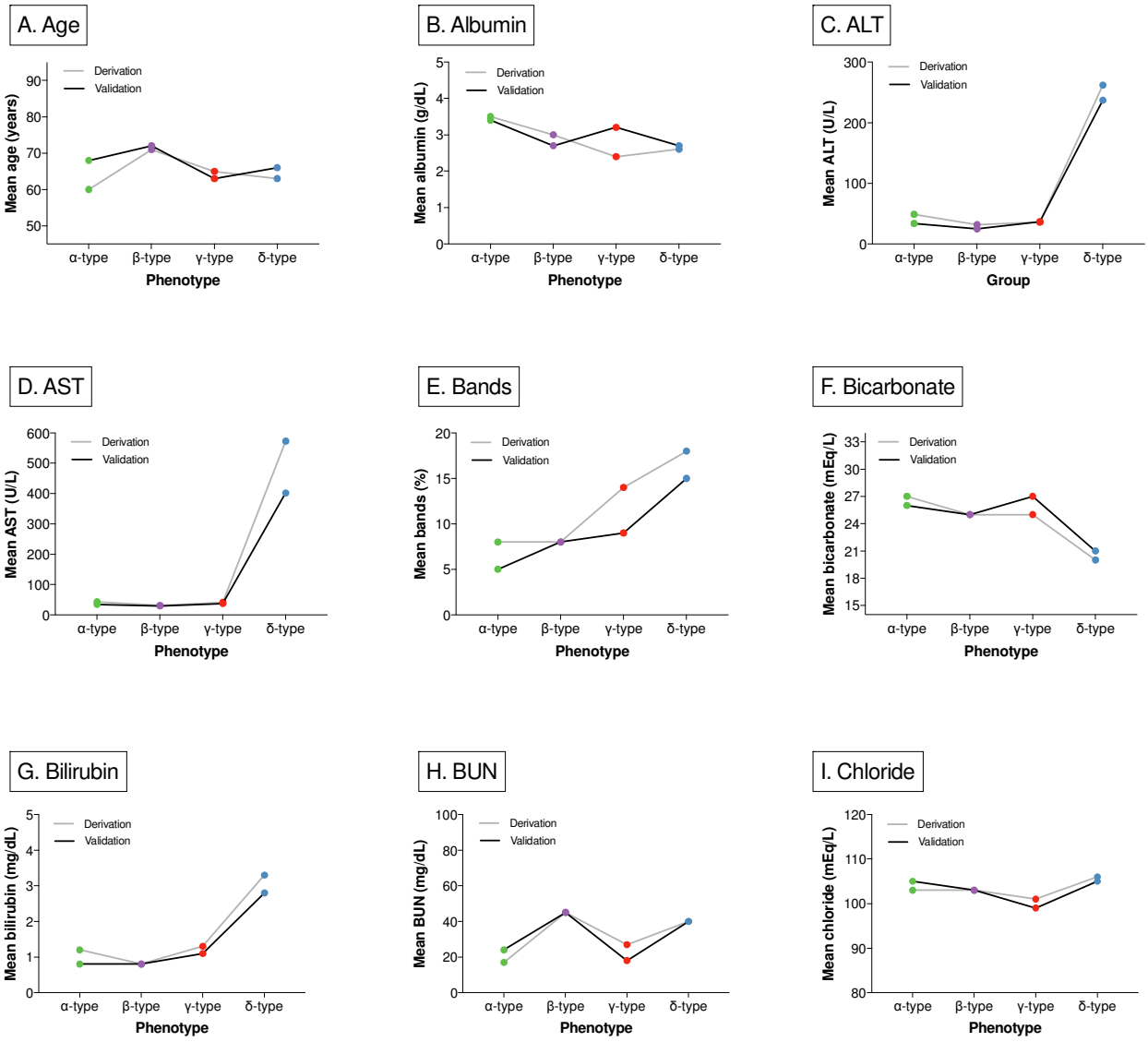
Interpretive example: The OPTICS plots shows a smooth rise in reachability distance (as opposed to well demarcated sets). This implies that a partioning approach such as consensus K means clustering is the preferred statistical algorithm, as opposed to a clustering approach such as hierarchical clustering.

eFigure 5. Consensus *k* clustering results in SENECA derivation cohort (N=20,189)



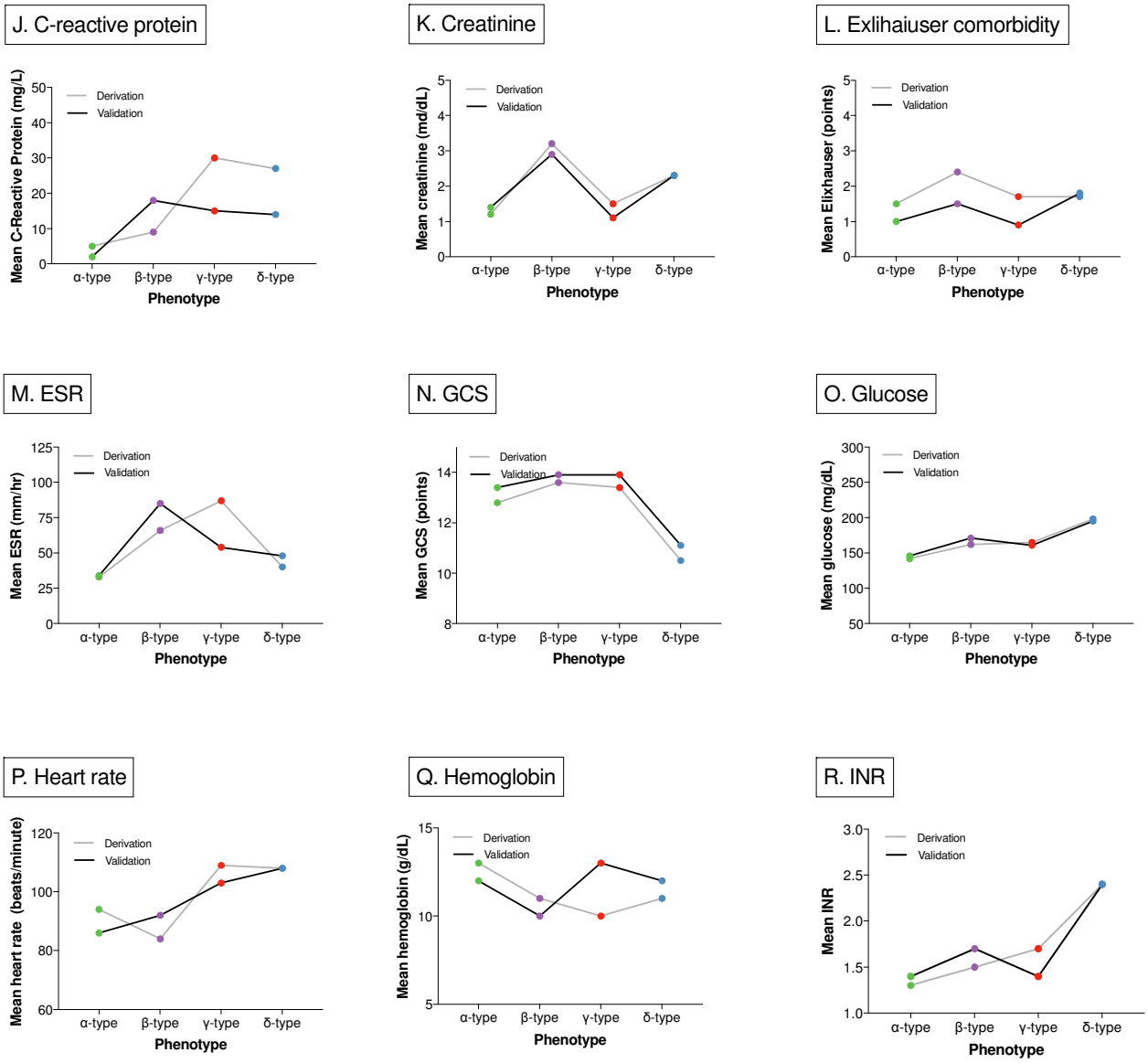
(A) Unsupervised consensus *k* clustering in derivation cohort (N=20,189) showing optimal partioning in consensus matrix for *k*=4. (B) Consensus cumulative distribution function (CDF) plot across *k*=2 to *k*=6, where higher and more horizontal curves suggest optimal fit. (C) Relative change in the area under the CDF curve with increasing clusters (*k*), with little change beyond *k*=4. (D) Cluster consensus plot showing the mean of all pairwise consensus values between a cluster members, for *k*=2 to *k*=6 where greater values for all bars suggest optimal fit.

eFigure 6. Descriptive plot(s) of mean of phenotyping variables, age through chloride.



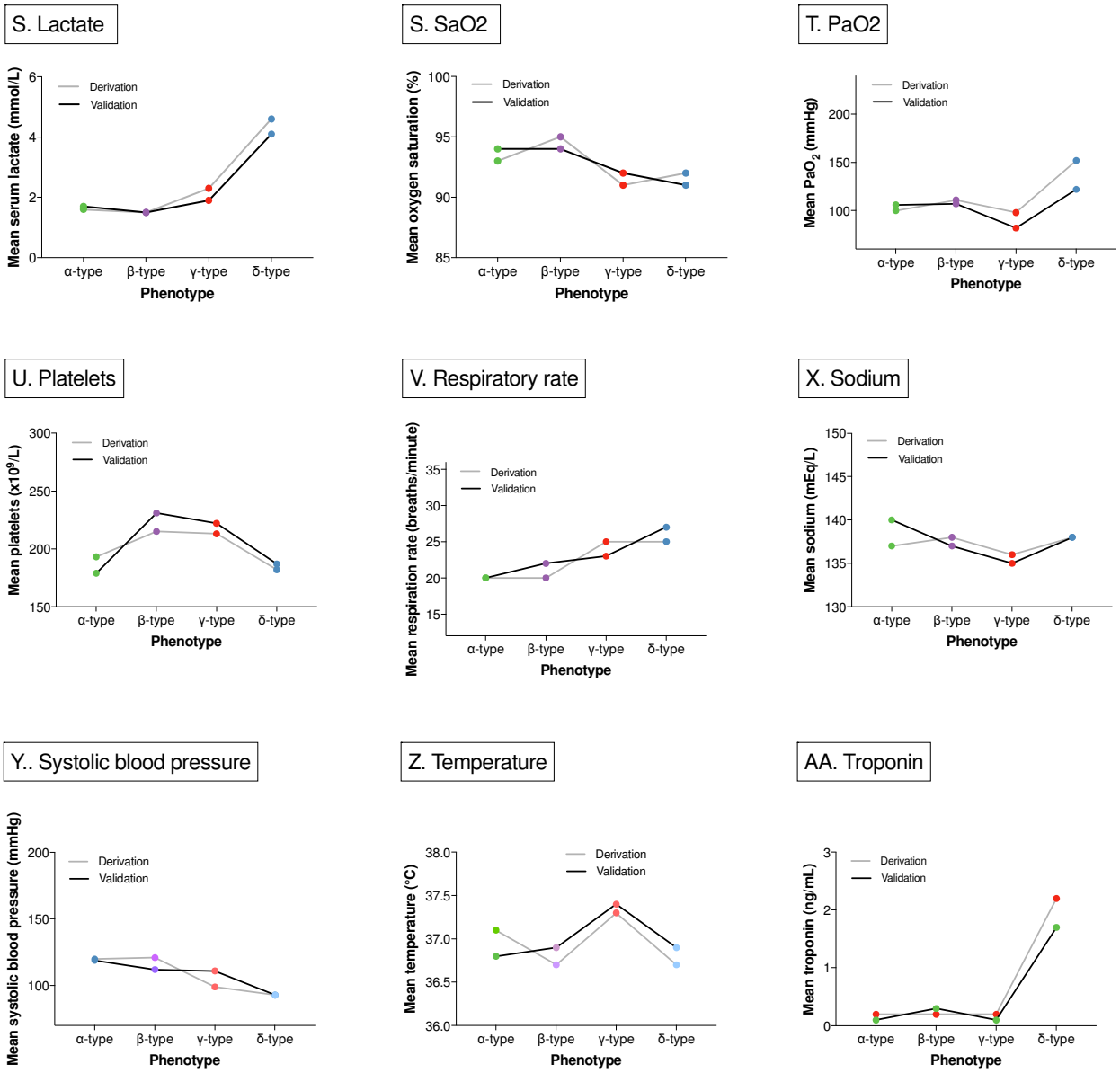
Panels individually show the mean value of the continuous variable by phenotype comparing values in the SENECA derivation data (N=20,189) and SENECA Validation data (N=43,086).

eFigure 7. Descriptive plot(s) of mean of phenotyping variables, c-reactive protein through INR.



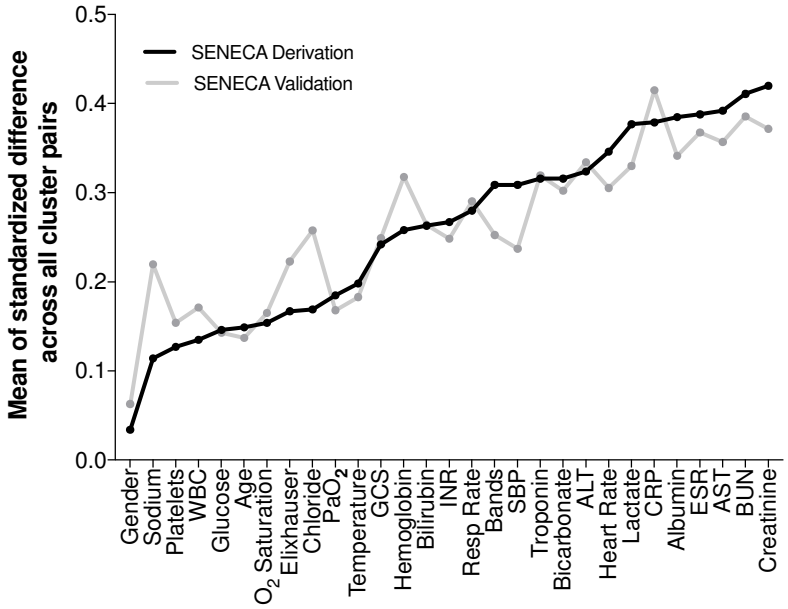
Panels individually show the mean value of the continuous variable by phenotype comparing values in the SENECA derivation data (N=20,189) and SENECA Validation data (N=43,086).

eFigure 8. Descriptive plot(s) of mean of phenotyping variables, serum lactate through troponin.



Panels individually show the mean value of the continuous variable by phenotype comparing values in the SENECA derivation data (N=20,189) and SENECA Validation data (N=43,086).

eFigure 9. Rank order of variables by mean of standardized differences across all phenotype pairs in SENECA derivation and validation cohorts.

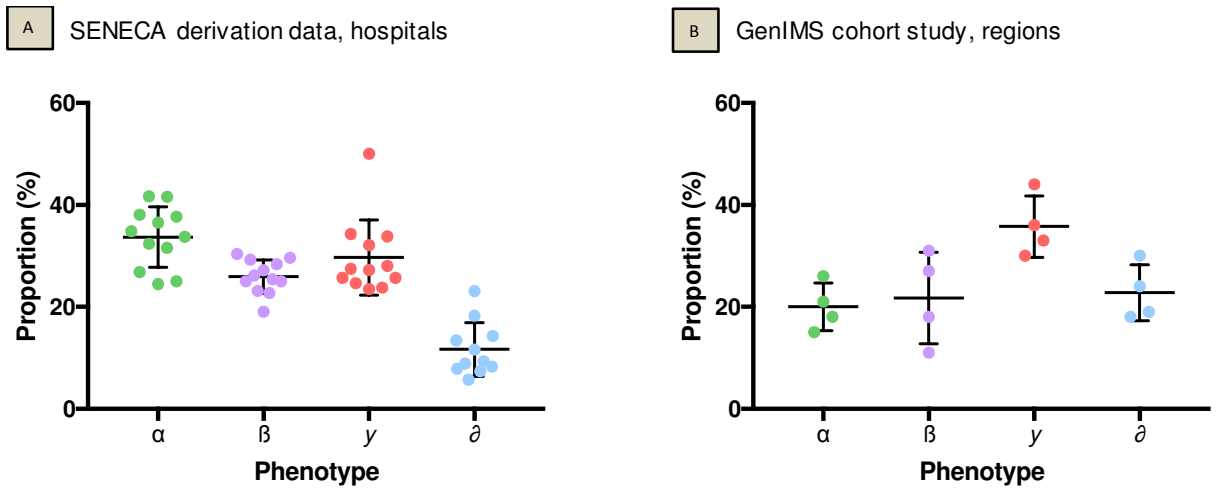


Differences in standardized mean absolute value of each variable ranked from minimum to maximum separation (*x*-axis) across all phenotype pairs in Figure 2, using the SENECA derivation cohort (N=20,189). Solid lines correspond to phenotypes derived using consensus *k* clustering. Light gray lines correspond to same comparisons but from phenotypes derived in a sensitivity analysis using the SENECA Validation cohort (N=43,086).

The variables are standardized such that all means are scaled to zero and standard deviations to one. A value of +1 for the standardized variable (y-axis) signifies that the mean of the absolute value for the phenotype differences was one standard deviation higher across all pairs.

Interpretive example: Across all phenotype pairs in Figure 2, the variables like creatinine, AST, albumin, or lactate tended to be more different, while variables like gender, sodium, glucose, or white blood cell count tended to be more similar.

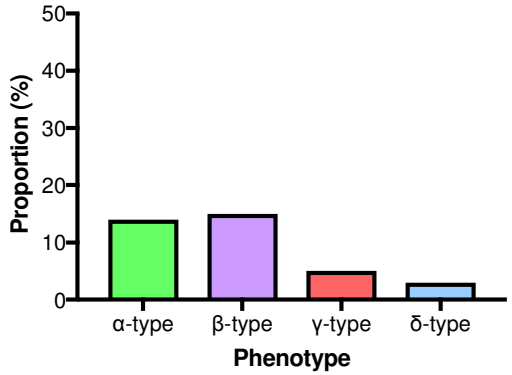
eFigure 10. Frequency of phenotypes across 12 hospitals in the SENECA derivation data (panel A, N=20,189) and 4 regions in the GenIMS cohort study (panel B, N=583).



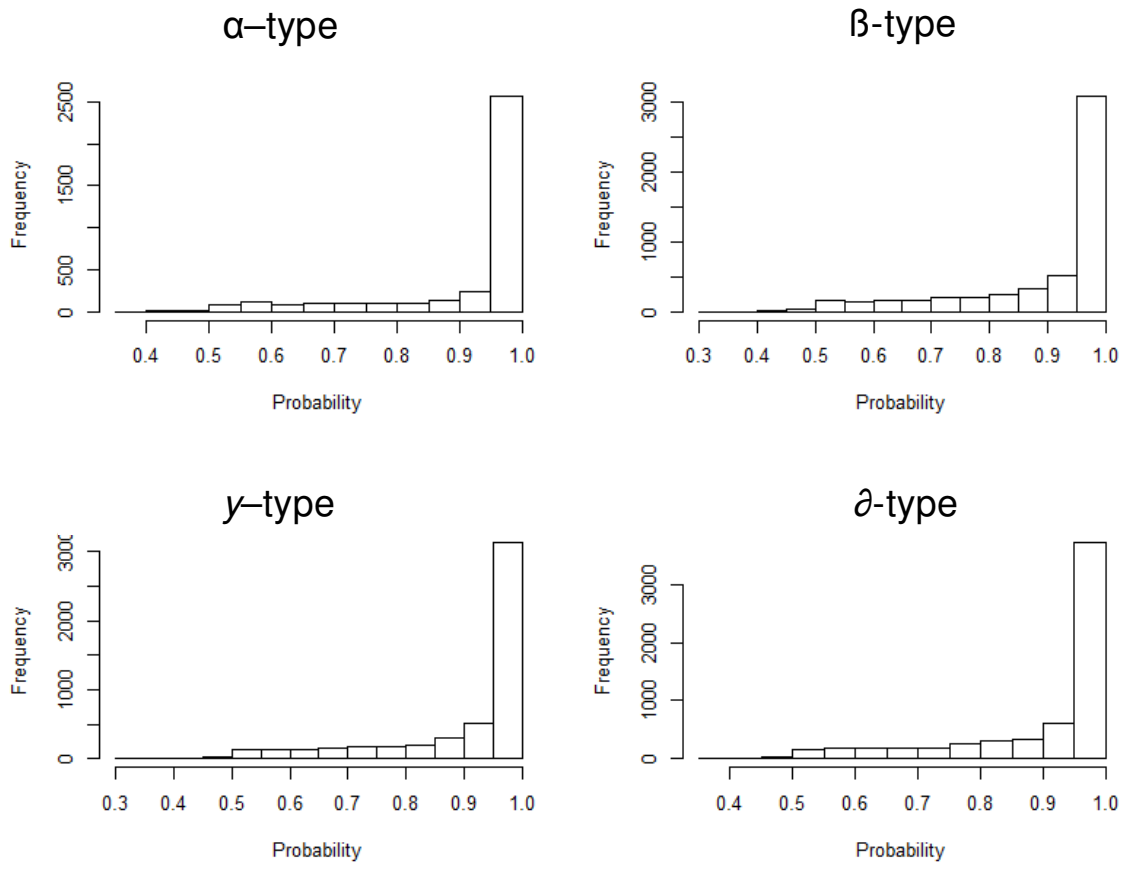
(A) Solid lines represent overall mean (SD) of proportion of phenotypes (%) across the 12 hospitals in SENECA derivation data. Light green corresponds to α–type, light purple to ß–type, light red to *y*–type, and light blue to ∂–type, where each point is a hospital. (B) GenIMS cohort study showing similar distribution of phenotypes (%) across 4 regions (e.g. Southwestern Pennsylvania, Connecticut, Michigan, Tennessee).

Interpretive example: This plot suggests that in 2 cohorts of community and academic hospitals there is variability in the rates of phenotypes across hospitals. α–type ranged from 15 to 42%, ß–type ranged from 11 to 31%, *y*–type ranged from 23 to 50%, and ∂–type ranged from 0 to 30%.

eFigure 11. Proportion of patients by phenotype in SENECA derivation cohort (N=20,189) who, i.) did not have blood cultures as their first body fluid culture and, ii.) did not have intravenous antibiotics administered as their first interventions after presentation.

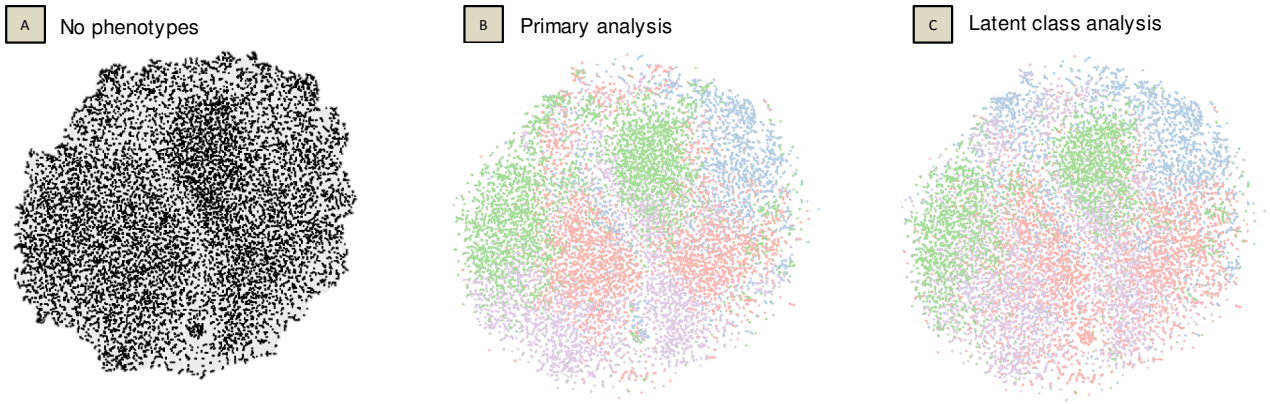


eFIgure 12. Sensitivity analysis using latent class clustering in the SENECA derivation cohort (N=20,189), showing probabilities of phenotype assignment.



Interpretive example: Using latent class analysis to derive phenotypes (called clusters in this output), histograms of within phenotype probability demonstrated that members have high probability of being a phenotype member (>0.9).

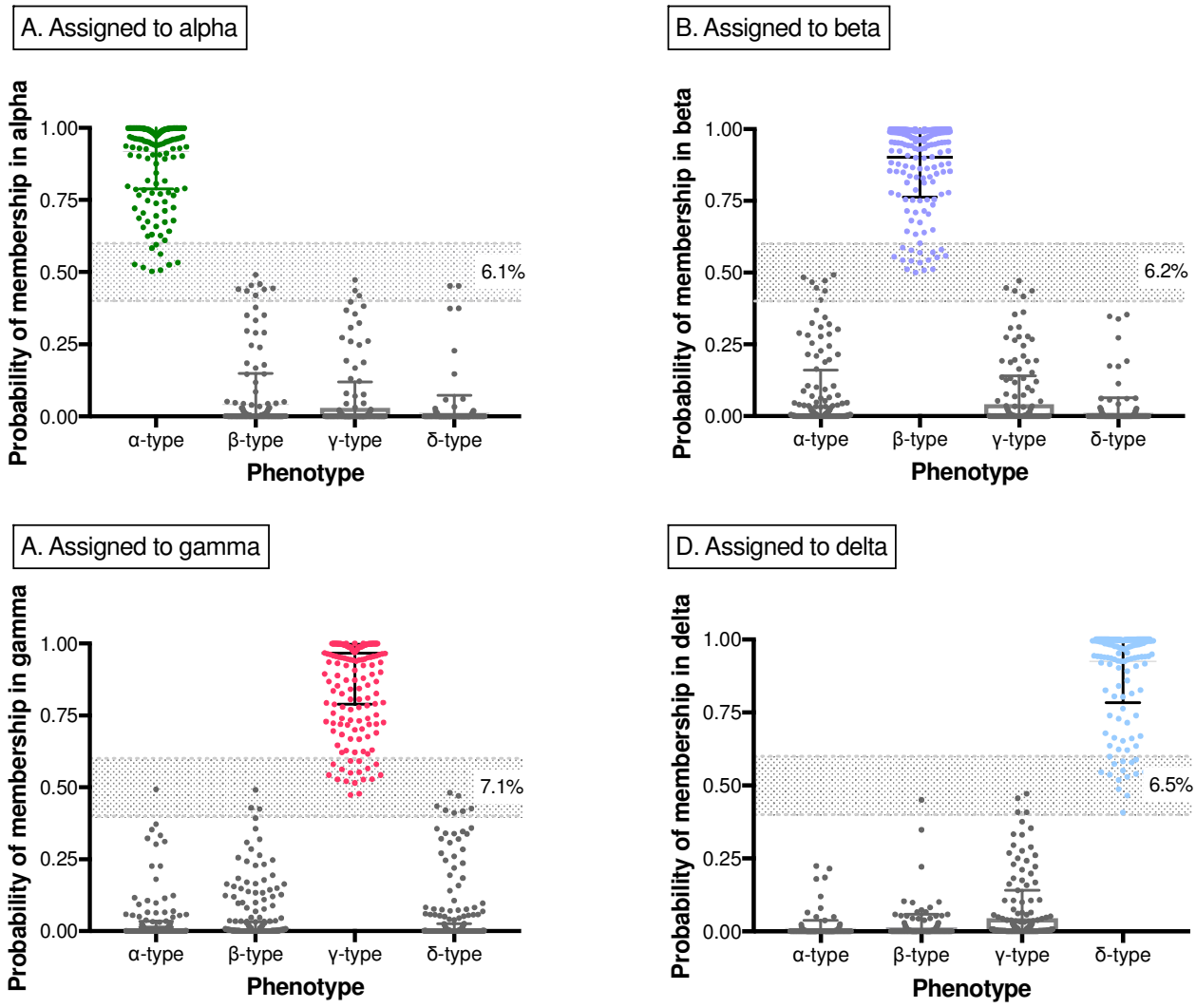
eFigure 13. t-SNE plot of phenotype assignments in SENECA derivation cohort (N=20,189)



(A) Visualization of phenotypes using t-distributed stochastic neighbor embedding (t-SNE) technique in the SENECA derivation data with no phenotypes shown in color, (B) phenotypes shown in color from the primary analysis, and (C) phenotypes shown from the latent class sensitivity analysis.

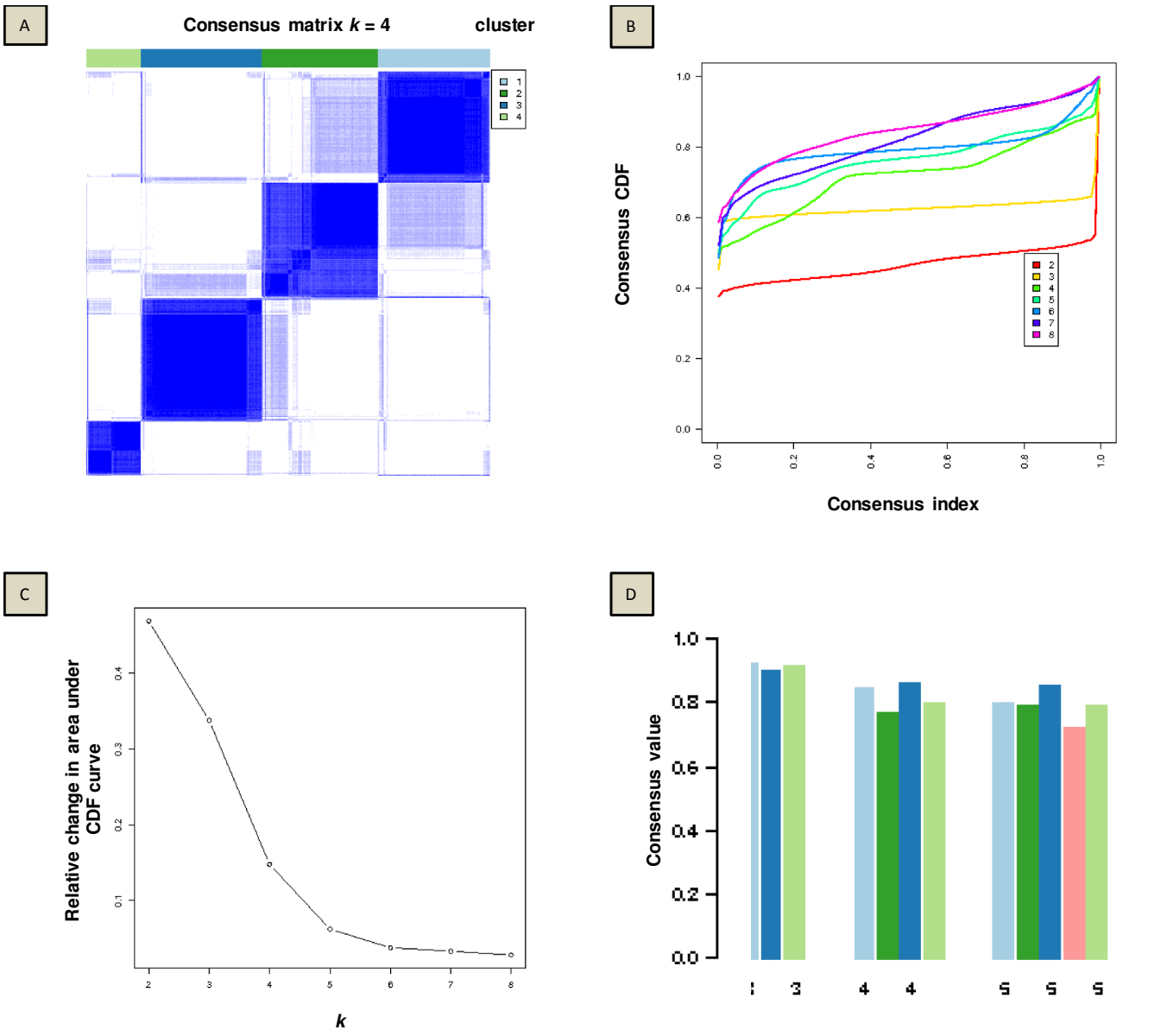
Interpretive example: Using a novel visualization method, phenotype members have a similar frequency and distribution across RCTs.

eFigure 14. Probabilities of assignment for phenotype members and for those not assigned, using latent class analysis in the SENECA Derivation cohort (N=20,189).



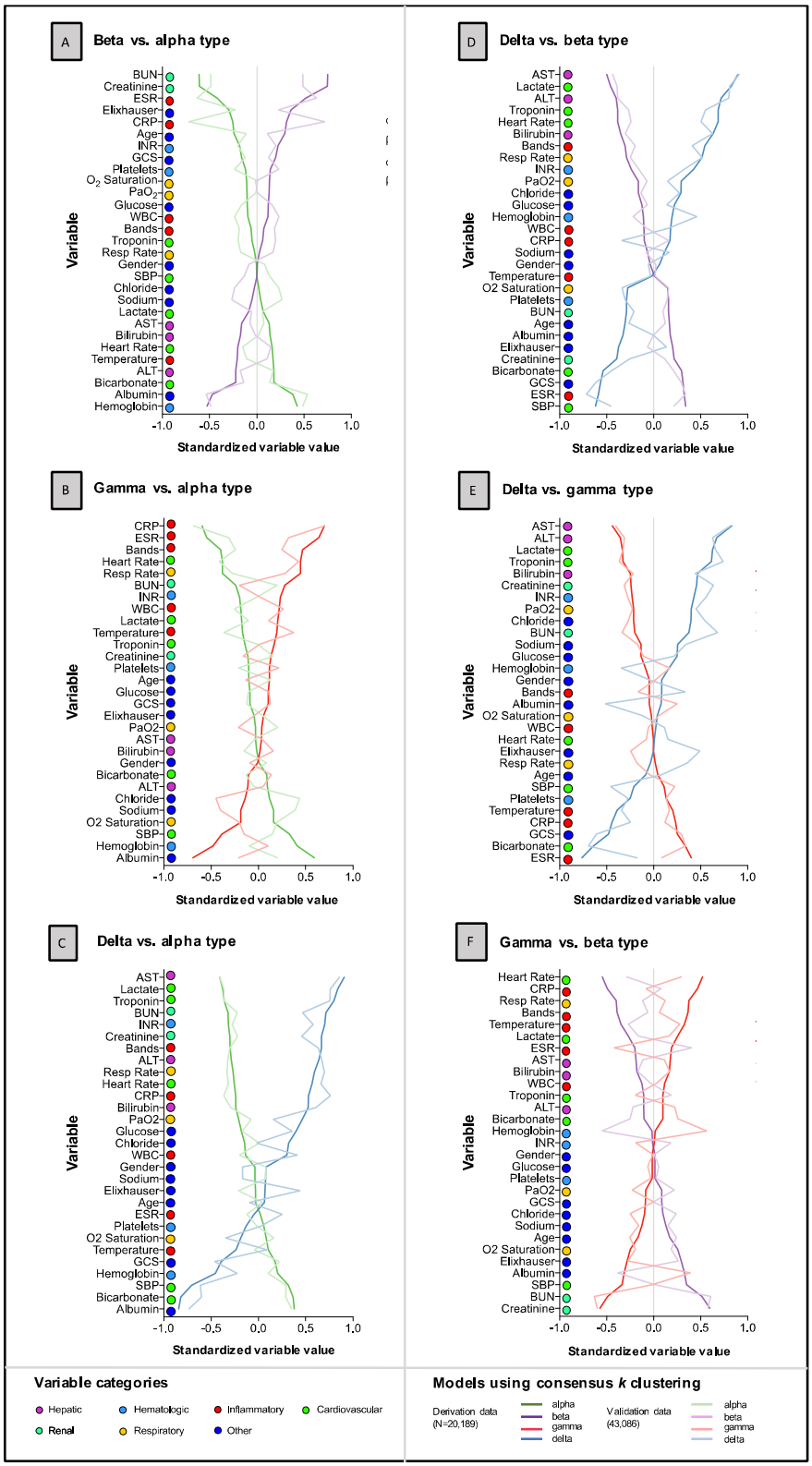
(A) Probabilities of assignment to alpha type, and *green* for those actually assigned to alpha, (B) Probabilities for patients assigned to beta type, and *purple* for those actually assigned to beta, (C) Probabilities for patients assigned to gamma type, and *red* for those actually assigned to gamma, and (D) probabilities for patients assigned to delta type, and *blue* for those actually assigned to delta. Black lines correspond to median [IQR] of probability. Gray shading corresponds to region with a 45-55% (low or marginal) probability of assignment. Inset proportion is the % of 20,189 in the marginal region.

eFigure 15. Consensus *k* means clustering results from SENECA validation cohort (N=43,086)



(A) Unsupervised consensus *k* clustering in SENECA validation cohort (N=43,086) showing optimal partioning in consensus matrix for *k*=4. (B) Consensus cumulative distribution function (CDF) plot across *k*=2 to *k*=8, where higher and more horizontal curves suggest optimal fit. (C) Relative change in the area under the CDF curve with increasing clusters (*k*), with little change beyond *k*=4. (D) Cluster consensus plot showing the mean of all pairwise consensus values between a cluster members, for *k*=2 to *k*=5 where greater values for all bars suggest optimal fit.

eFigure 16. Mean standardized differences between variables across phenotype pairs for primary analysis (dark line) and the SENECA validation cohort (N=43,086).

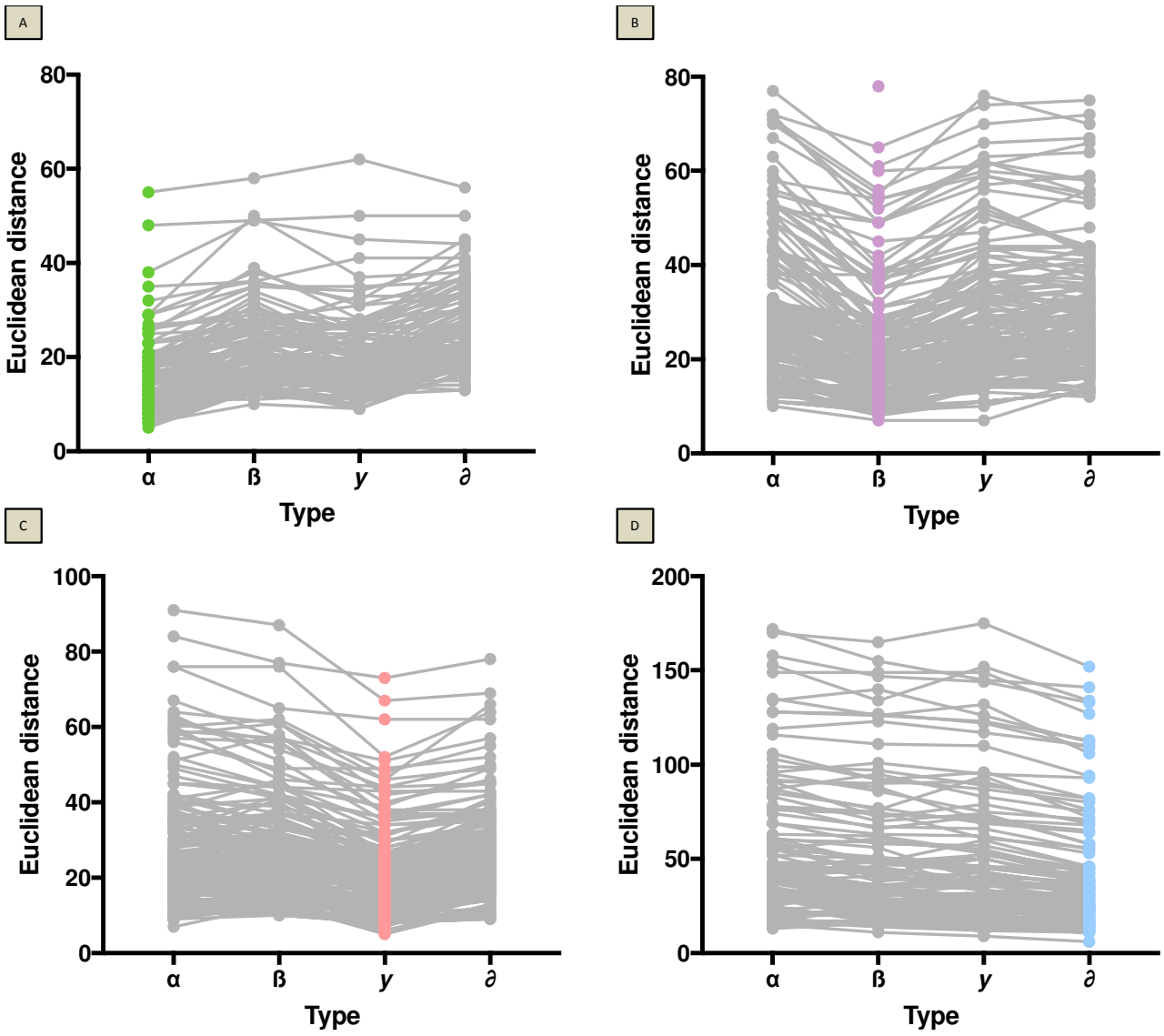


Differences in standardized mean value of each variable ranked from maximum positive to negative separation (*x*-axis) in the SENECA derivation cohort (N=20,189). Solid lines correspond to phenotypes derived using consensus *k* clustering. Light lines correspond to same comparisons but from phenotypes derived in a sensitivity analysis using the SENECA validation cohort (N=43,086). (A) ß-type (light purple) vs. α-type (light green). Variables ranked on the left x-axis are greater in ß-type than α-type (e.g., BUN, creatinine) while those on the right x-axis are lower in ß-type than α-type (e.g., albumin, hemoglobin). (B) Comparison between *y*-type (red) and α-type (light green). (C) Comparison between ∂-type (light blue) and α-type (light green).(D) Comparison between ∂-type (light blue) and ß-type (light purple), (E) Comparison between ∂-type (light blue) and *y*-type (red), and (F) Comparison between *y*-type (red) and ß-type (light purple). Colored circles correspond to the broad category of the variable as described in the Legend (e.g. renal, cardiovascular, inflammation).

In all panels, the variables are standardized such that all means are scaled to zero and standard deviations to one. A value of +1 for the standardized variable (y-axis) signifies that the mean value for the phenotype was one standard deviation higher than the mean value for both phenotypes shown on the graph as a whole.

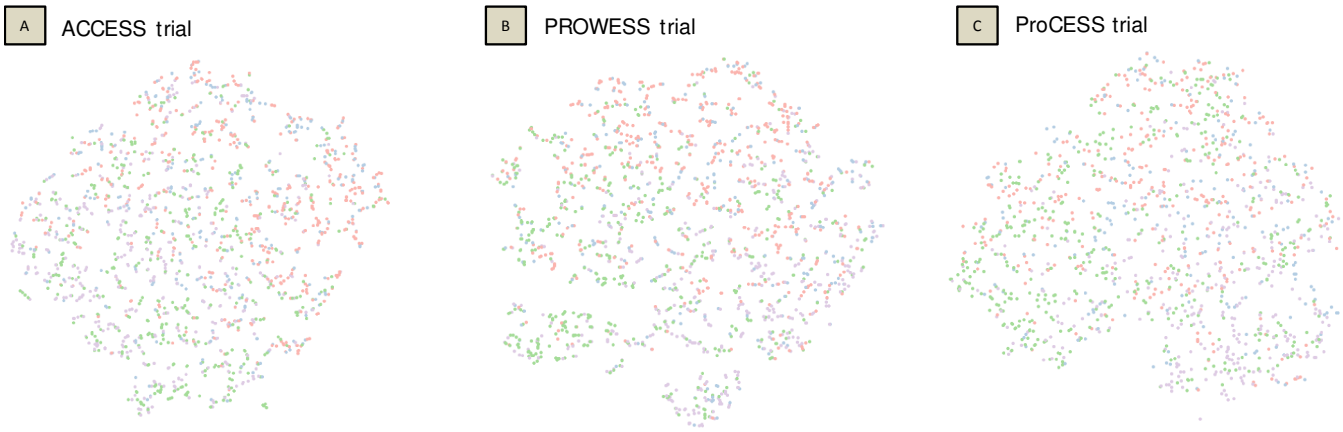
Interpretive example: Clinical variables differ broadly between sepsis phenotypes at the time of presentation, and are consistent using different clustering methods.

eFigure 17. Example of Euclidean distances for predicted phenotype members in the GenIMS cohort study (N=583).



(A) Predicted α–type members (N=118, 20%) with Euclidean distance to centroids from SENEVA derivation set. Phenotype assignment derives from the lowest Euclidean distance to the respective centroids; thus, the distance to α–type centroid among predicted α–type members is the lowest. Similar distribution of distances is shown for predicted ß–type members (B, N=162, 28%), predicted *y*–type members (C, N=192, 33%), and predicted *∂*–type members (D, N=111, 19%).

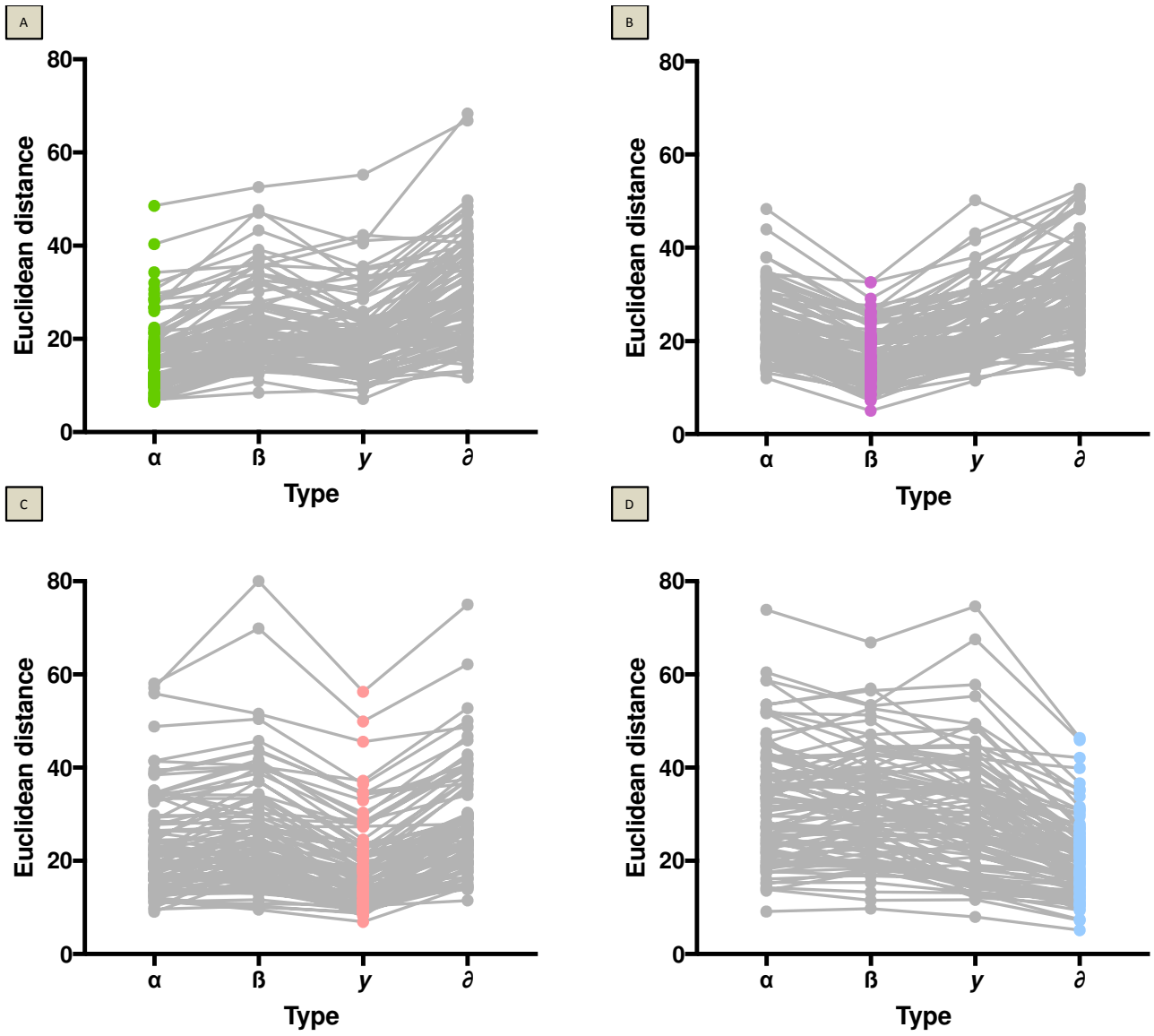
eFigure 18. t-SNE plot of phenotype assignments in 3 RCTs



(A) Visualization of phenotypes using t-distributed stochastic neighbor embedding (t-SNE) technique in the ACCESS trial, (B) PROWESS trial, and (C) ProCESS trial.

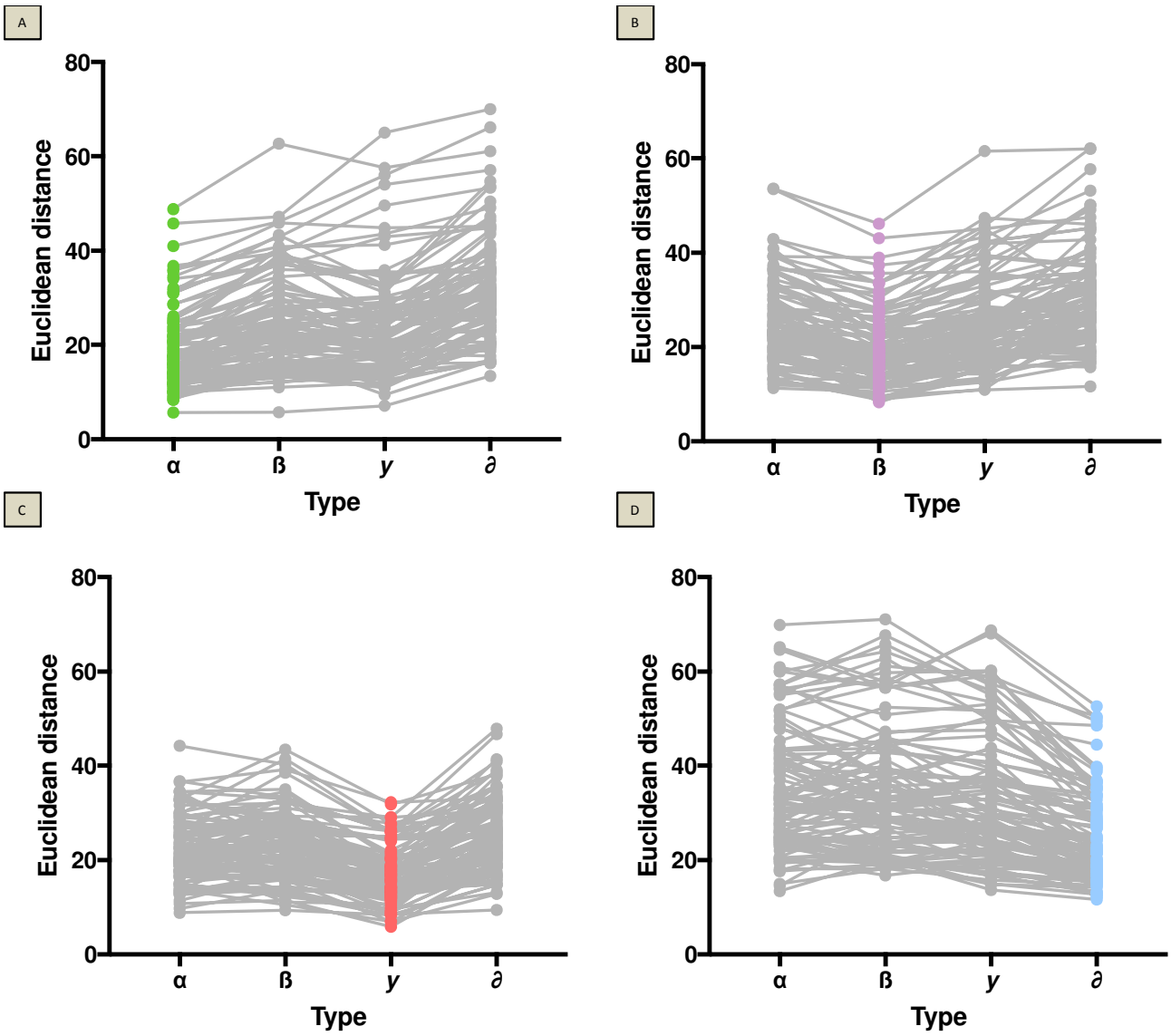
Interpretive example: Using a novel visualization method, phenotype members have a similar frequency and distribution across RCTs.

eFigure 19. Example of Euclidean distances for predicted phenotype membership in the ACCESS randomized trial (N=1,706).



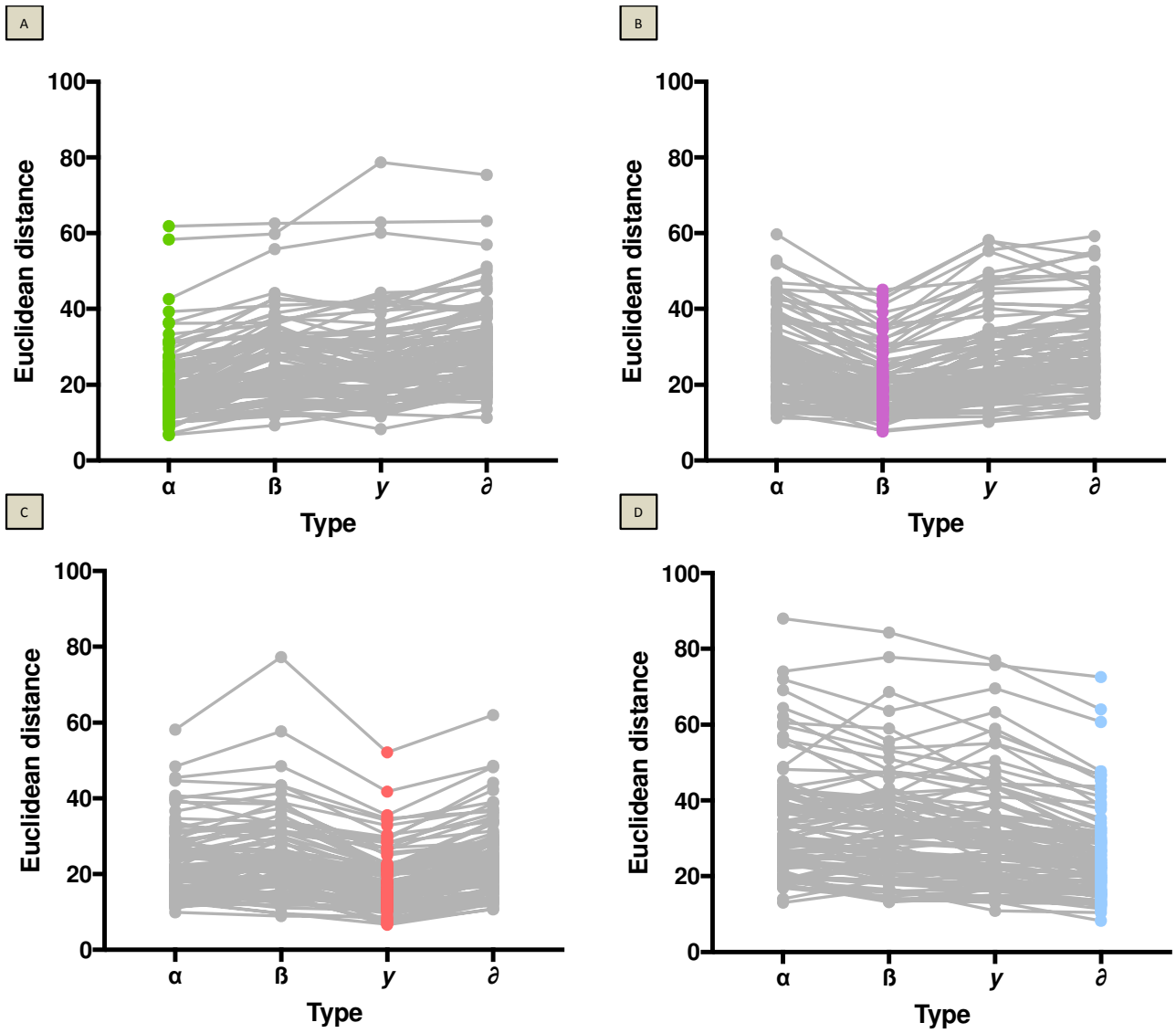
(A) Predicted α–type members (N=466, 27%) with Euclidean distance to centroids from SENEVA derivation set. Phenotype assignment derives from the lowest Euclidean distance to the respective centroids; thus, the distance to α–type centroid among predicted α–type members is the lowest. Similar distribution of distances is shown for predicted ß–type members (B, N=473, 28%), predicted *y*–type members (C, N=471, 28%), and predicted ∂–type members (D, N=296, 17%).

eFigure 20. Example of Euclidean distances for predicted phenotype membership in the PROWESS randomized trial (N=1,690).



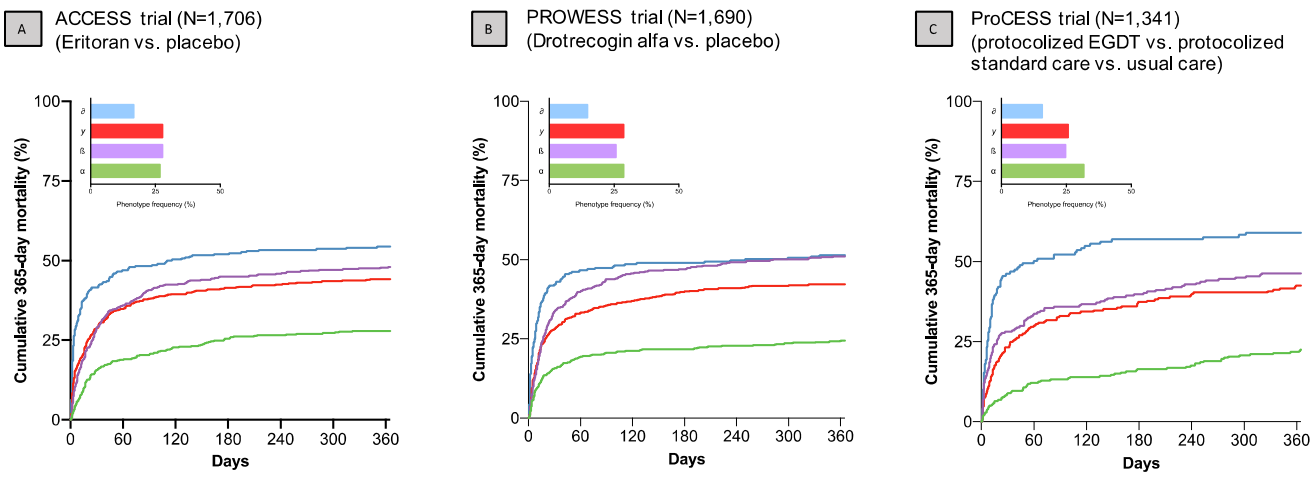
(A) Predicted α–type members (N=496, 29%) with Euclidean distance to centroids from SENEVA derivation set. Phenotype assignment derives from the lowest Euclidean distance to the respective centroids; thus, the distance to α–type centroid among predicted α–type members is the lowest. Similar distribution of distances is shown for predicted ß–type members (B, N=445, 26%), predicted *y*–type members (C, N=498, 29%), and predicted ∂–type members (D, N=251, 15%).

eFigure 21. Example of Euclidean distances for predicted phenotype membership in the ProCESS randomized trial (N=1,341).



(A) Predicted α–type members (N=430, 32%) with Euclidean distance to centroids from SENEVA derivation set. Phenotype assignment derives from the lowest Euclidean distance to the respective centroids; thus, the distance to α–type centroid among predicted α–type members is the lowest. Similar distribution of distances is shown for predicted ß–type members (B, N=340, 25%), predicted *y*–type members (C, N=353, 26%), and predicted ∂–type members (D, N=218, 16%).

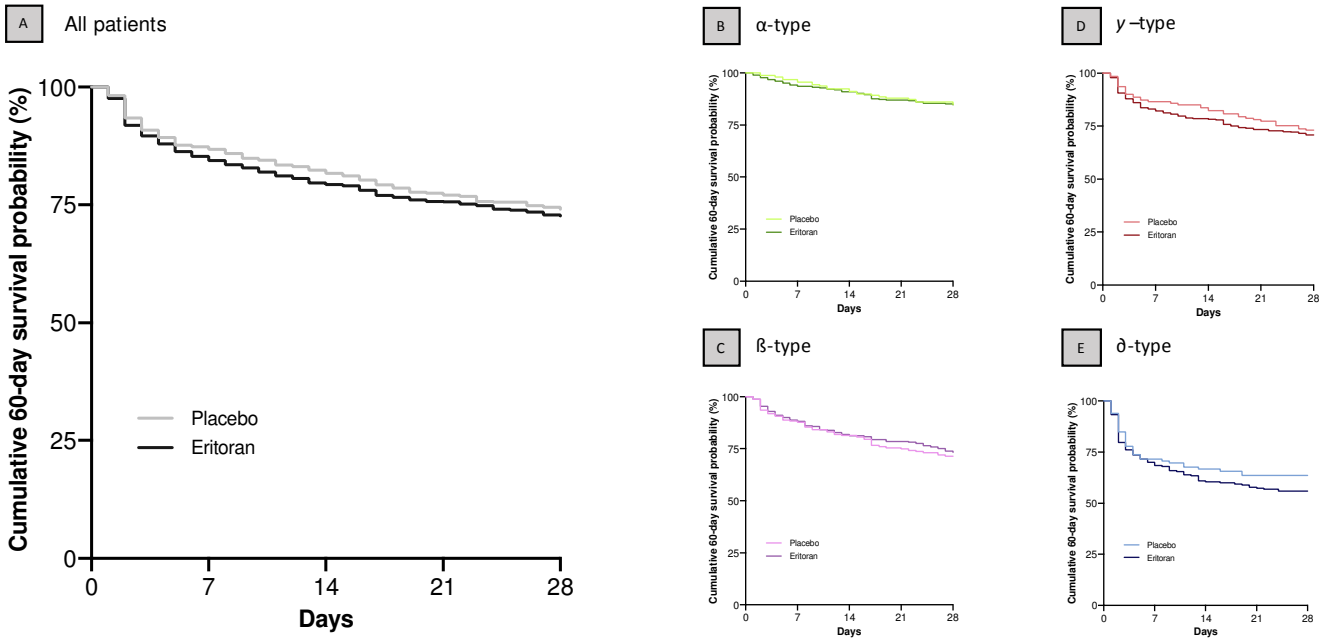
eFigure 22. 365-day mortality by phenotype in the ACCESS, PROWESS, and ProCESS trials.



(A) 365-day mortality in the ACCESS trial (N=1,706), (B) 365-day mortality in PROWESS trial (N=1,690), and (C) 365-day mortality in the ProCESS trial, by phenotype, where α–type is light green, ß–type is light purple, *y*–type is light red, and ∂–type is light blue. All panels show significant differences in mortality by phenotype (log rank P<0.001). Inset histograms show the proportion of patients in each phenotype.

Interpretive example: In 3 randomized clinical trials with follow up to 365 days after enrollment, phenotypes are significantly and consistently associated with outcome.

eFigure 23. Cumulative 28-day survival by treatment arm within phenotypes in the ACCESS trial (N=1,706).



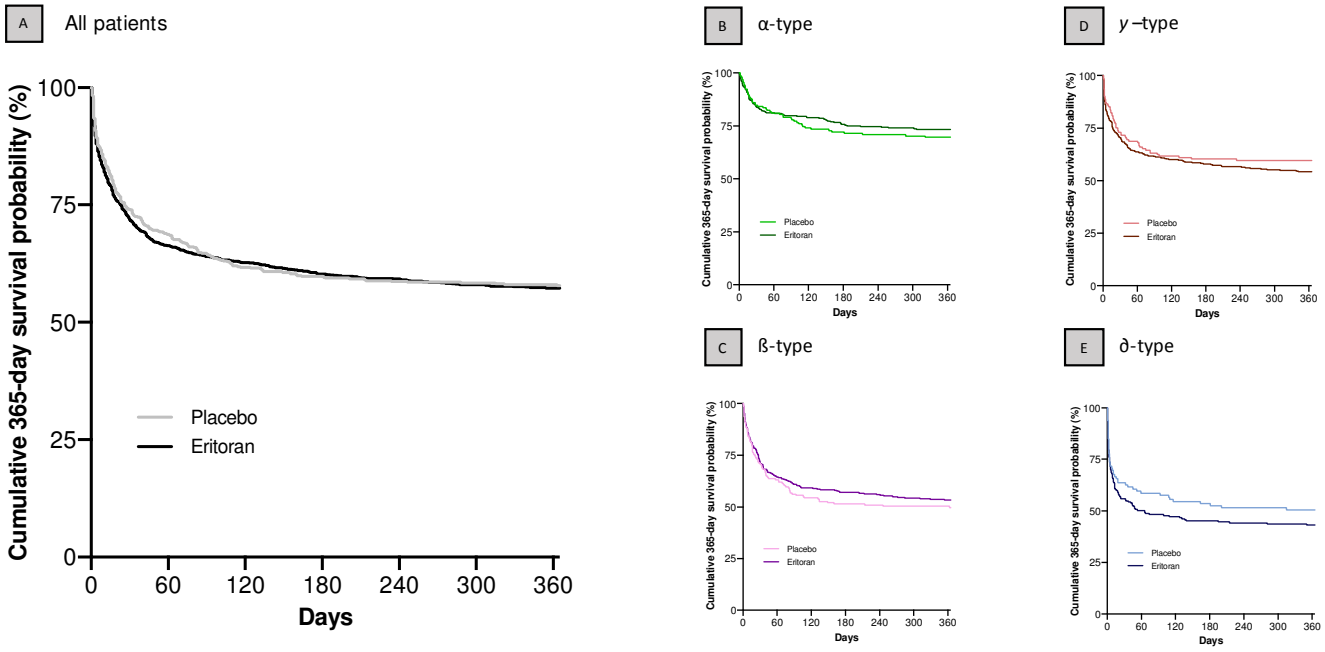
(A) ACCESS randomized trial 28-day survival for all patients (N=1,706), stratified by treatment arm with Eritoran the dark solid line, and placebo the lighter line, (B) alpha type (N=466), (C) beta type (N=473), (D) gamma type (N=471), and (E) delta type (N=296). P value for interaction = 0.64.

Table. 28-day mortality by phenotype and arm with absolute risk difference and 95% confidence interval

Phenotype	All	Eritoran	Placebo	Absolute risk difference, %, (95%CI)*
α-type	71/466 (15.2)	47/308 (15.3)	24/158 (15.2)	0.0 (-6.8, 7.0)
ß-type	130/473 (27.5)	81/302 (26.8)	49/171 (28.7)	-1.8 (-10.2, 6.6)
y-type	134/471 (28.5)	96/330 (29.1)	38/141 (27.0)	2.1 (-6.6, 11.0)
∂-type	123/296 (41.6)	87/197 (44.2)	36/99 (36.4)	7.8 (-3.9, 19.5)

*Absolute risk difference comparing Eritoran to placebo, where positive risk difference favors placebo and negative difference favors Eritoran

eFigure 24. Cumulative 365-day survival by treatment arm within phenotypes in the ACCESS trial (N=1,706).



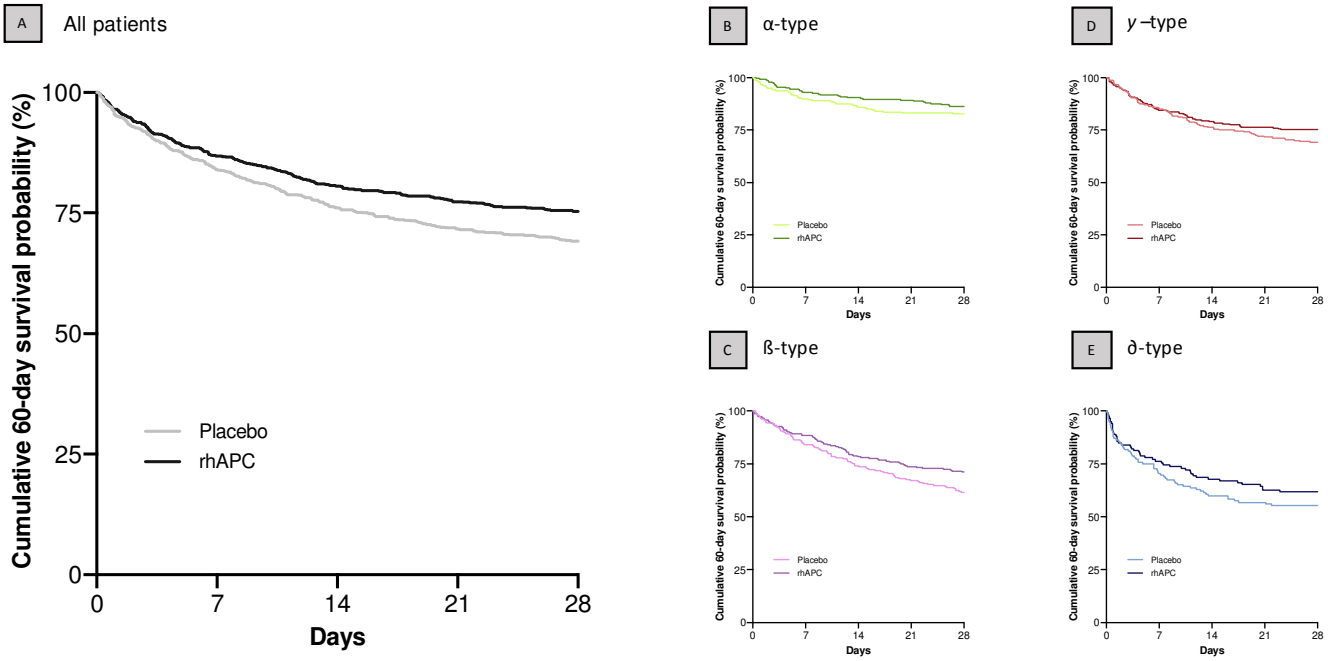
(A) ACCESS randomized trial 365-day survival for all patients (N=1,706), stratified by treatment arm with Eritoran the dark solid line, and placebo the lighter line, (B) alpha type (N=466), (C) beta type (N=473), (D) gamma type (N=471), and (E) delta type (N=296). P value for interaction = 0.28.

Table. 365-day mortality by phenotype and arm with absolute risk difference and 95% confidence interval

Phenotype	All	Eritoran	Placebo	Absolute risk difference, %, (95%CI)*
α-type	130/466 (28)	82/308 (27)	48/158 (30)	-3.7 (-12.5, 4.9)
ß-type	227/473 (48)	141/302 (47)	86/171 (50)	-3.6 (-13.0, 5.8)
y-type	208/471 (44)	151/330 (46)	57/141 (40)	4.5 (-3.7, 12.8)
∂-type	161/296 (54)	112/197 (57)	49/99 (49)	7.4 (-4.6, 19.4)

*Absolute risk difference comparing Eritoran to placebo, where positive risk difference favors placebo and negative difference favors Eritoran

eFigure 25. Cumulative 28-day survival by treatment arm within phenotypes in the PROWESS trial (N=1,690).



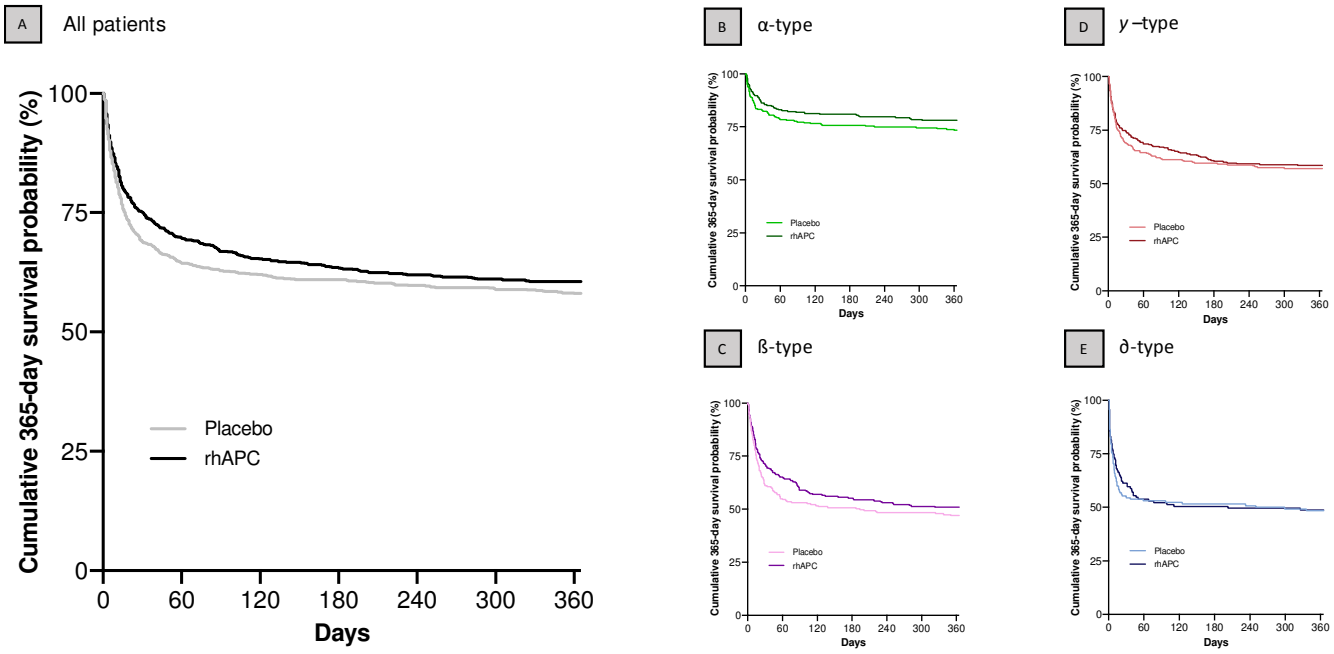
(A) PROWESS randomized trial 28-day survival, stratified by treatment arm for all patients (N=1,690), Intervention with rhAPC is dark solid line, and placebo is lighter line. (B) alpha type (N=496), (C) beta type (N=445), (D) gamma type (N=498), and (E) delta type (N=251). P value for test of interaction = 0.93.

Table. 28-day mortality by phenotype with absolute risk difference (95%CI).

Phenotype	All	rhAPC	Placebo	Absolute risk difference, %, (95%CI)*
α-type	77/496 (16)	33/241 (14)	44/255 (17)	-3.5 (-9.9, 2.8)
ß-type	149/445 (33)	67/232 (29)	82/213 (39)	-9.6 (-18.3, -0.9)
y-type	138/498 (28)	64/258 (25)	74/240 (31)	-6.0 (-13.9, 1.8)
∂-type	105/251 (42)	46/119 (39)	59/132 (45)	-6.0 (-18.2, 6.1)

*Absolute risk difference comparing rhAPC to placebo, where positive risk difference favors placebo and negative difference favors rhAPC

eFigure 26. Cumulative 365-day survival by treatment arm within phenotypes in the PROWESS trial (N=1,690).



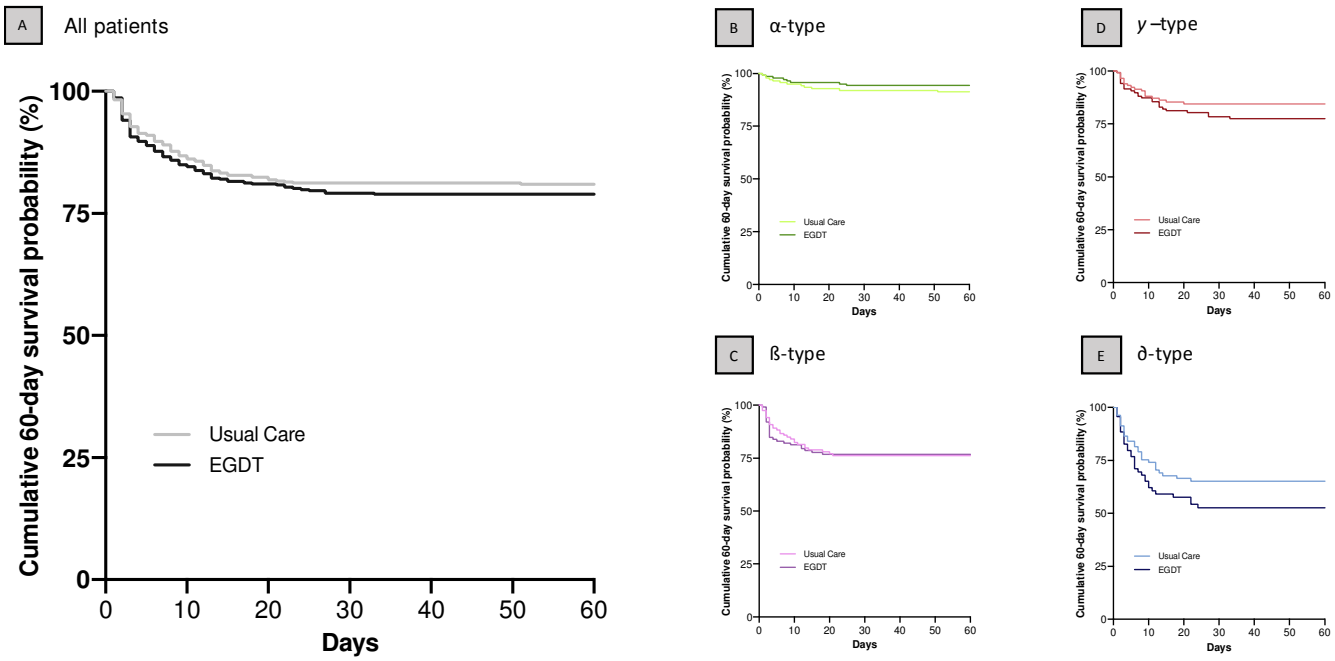
(A) PROWESS randomized trial 365-day survival, stratified by treatment arm for all patients (N=1,690), Intervention with rhAPC is dark solid line, and placebo is lighter line. (B) alpha type (N=496), (C) beta type (N=445), (D) gamma type (N=498), and (E) delta type (N=251), P value for test of interaction = 0.86

Table. 365-day mortality by phenotype with absolute risk difference (95%CI).

Phenotype	All	rhAPC	Placebo	Absolute risk difference, %, (95%CI)*
α-type	121/496 (24.4)	53/241 (22.0)	68/255 (26.7)	-4.7 (-12.2., 2.9)
ß-type	227/445 (51.0)	114/232 (49.1)	113/213 (53.1)	-3.9 (-13.2, 5.4)
y-type	210/498 (42.2)	107/258 (41.5)	103/240 (42.9)	-1.4 (-10.1, 7.2)
∂-type	129/251 (51.4)	61/119 (51.3)	68/132 (51.5)	-0.3 (-12.6, 12.1)

*Absolute risk difference comparing rhAPC to placebo, where positive risk difference favors placebo and negative difference favors rhAPC

eFigure 27. Cumulative 60-day inpatient survival by treatment arm within phenotypes in the ProCESS trial (N=895), comparing protocolized early goal directed therapy vs. usual care.



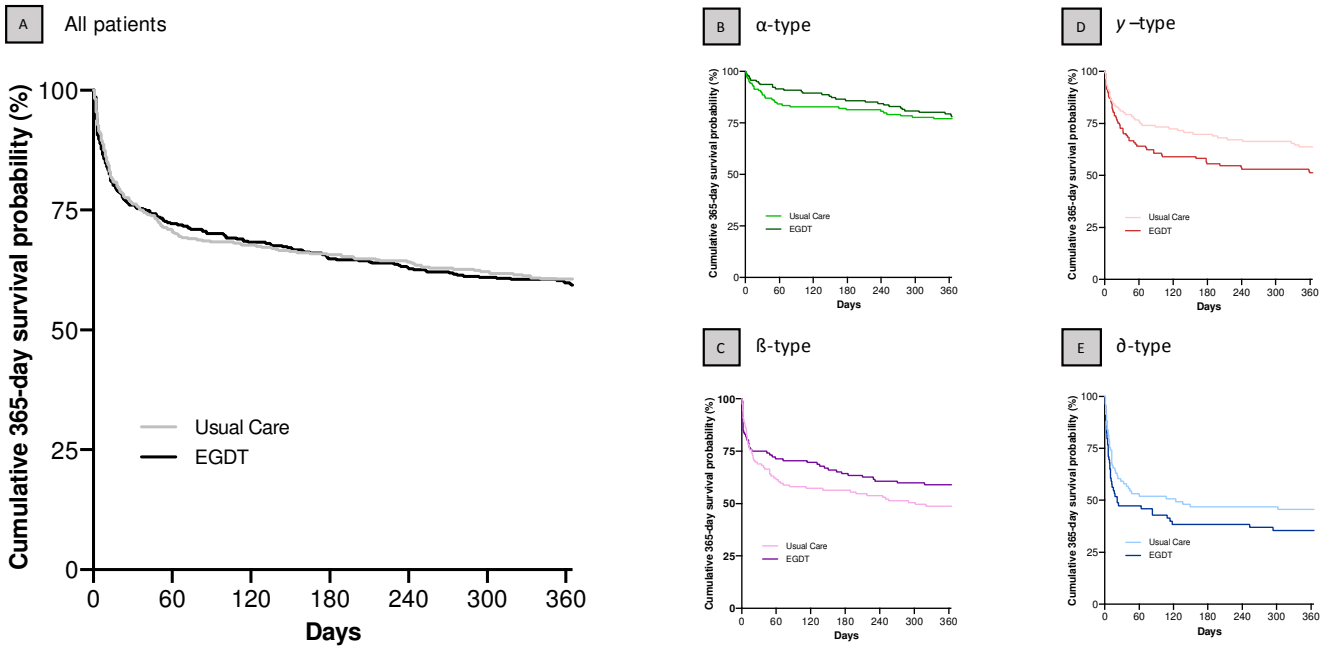
(A) Primary outcome of ProCESS trial, cumulative 60-day inpatient survival probability, stratified by treatment arm for all patients (N=895), (B) patients in alpha type (N=280), (C) patients in beta type (N=232), (D) gamma type (N=233), (E) delta type (N=150). Protocolized early, goal directed therapy is dark solid line, and placebo is lighter line. P value for test of interaction = 0.29.

Table. 60-day inpatient mortality by phenotype with absolute risk difference (95%CI).

Phenotype	All	Protocolized, early goal-directed therapy	Usual care	Absolute risk difference, %, (95%CI)*
α-type	20/280 (7.1)	8/141 (5.7)	12/139 (8.6)	-1.9 (-9.4, 4.5)
ß-type	54/232 (23.3)	26/112 (23.2)	28/120 (23.3)	-0.1 (-11.0, 10.7)
y-type	44/233 (18.9)	26/117 (22.2)	18/116 (15.5)	6.7 (-3.3, 1.7)
∂-type	60/150 (40.0)	32/69 (46.4)	28/81 (34.6)	11.8 (-3.9, 27.5)

*Absolute risk difference comparing protocolized, early goal-directed therapy to usual care, where positive risk difference favors usual care and negative difference favors protocolized, early goal-directed therapy

eFigure 28. Cumulative 365-day survival by treatment arm within phenotypes in the ProCESS trial (N=895), comparing protocolized early goal directed therapy vs. usual care



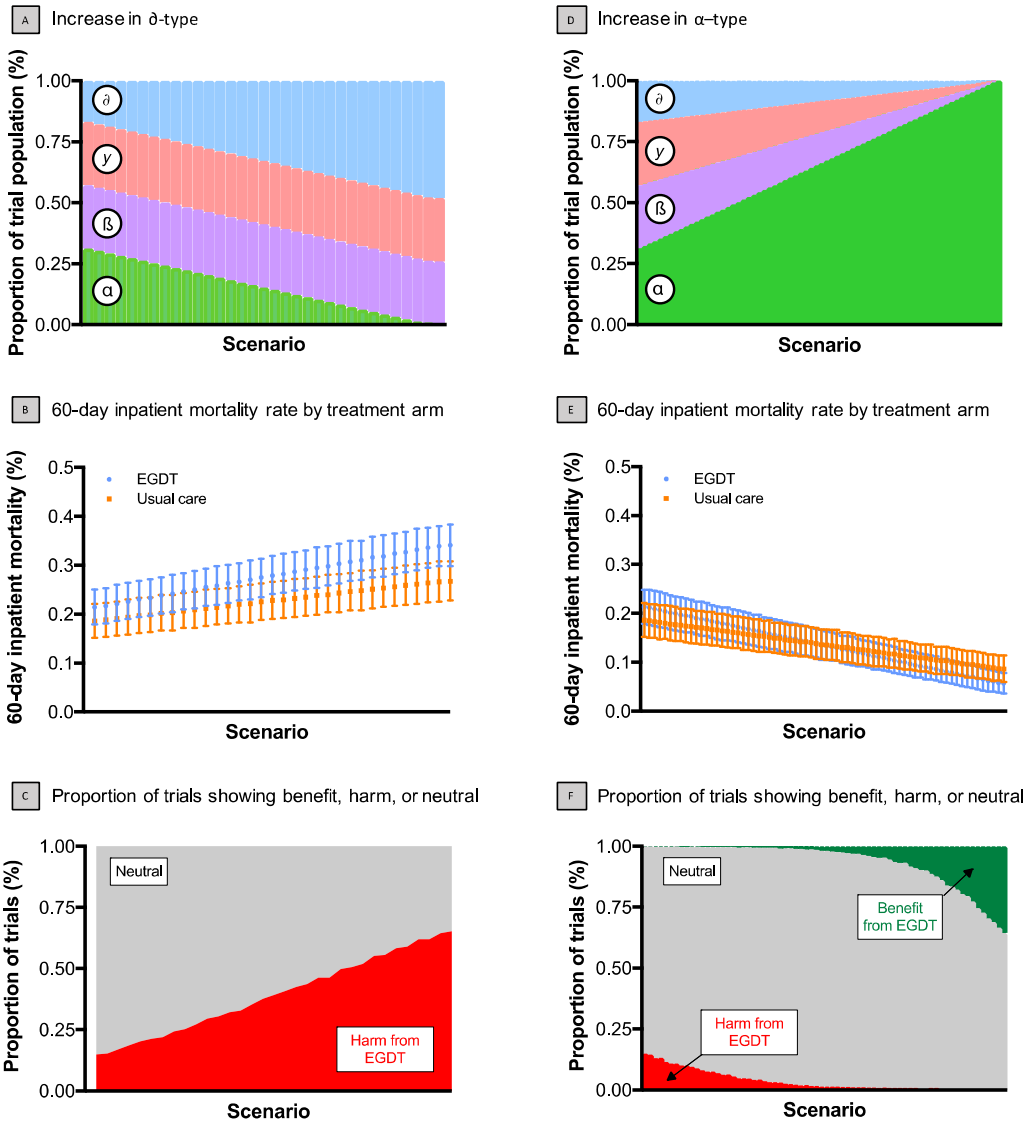
(A) Primary outcome of ProCESS trial, cumulative 365-day survival probability, stratified by treatment arm for all patients (N=895), (B) patients in alpha type (N=280), (C) patients in beta type (N=232), (D) gamma type (N=233), (E) delta type (N=150). Protocolized early, goal directed therapy is dark solid line, and placebo is lighter line. P value for interaction = 0.05.

Table. 365-day mortality by phenotype with absolute risk difference (95%CI).

Phenotype	All	Protocolized, early goal-directed therapy	Usual care	Absolute risk difference, %, (95%CI)*
α-type	63/280 (22.5)	31/141 (22.0)	32/139 (23.0)	-1.0 (-10.8, 8.7)
ß-type	107/232 (46.1)	46/112 (41.1)	61/120 (50.8)	-9.8 (-22.5, 3.0)
y-type	99/233 (42.5)	57/117 (48.7)	42/116 (36.2)	12.5 (-0.1, 25.1)
∂-type	88/150 (58.7)	44/69 (63.8)	44/81 (54.3)	9.4 (-6.2, 25.1)

*Absolute risk difference comparing protocolized, early goal-directed therapy to usual care, where positive risk difference favors usual care and negative difference favors protocolized, early goal-directed therapy

eFigure 29. Simulation of clinical phenotype enrichment in the ProCESS randomized trial population (N=895) for early, goal-directed therapy (EGDT) vs. usual care

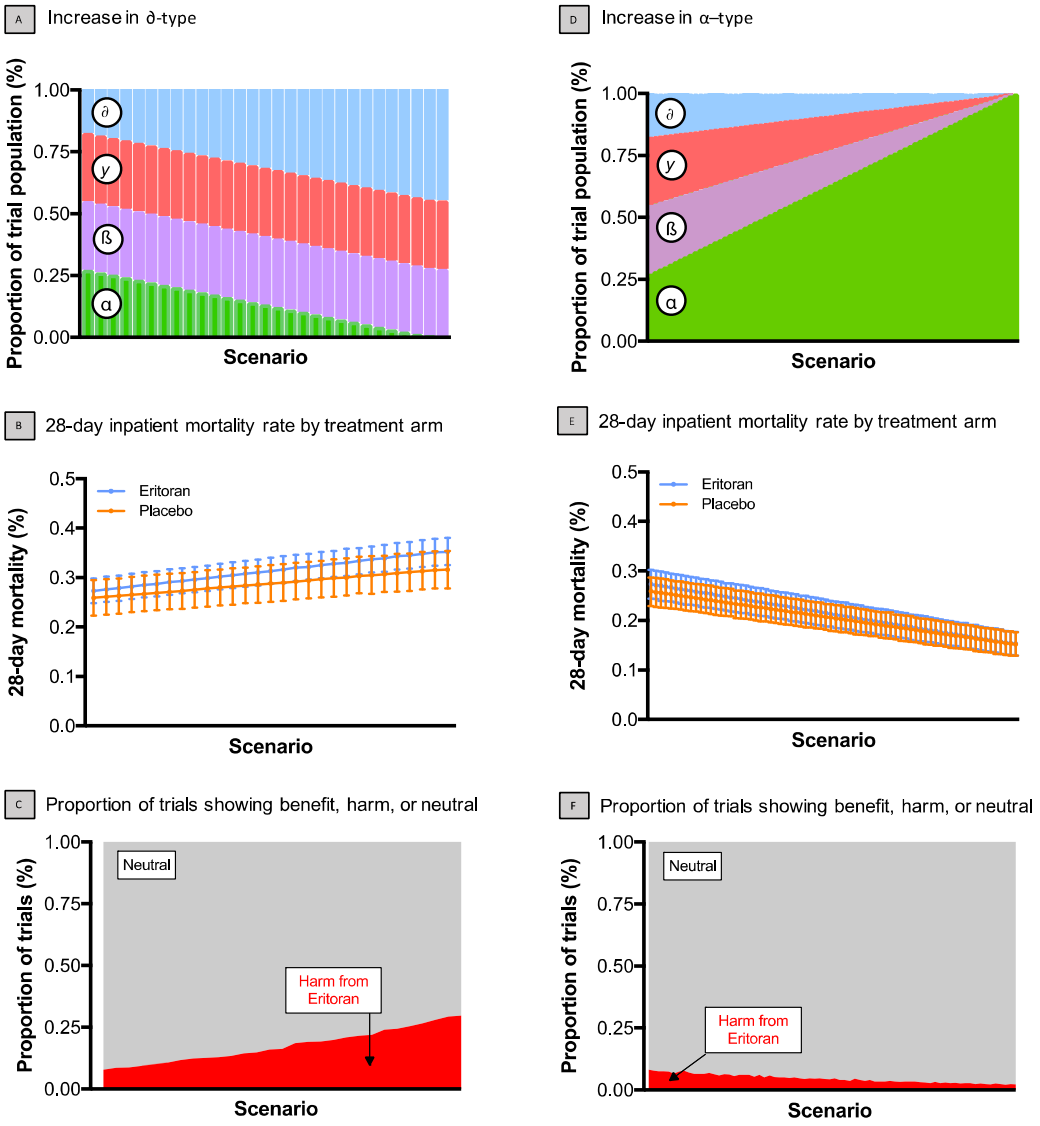


(A) X-axis shows trial scenarios (Monte Carlo simulation with replacement, 10,000 iterations each) where the proportion of ∂–type (light blue) is increased while the proportion of α–type is decreased (light green). Proportions of ß–type and *y*–type were unchanged. (B) 60-day inpatient mortality rate, comparing EGDT (blue) vs. usual care (orange). Errors bars are 95% CI. (C) Proportions of trial in each scenario which found no difference (gray, chi square $p>0.05$) or significant result ($p<0.05$) for harm for EGDT (red) or benefit for EGDT (green).

(D-F) Similar graphs as above except that α–type is enriched (light green) with corresponding decrease in other groups.

Interpretive example: Plausible increases in the proportion of ∂–type in the ProCESS trial would have led to unstable trial results. Specifically, the increase in ∂–type from approximately 14 to 45% would result in a consistent finding of harm for EGDT in the majority of trials.

eFigure 30. Simulation of phenotype enrichment in the ACCESS randomized trial (N=1,706)

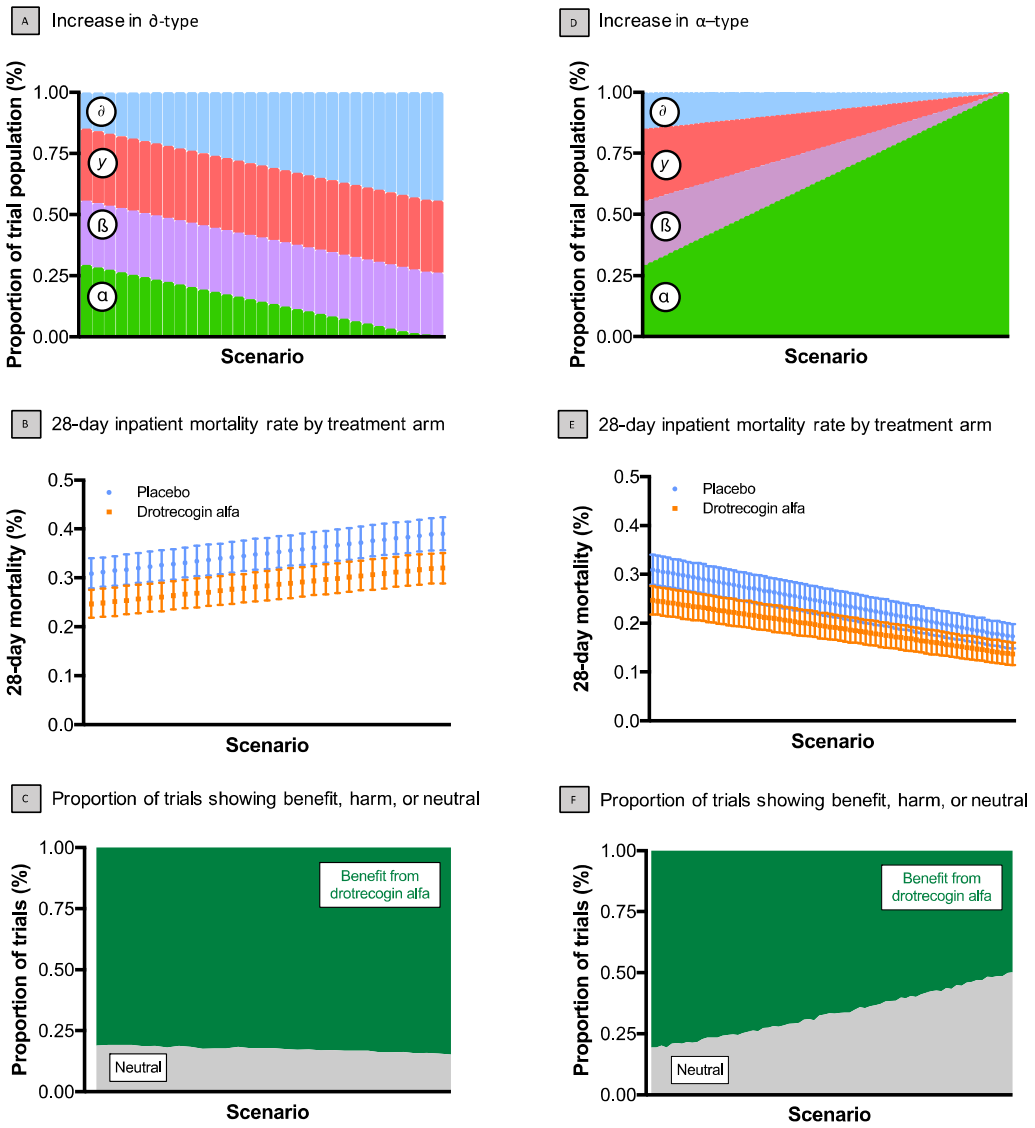


(A) X-axis shows trial scenarios (Monte Carlo simulation with replacement, 10,000 iterations each) where the proportion of ∂–type light blue) is increased while the proportion of α–type is decreased (light green). Proportions of ß–type and *y*–type were unchanged. (B) 28-day inpatient mortality rate across scenarios, comparing Eritoran (blue) versus placebo (orange). (C) Proportions of trial in each scenario which found no difference (gray, chi square p>0.05) or significant result for harm for Eritoran (red) or benefit for Eritoran (green).

(D-F) Similar graphs as above except that α–type is enriched (light green) with corresponding decrease in others.

Interpretive example: Plausible increases in the proportion of ∂–type in the ACCESS trial would have led to unstable trial results. Specifically, the increase in ∂–type from approximately 17 to 44% would result in a consistent finding of harm for Eritoran in more than one third of trials.

eFigure 31. Simulation of phenotype enrichment in the PROWESS randomized trial (N=1,690)



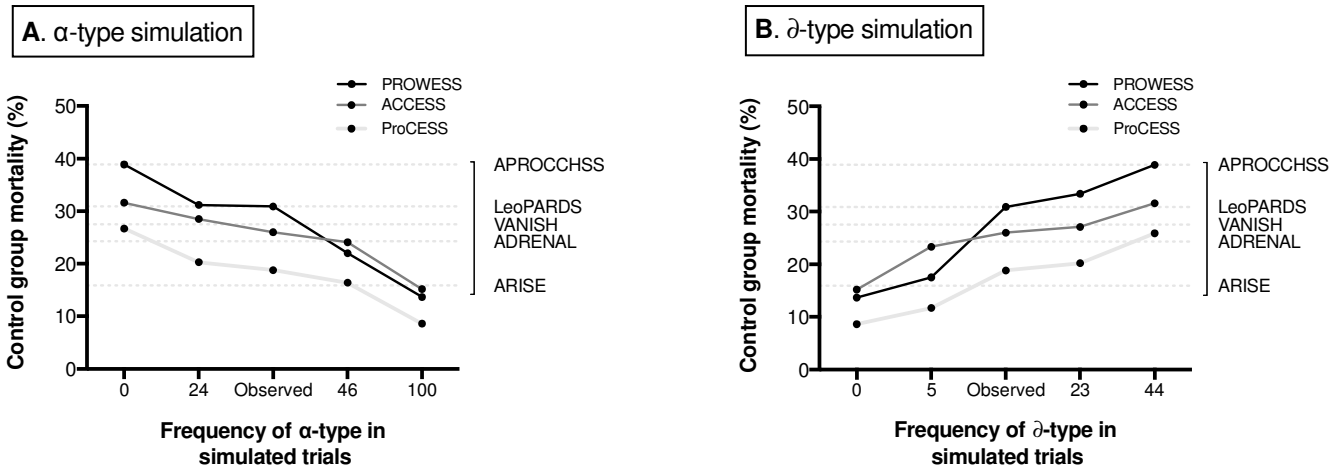
(A) X-axis shows trial scenarios (Monte Carlo simulation with replacement, 10,000 iterations each) where the proportion of ∂–type (light blue) is increased while the proportion of α–type is decreased (light green). Proportions of ß–type and *y*–type were unchanged. (B) 28-day inpatient mortality rate across scenarios, comparing Drotrecogin alfa (orange) versus placebo (blue). (C) Proportions of trial in each scenario which found no difference (grey, chi square p>0.05) or significant result for benefit for Drotrecogin alfa (green).

Interpretive example: Plausible increases in the proportion of ∂–type in the PROWESS trial would not have led to unstable trial results.

(D-F) Similar graphs as above except that α–type is enriched (light green) with corresponding decrease in others.

Interpretive example: Plausible increases in the proportion of α–type in the PROWESS trial from 31 to 100% would lead to more than 50% of trials finding no benefit.

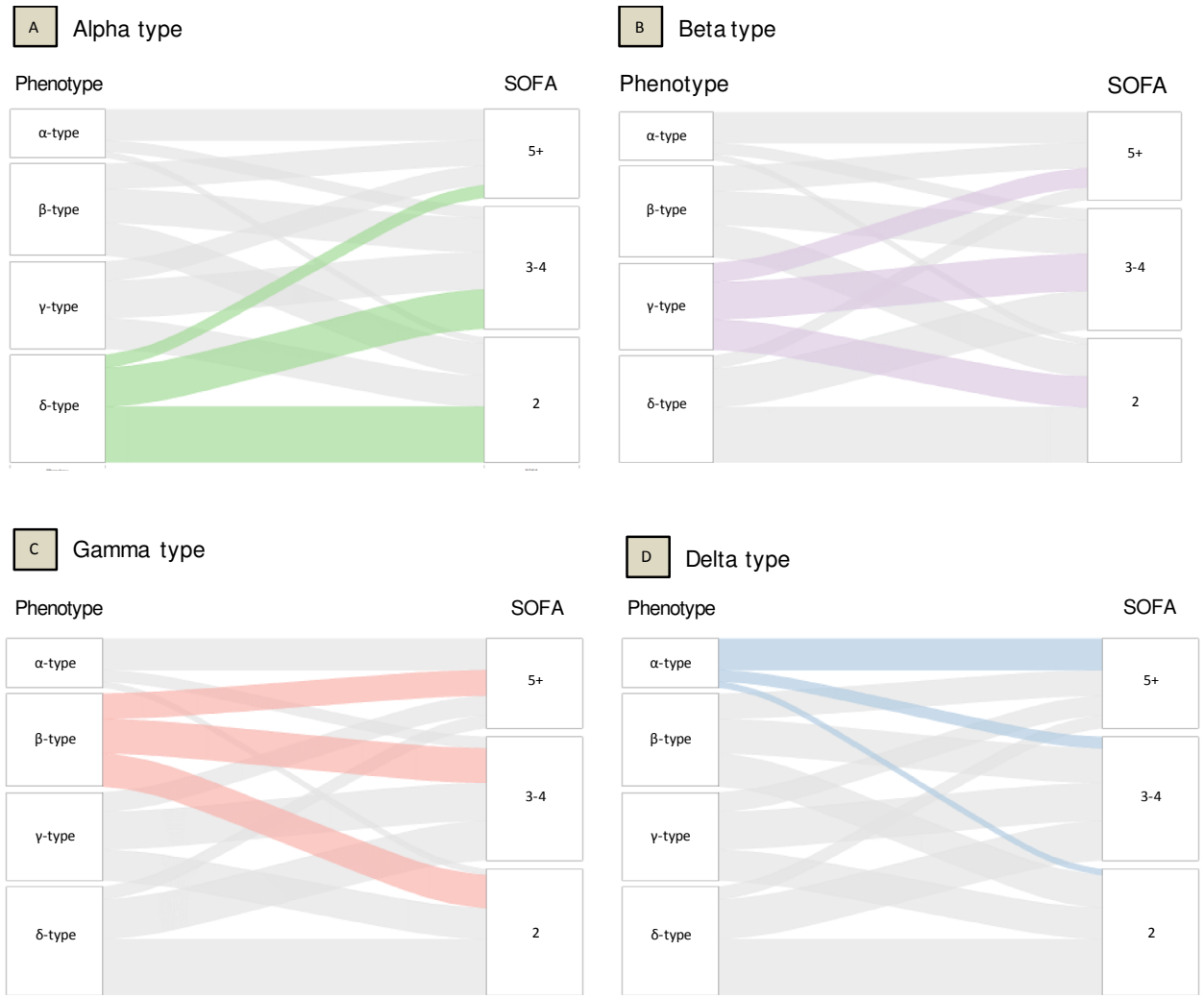
eFigure 32. Control group mortality of simulated trials compared to recent contemporary RCTs



(A) Control group mortality (y-axis) in the PROWESS (black line), ACCESS trial (grey line) and ProCESS trial (light grey line) across range of simulated α–type frequencies. Shaded region (blue) represents the range of observed placebo or usual care mortality rates in the APROCCHSS, LeoPARDS, VANISH, ADRENAL, and ARISE trials.[15-19] (B) Similar graph showing control group mortality for the trials across a range of simulated ∂–type frequencies.

Interpretive example: Simulation of changes in α–type and ∂–type frequencies in 3 large RCTs resulted in control grop mortality rates that were similar to those reported in many contemporary RCTs.[15-19]

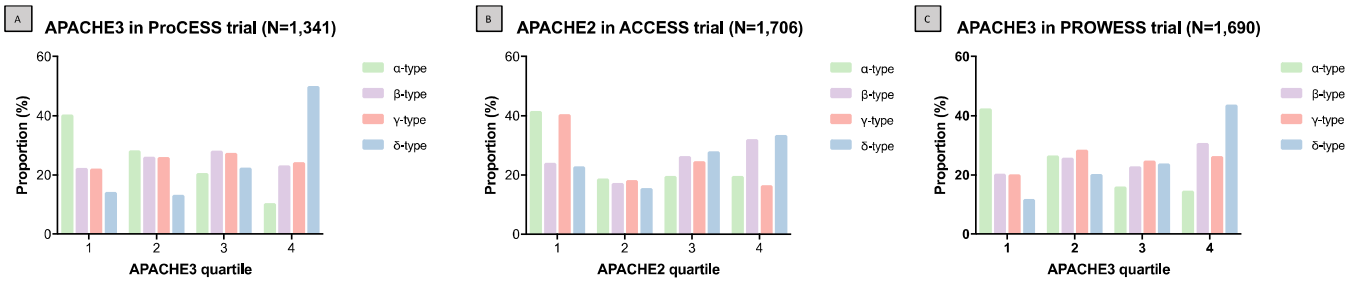
eFigure 33. Alluvial plot showing distribution of phenotypes across baseline SOFA score in SENECA derivation data (N=20,189).



(A) Distribution of α–type members (light green left column, N=6,625) across categories of SOFA score in the first 6 hours (right column), (B) ß–type distribution (light purple, N=5,512), (C) *y*–type distribution (light red, N=5,385), (D) *∂*–type distribution (light blue, N=2,667)

Interpretive example: In these alluvial plots, Phenotype members are shown by color on the left column and distribute across SOFA score in the right column. In general, ß–type and *y*–type distributed evenly across high and low SOFA scores, while α–type tended towards lower SOFA scores, and *∂*–type towards higher SOFA scores.

eFigure 34. Distribution of phenotypes across APACHE quartiles in 3 randomized trials



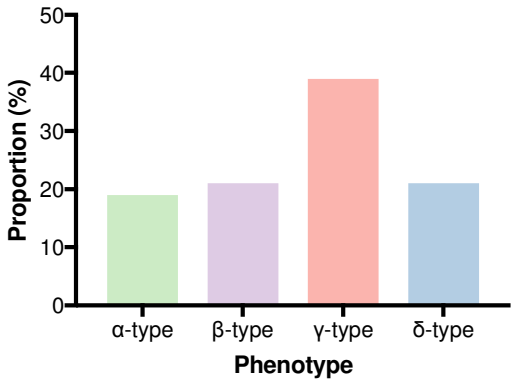
(A) Distribution of phenotypes across APACHE3 quartiles in the ProCESS trial (N=1,341), (B) APACHE 2 quartiles in ACCESS trial (N=1,706), and (C) APACHE3 quartiles in the PROWESS trial (N=1,690). α–type is light green, ß–type is light purple, *y*–type distribution is light red, and ∂–distribution is light blue.

eFigure 35. Alluvial plot showing distribution of phenotypes across site of infection in the ACCESS trial (N=1,706).

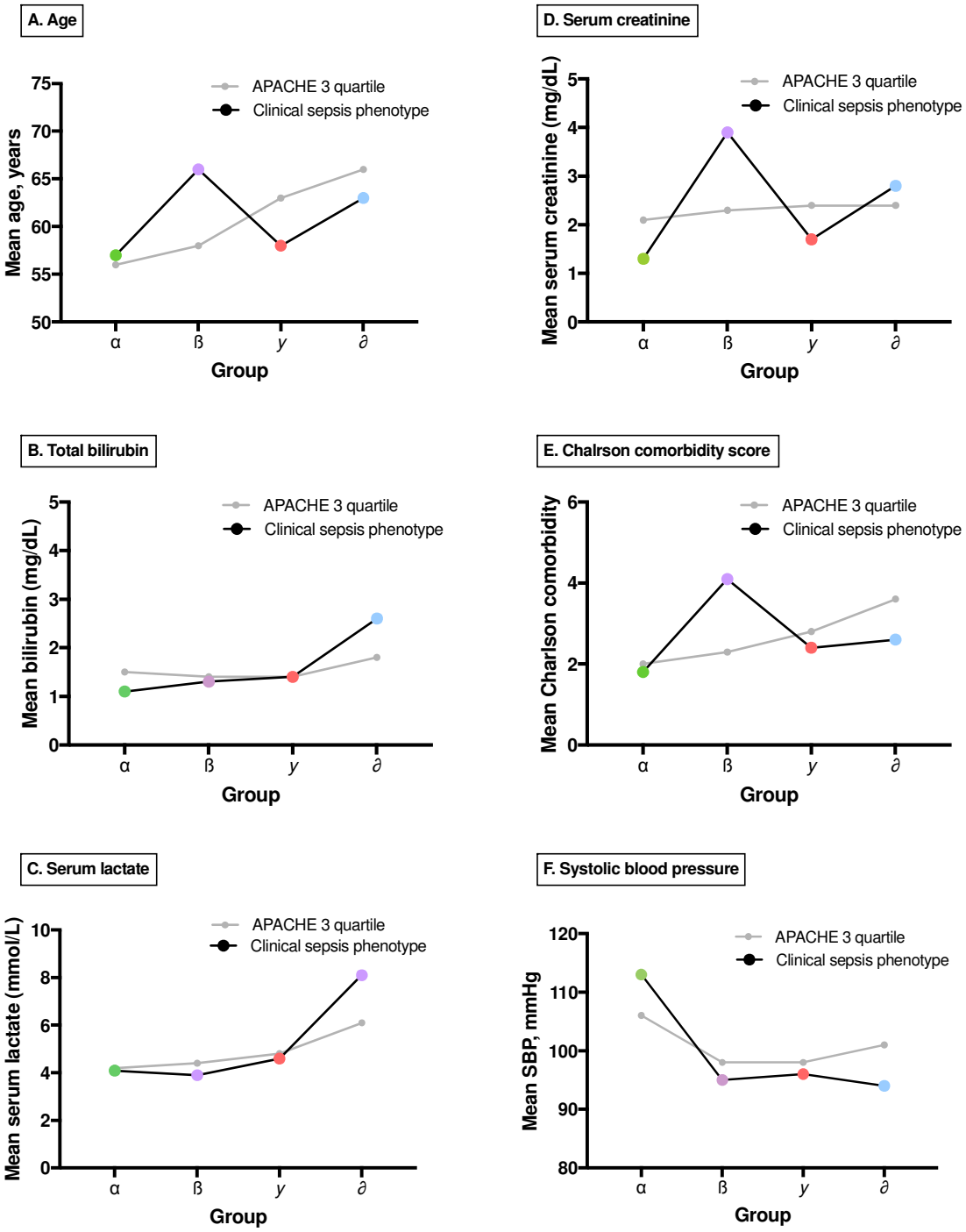
(A) Distribution of α–type members (light green, left column) across categories of site of infection (right column), (B) ß–type distribution (light purple), (C) *y*–type distribution (light red), (D) ∂–distribution (light blue).

Interpretive example: In these alluvial plots, phenotypes are shown by color on the left column and distribute across site of infection in the right column. In general, ß–type, *y*–type, and ∂–type distributed evenly across all site of infection while α–type tended towards a lung site.

eFigure 36. Distribution of phenotypes among SENECA derivation cohort with sepsis due to bacteremia (N=1,714).

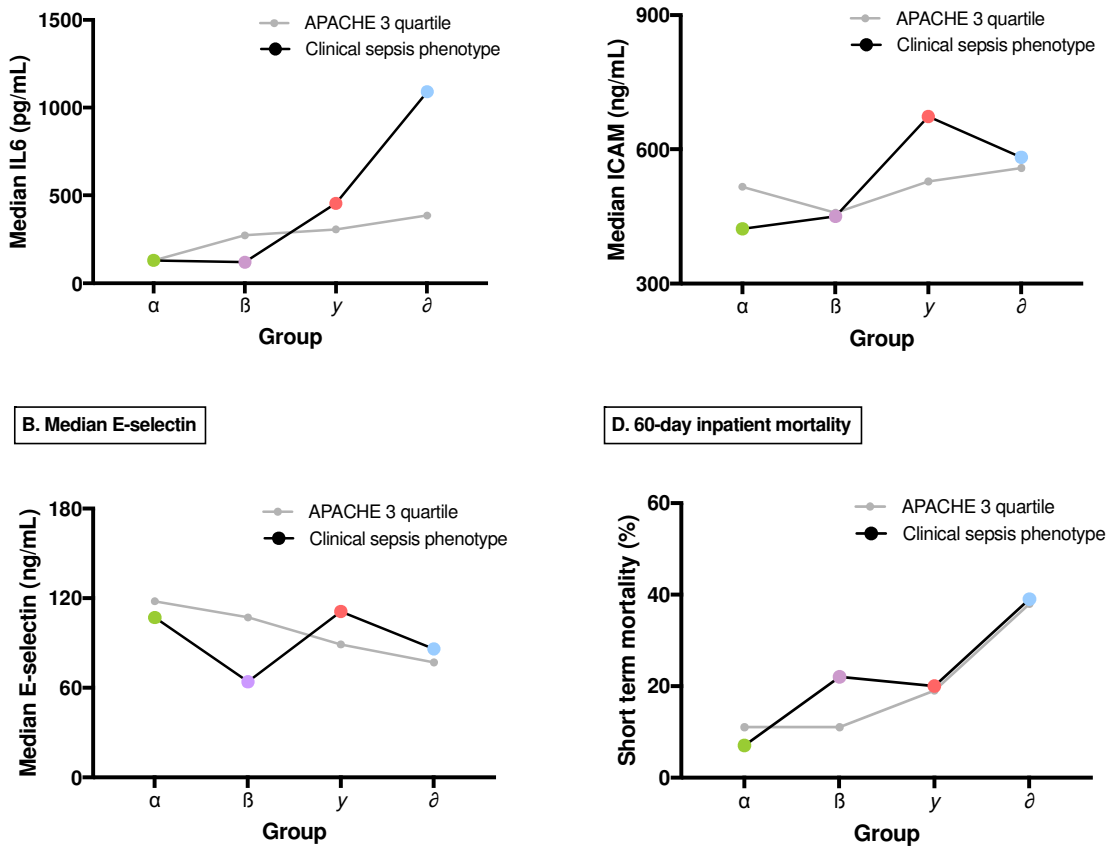


eFigure 37. Comparison of mean values of variables between phenotypes and APACHE 3 quartiles in the ProCESS randomized trial (N=1,341).



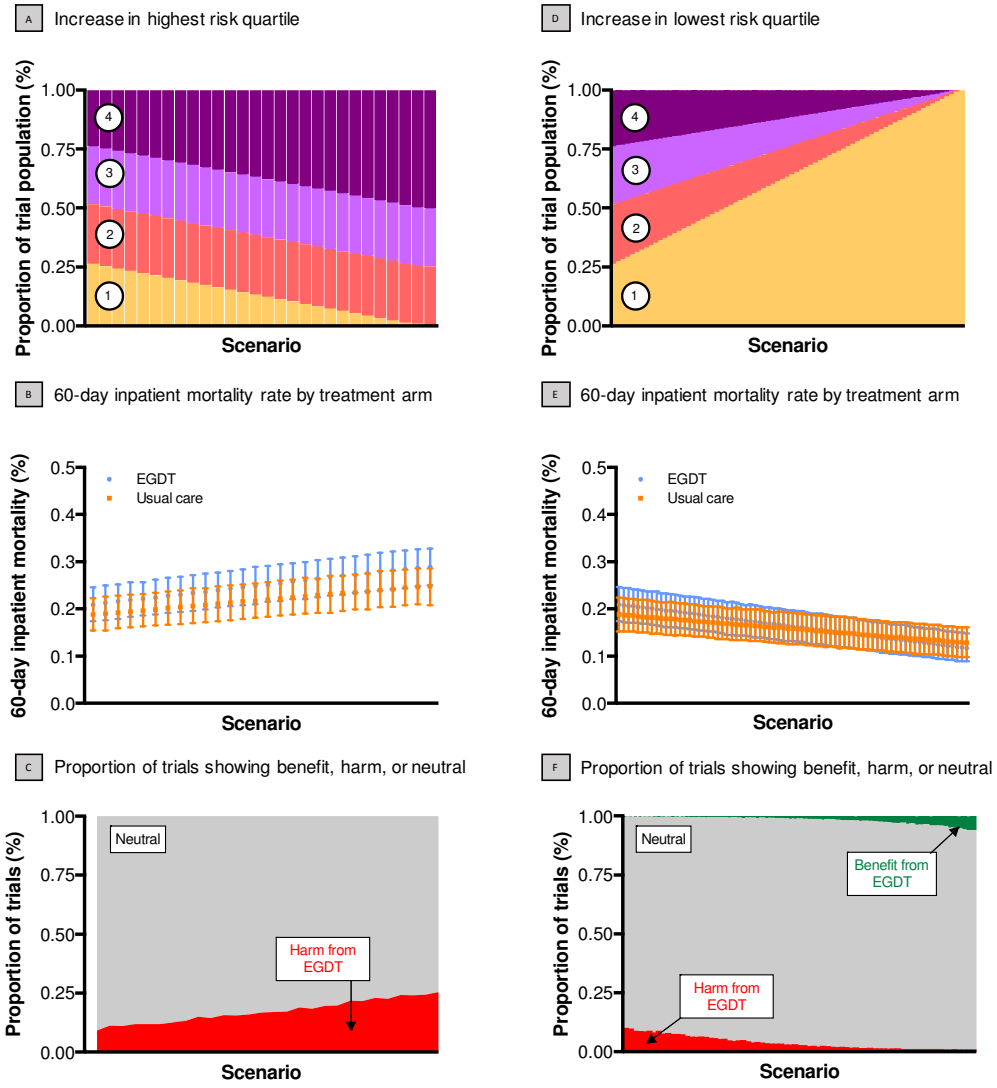
Interpretive example: Across many important clinical variables, there are differences between sepsis clinical phenotypes derived from unsupervised modeling that are not explained by differences in APACHE 3 quartiles.

eFigure 38. Comparison of candidate biomarkers of the host immune response and short term mortality between phenotypes and APACHE 3 quartiles in the ProCESS randomized trial (N=1,341).



Interpretive example: There are differences in biomarkers of the host immune response that relate to inflammation and endothelial function between sepsis clinical phenotypes derived from unsupervised modeling that are not explained by differences in APACHE 3 quartiles (A-C). However, short term mortality in the ProCESS RCT was similar comparing phenotypes to APACHE 3 quartiles (D).

eFigure 39. Sensitivity analysis of enrichment by APACHE 3 risk quartile in the ProCESS randomized trial (N=895)



(A) X-axis shows trial scenarios (Monte Carlo simulation with replacement, 10,000 iterations each) where the proportion of highest risk quartile (plum) is increased while the proportion of lowest risk quartile is decreased (light orange). Proportions of middle risk quartiles (2,3) were unchanged. (B) 60-day inpatient mortality rate across scenarios, comparing protocol-based EGDT (blue) versus usual care (orange), error bars are 95% CI (C) Proportions of trial in each scenario which found no difference (gray, chi square $p>0.05$) or significant result for harm for protocol based EGDT (red) or benefit (green).

Interpretive example: Plausible increases in the proportion of highest risk quartile in the ProCESS trial would have led to fewer changes in trial results than enrichment by clinical sepsis phenotype.

(D-F) Similar graphs as above except that low risk quartile is enriched (light orange) with corresponding decrease in other risk quartiles

eTable 1. Availability of clinical variables for phenotyping by dataset

Variable	SENECA derivation	SENECA validation	GenIMS	ACCESS	PROWESS	ProCESS
Age	X	X	X	X	X	X
Albumin	X	X	X	X	X	X
ALT	X	X		X	X	
AST	X	X		X	X	
Bands	X	X		X	X	X
Bicarbonate	X	X		X		
Bilirubin	X	X	X	X	X	X
BUN	X	X	X	X	X	X
Chloride	X	X		X	X	X
C-Reactive Protein	X	X				
Creatinine	X	X	X	X	X	X
Comorbidity score	X	X	X	X	X	X
Erythrocyte sedimentation rate	X	X				
Glasgow coma scale score	X	X	X		X	X
Gender	X	X	X	X	X	X
Glucose	X	X	X	X	X	X
Heart Rate	X	X	X	X	X	X
Hemoglobin	X	X	X	X	X	X
INR	X	X	X			
Lactate	X	X	X			X
Oxygen Saturation	X	X	X		X	X
PaO_2	X	X	X		X	X
Platelets	X	X	X	X	X	X
Respiratory rate	X	X	X	X	X	X
Sodium	X	X	X	X	X	X
Systolic blood pressure	X	X	X	X	X	X
Temperature	X	X	X	X	X	X
Troponin	X	X				
White blood cell count	X	X	X		X	X

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen

eTable 2. Availability of 27 biomarker measurements by dataset at baseline

Biomarkers*	GenIMS	ACCESS	PROWESS	ProCESS
Antithrombin III	X		X	
C-Reactive Protein				X
COL-4				X
D-Dimer	X		X	X
E-Selectin				X
Factor V			X	
Factor IX	X			
ICAM				X
IGFBP-7				X
Interleukin-1b		X	X	
Interleukin-6	X	X	X	X
Interleukin-8		X	X	
Interleukin-10	X	X	X	X
Interleukin-12		X		
KIM-1				X
PAI-1	X		X	X
Plasminogen activity			X	
Procalcitonin	X	X		
Protein C Activity			X	
Protein S Activity			X	
Prothrombin			X	X
Prothrombin Fragment 1-2			X	
P-Selectin				X
TAT Complex	X		X	X
TIMP-2				X
TNF	X	X	X	X
VCAM				X

Abbreviations: ATP: adenosine triphosphate; COL: collage; ICAM: intracellular adhesion molecule; IGFBP: insulin-like growth factor-binding protein; KIM: kidney injury molecule; PAI: plasminogen activator inhibitor; TAT: Thrombin-Antithrombin; TIMP: tissue inhibitor of metalloproteinases TNF: tumor necrosis factor; VCAM: vascular adhesion molecule

eTable 3. Range of values, direction of abnormal values for models, and transformation of non-normal variables in SENECA derivation cohort (N=20,189)

Variable	Range	Directionality of abnormal value in chord plots	Transformation for consensus k models
Age	18 - 90	Maximum	-
Albumin	0.6 – 6.0	Maximum	-
ALT	5 – 15,000	Maximum	Ln
AST	3 – 15,000	Maximum	Ln
Bands	0.9 - 90	Maximum	Ln
Bicarbonate	3 - 62	Minimum	-
Bilirubin	0.03 - 44	Maximum	Ln
BUN	1 - 200	Maximum	Ln
Chloride	36 - 150	Maximum	-
C-Reactive Protein	0.02 - 280	Maximum	Ln
Creatinine	0.1 - 20	Maximum	Ln
Elixhauser	0 - 30	Maximum	-
ESR	1 - 140	Maximum	Ln
GCS	3 - 15	Minimum	-
Gender	Male / female	-	-
Glucose	25 - 1,400	Maximum	Ln
Heart Rate	18 - 260	Maximum	-
Hemoglobin	3.0 - 23	Minimum	-
INR	0.8 – 18.0	Maximum	Ln
Lactate	0.3 - 28	Maximum	Ln
Oxygen Saturation	40 - 100%	Minimum	Inverse Ln
PaO_2	2 - 600	Minimum	-
Platelets	2 - 1900	Minimum	Ln
Respiratory rate	8 – 60	Maximum	-
Sodium	80 – 190	Maximum	-
Systolic blood pressure	0 – 230	Minimum	Ln
Temperature	30.0 – 42.0	Maximum	-
Troponin	0 – 48	Maximum	Ln
White blood cell count	0.1 – 240	Maximum	Ln

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; GCS: Glasgow coma scale; INR: international normalized ratio; PaO_2: partial pressure of oxygen

eTable 4. Missing data (no., %) across cohorts and trials for phenotyping variables at presentation

Variable	SENECA derivation	SENECA validation	GenIMS	ACCESS	PROWESS	ProCESS
No. of patients	20,189	43,086	583	1,706	1,690	1,341
Age	0 (0%)	0 (0%)	96 (16%)	0 (0%)	0 (0%)	26 (2%)
Albumin	12,139 (60%)	30,468 (71%)	361 (62%)	55 (3%)	84 (5%)	331 (25%)
ALT	11,707 (58%)	30,410 (71%)	-	78 (5%)	83 (5%)	-
AST	11,714 (58%)	30,397 (71%)	-	86 (5%)	83 (5%)	-
Bands	17,303 (86%)	38,756 (92%)	-	1,293 (76%)	1,238 (73%)	656 (49%)
Bicarbonate	6,586 (33%)	22,695 (53%)	-	78 (5%)	-	-
Bilirubin	11,763 (58%)	30,443 (71%)	345 (59%)	75 (4%)	710 (42%)	253 (19%)
BUN	6,962 (34%)	22,811 (53%)	26 (4%)	1,214 (71%)	43 (3%)	31 (2%)
Chloride	6,428 (32%)	21,937 (51%)	-	56 (3%)	42 (2%)	22 (2%)
C-Reactive Protein	19,769 (98%)	42,078 (98%)	-	-	-	-
Creatinine	6,647 (33%)	22,900 (53%)	27 (5%)	63 (4%)	664 (39%)	23 (3%)
Elixhauser/Charlson	0 (0%)	138 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 0%)
ESR	19,596 (97%)	41,911 (97%)	-	-	-	-
GCS	14,271 (71%)	34,869 (81%)	0 (0%)	-	181 (11%)	227 (17%)
Gender	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 0%)
Glucose	6,102 (30%)	17,816 (41%)	24 (4%)	61 (4%)	103 (6%)	25 2%)
Heart Rate	260 (1%)	1,275 (3%)	36 (6%)	36 (2%)	0 (0%)	1 (0%)
Hemoglobin	6,258 (31%)	21,405 (50%)	18 (3%)	229 (13%)	1,033 (61%)	20 (1%)
INR	11,824 (59%)	30,799 (71%)	330 (57%)	-	-	-
Lactate	16,180 (80%)	33,886 (79%)	569 (98%)	-	-	42 (3%)
Oxygen Saturation	458 (2%)	1,353 (3%)	20 (3%)	-	204 (12%)	8 (1%)
PaO_2	16,161 (80%)	37,701 (88%)	380 (65%)	-	31 (2%)	613 (46%)
Platelets	7,024 (35%)	23,429 (54%)	26 (4%)	363 (21%)	1 (0.1%)	32 (2%)
Respiratory rate	448 (2%)	2,024 (5%)	47 (8%)	72 (4%)	5 (0.3%)	2 (0%)
Sodium	6,074 (30%)	21,413 (50%)	20 (3%)	54 (3%)	0 (0%)	18 (1%)
Systolic blood pressure	262 (1%)	1,295 (3%)	1 (0.2%)	37 (2%)	3 (0.2%)	1 (0%)
Temperature	1,357 (7%)	5,072 (12%)	82 (14%)	206 (12%)	0 (0%)	13 (1%)
Troponin	15,757 (78%)	32,526 (75%)	-	-	-	-
White blood cell count	7,102 (35%)	23,561 (55%)	17 (3%)	-	0 (0%)	24 (2%)

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; GCS: Glasgow coma scale; INR: international normalized ratio; PaO_2: partial pressure of oxygen

eTable 5. Clinical characteristics of cohorts

Variable [a]	SENECA derivation	SENECA validation	GenIMS cohort
No.	20,189	43,086	583
Demographics and Burden of Organ Dysfunction			
Age, years, mean (SD)	64 (17)	67 (17)	67 (17)
Male gender, no. (%)	10,022 (50%)	21,993 (51%)	329 (56%)
Race, no. (%) [b]			
White	15,640 (77%)	36,820 (85%)	493 (85%)
Black	2,428 (12%)	5,008 (12%)	74 (13%)
Other	2,121 (11%)	1,258 (3%)	16 (3%)
Elixhauser/Charlson comorbidity, mean (SD) [c]	1.8 (1.2)	1.2 (1.2)	2.3 (2.5)
Surgery, no. (%) [d]	2,727 (14%)	5,122 (12%)	-
Max SIRS Criteria within 24 hours, mean (SD)	1.8 (1.2)	1.4 (1.1)	-
Max SOFA Score within 24 hours, mean (SD) [f]	3.9 (2.4)	3.6 (2.0)	-
Inflammation			
Bands, %, median [IQR]	7 [3 - 15]	5 [2 - 10]	-
C-reactive protein, mg/L, median [IQR]	6 [2 - 16]	7 [2 - 16]	-
ESR, mm/hr, median [IQR]	48 [25 - 88]	50 [27 - 84]	-
Temperature, °C, mean (SD)	37.0 (1.0)	37.0 (0.9)	37.9 (1.1)
White blood cell count, $x10^9$/L, median [IQR]	10 [7 - 14]	10 [7 - 13]	13 [9 - 17]
Pulmonary			
Oxygen Saturation, %, median [IQR]	94 [91 - 97]	94 [92 - 96]	90 [86 - 94]
PaO_2, mmHg, mean (SD)	123 (89)	116 (76)	85 (64)
Respiratory rate, breaths per minute, mean	22 (6)	22 (7)	28 (8)
Cardiovascular/Hemodynamic			
Bicarbonate, mEq/L, mean (SD)	25 (5)	25 (5)	-
Heart rate, beats per minute, mean (SD)	97 (22)	96 (21)	109 (23)
Serum lactate, mmol/L, median [IQR]	1.5 [1.0 - 2.4]	1.5 [1.0 - 2.3]	2.1 [1.6 - 4.1]
Systolic blood pressure, mmHg, median [IQR]	110 [93 - 128]	110 [95 - 127]	109 [93 - 125]
Troponin, ng/mL, median [IQR]	0.1 [0.0 - 0.1]	0.0 [0.0 - 0.1]	-
Renal			
BUN, mg/dL, median [IQR]	24 [15 - 38]	23 [15 - 38]	23 [16 - 34]
Creatinine, mg/dL, median [IQR]	1.4 [1 - 2.2]	1.3 [0.9 - 2.1]	1.2 [0.9 - 1.7]

Hepatic				
	ALT, U/L, median [IQR]	30 [20 - 48]	25 [17 - 40]	-
	AST, U/L, median [IQR]	30 [20 - 53]	26 [18 - 45]	-
	Bilirubin, mg/dL, median [IQR]	0.8 [0.5 - 1.3]	0.7 [0.4 - 1.1]	0.6 [0.4 - 0.9]
Hematologic				
	Hemoglobin, g/dL, mean (SD)	12 (2)	12 (2)	13 (2)
	INR, mean (SD)	1.3 [1.1 - 1.6]	1.2 [1.1 - 1.7]	1.2 [1 - 1.6]
	Platelets, $x10^9$/L, mean (SD)	188 [130 - 256]	192 [134 - 260]	249 [193 - 323]
Neurological				
	Glasgow Coma Scale score, mean (SD)	11.4 (4.0)	11.7 (3.9)	14.3 (2.0)
Other				
	Albumin, g/dL, mean (SD)	2.9 (0.7)	3.0 (0.6)	3.3 (0.6)
	Chloride, mEq/L, mean (SD)	103 (7)	103 (7)	-
	Glucose, mg/dL, median [IQR]	130 [105 - 179]	135 [107 - 188]	126 [105 - 160]
	Sodium, mEq/L, mean (SD)	137 (5)	137 (5)	137 (5)
Outcomes				
	Days of Mechanical Ventilation, median [IQR]	5 [2 - 10]	4 [2 - 8]	5 [2 - 9]
	Days of Vasopressors, median [IQR] [d]	3 [2 - 5]	3 [2 - 5]	2 [1 - 4]
	Admitted to intensive care, no. (%) [d]	9,063 (45%)	14,337 (33%)	224 (38%)
	Inpatient Mortality, no. (%)	2,082 (10%)	2,666 (6%)	83 (14%)
	Inpatient mortality among those requiring intensive care, no. (%)	1,916 (21%)	2,286 (16%)	52 (23%)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Chinese, Filipino, Hawaiian, American Indian/Alaskan, Asian, Hawaiian/Other Pacific Islander, Middle Eastern, Native American, Not specified, or Pacific Islander in SENECA cohorts. Other race corresponds to Asian, Oriental, Pacific Islander, Hispanic origin, Other, or Unknown from case report form in GenIMS

[c] Elixhauser, used in SENECA cohorts, is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 31. Charlson, used in GenIMS cohort, is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24.

[d] At any time during hospitalization

[e] SIRS criteria are a scoring system that measures the inflammatory response, ranging from 0 to 4 points

[f] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation; SIRS: systemic inflammatory response syndrome criteria; SOFA: sequential organ failure assessment score

eTable 6. Characteristics of SENECA derivation and validation encounters with regard to suspected infection, blood cultures, and screening tests for organ dysfunction.

Variable		SENECA derivation (2010 - 2012)	SENECA validation (2013 - 2014)
No. of total encounters		1,309,025	1,119,388
Variables concerning suspected infection			
	Any suspected Infection in first 6 hours, no. (% of total encounters)	87,844 (6.7)	103,259 (9.2)
	Any blood culture drawn, no. (% of above row)	33,727 (39)	56,050 (54)
	Positive blood cultures, no. (% of above row)	4,265 (13)	7,384 (13)
Variables concerning organ dysfunction, no. (% of suspected infection) [a]			
	Platelets	25,795 (29)	42,160 (41)
	Total bilirubin	13,527 (15)	24,178 (23)
	Creatinine	26,477 (30)	42,143 (41)
	Serum lactate	6,071 (6.9)	13,234 (12.8)
	Any of the above	35,758 (41)	52,958 (51)

[a] Includes patients who had laboratory test obtained during the first 6 hours after presentation

Interpretive example: When comparing the SENECA derivation and validation cohorts, the frequency of Sepsis-3 encounters increased. The data above show that the rate of suspected infection, and particularly obtaining blood cultures increased over time. Similarly, the rate of blood sampling for tests that screen for organ dysfunction also increased.

eTable 7. Clinical characteristics and outcomes of RCTs

Variable [a]	ACCESS	PROWESS	ProCESS
No.	1,706	1,690	1,341
Demographics and Burden of Organ Dysfunction			
Age, years, mean (SD)	66 (15)	61 (17)	61 (16)
Male gender, no. (%)	1,003 (59%)	964 (57%)	748 (56%)
Race, no. (%) [b]			
White	1,360 (80%)	1,384 (82%)	916 (68%)
Black	105 (6%)	131 (8%)	333 (25)
Other	241 (14%)	175 (10%)	92 (7%)
Charlson Comorbidity Index, mean (SD) [c]	2.6 (2.5)	1.3 (1.2)	2.7 (2.6)
SIRS criteria at baseline, mean (SD) [d]	-	3.6 (0.5)	-
SOFA score at baseline, mean (SD) [e]	-	7.8 (2.8)	7.2 (3.6)
Inflammation			
Bands, %, median [IQR]	16 [7 - 28]	1 [1 - 3]	12 [4 - 22]
Temperature, °C, mean (SD)	37.3 (1.2)	38.2 (1.7)	37.4 (1.6)
White blood cell count, x 10^9/L, median [IQR]	-	14 [9 - 20]	14 [8 - 20]
Pulmonary			
Oxygen Saturation, %, median [IQR]	-	95 [91 - 97]	97 [94 - 99]
PaO_2, mmHg, mean (SD)	-	94 (66)	118 (93)
Respiratory rate, breaths per minute, mean (SD)	22 (8)	31 (12)	23 (7)
Cardiovascular/Hemodynamic			
Bicarbonate, mEq/L, mean (SD)	18 (5)	-	-
Heart rate, beats per minute, mean (SD)	103 (22)	130 (28)	111 (24)
Serum lactate, mmol/L, median [IQR]	-	-	4.4 [2.5 - 6]
Systolic blood pressure, mmHg, median [IQR]	110 [97 - 125]	80 [70 - 95]	94 [81 - 116]
Renal			
BUN, mg/dL, median [IQR]	13 [8 - 19]	10 [6 - 15]	27 [18 - 44]
Creatinine, mg/dL, median [IQR]	1.8 [1.1 - 2.7]	1.3 [0.9 - 2.0]	1.6 [1.1 - 2.7]
Hepatic			
ALT, U/L, median [IQR]	32 [18 - 70]	28 [16 - 55]	-
AST, U/L, median [IQR]	53 [29 - 123]	43 [24 - 93]	-

	Bilirubin, mg/dL, median [IQR]	0.7 [0.4 - 1.3]	0.7 [0.4 - 1.3]	0.9 [0.5 - 1.5]
Hematologic				
	Hemoglobin, g/dL, mean (SD)	11 (2)	11 (2)	12 (3)
	Platelets, $x10^9$/L, median [IQR]	181 [115 - 258]	168 [105 - 240]	212 [139 - 293]
Neurological				
	Glasgow Coma Scale score, mean (SD)	-	12.8 (3.1)	13.6 (2.9)
Other				
	Albumin, g/dL, mean (SD)	2.3 (0.6)	2.0 (0.6)	3.1 (0.9)
	Chloride, mEq/L, mean (SD)	106 (8)	106 (7)	100 (8)
	Glucose, mg/dL, median [IQR]	139 [108 - 187]	146 [115 - 198]	129 [99 - 182]
	Sodium, mEq/L, mean (SD)	139 (7)	139 (6)	136 (6)
Outcomes				
	Days of mechanical ventilation, median [IQR] [f]	8 [3 - 16]	18 [6 - 28]	-
	Days of vasopressors, median [IQR] [f]	3 [2 - 7]	7 [2 - 26]	-
	Admitted to intensive care, no. (%) [f]	1,687 (99%)	1,679 (99%)	1,175 (88%)
	Short term mortality, no. (%) [g]	458 (27%)	469 (28%)	259 (19%)
	365-day mortality, no. (%)	726 (43%)	687 (35%)	533 (40%)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Asian non-Japanese, Japanese, or Other from the ACCESS trial. Other corresponds to East/Southeast Asian, Western Asian, Hispanic, or Other from the PROWESS trial. Other corresponds to Asian, American Indian, Native Alaskan, Native Hawaiian, Other Pacific islander, Unknown, or Other from the ProCESS trial

[c] Charlson is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24; For the PROWESS trial, Charlson was approximated from categories found on the case report form

[d] SIRS criteria are a scoring system that measures the inflammatory response, ranging from 0 to 4 points

[e] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

[f] At any time during hospitalization

[g] Short term mortality is 28-day mortality for ACCESS and PROWESS and 60-day inpatient mortality for the ProCESS trial

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation; SIRS: systemic inflammatory response syndrome criteria; SOFA: sequential organ failure assessment score

eTable 8. Variables before and after multiple imputation in the SENECA derivation (N=20,189) and validation (N=43,086)

Variable [a]	SENECA Derivation (observed)	SENECA Derivation (imputed) [b]		SENECA Validation (observed)	SENECA Validation (imputed) [b]
Age, years, mean (SD)	64 (17)	64 (17)		67 (17)	67 (17)
Albumin, g/dL, mean (SD)	2.9 (0.7)	2.9 (0.7)		3.0 (0.6)	3.0 (0.6)
ALT, U/L, median [IQR]	31 [20 - 50]	30 [20 - 48]		25 [17 - 42]	25 [17 - 40]
AST, U/L, median [IQR]	31 [20 - 58]	30 [20 - 53]		27 [18 - 48]	26 [18 - 45]
Bands, %, median [IQR]	9 [4 - 19]	7 [3 - 15]		7 [3 - 16]	5 [2 - 10]
Bicarbonate, mEq/L, mean (SD)	25 (5)	25 (5)		25 (5)	25 (5)
Bilirubin, mg/dL, median [IQR]	0.9 [0.6 - 1.6]	0.8 [0.5 - 1.3]		0.7 [0.4 - 1.2]	0.7 [0.4 - 1.1]
BUN, mg/dL, median [IQR]	23 [15 - 38]	24 [15 - 38]		24 [15 - 39]	23 [15 - 38]
Chloride, mEq/L, mean (SD)	103 (7)	103 (7)		103 (7)	103 (7)
C-Reactive Protein, mg/L, median [IQR]	5 [2 - 16]	6 [2 - 16]		8 [2 - 17]	7 [2 - 16]
Creatinine, mg/dL, median [IQR]	1.4 [1.0 - 2.3]	1.4 [1.0 - 2.2]		1.3 [0.9 - 2.1]	1.3 [0.9 - 2.1]
Elixhauser Comorbidity Index, mean (SD) [c]	1.8 (1.2)	1.8 (1.2)		1.2 (1.2)	1.2 (1.2)
ESR, mm/hr, median [IQR]	48 [26 - 86]	48 [25 - 88]		53 [29 - 88]	50 [27 - 84]
Glasgow Coma Scale score, mean (SD)	11.4 (4.0)	12.9 (3.1)		11.7 (3.9)	13.4 (2.8)
Gender (male), no. (%)	10,022 (50%)	10,022 (50%)		21,993 (51%)	21,993 (51%)
Glucose, mg/dL, median [IQR]	130 [105 - 180]	130 [105 - 179]		137 [108 - 193]	135 [107 - 188]
Heart Rate, beats per minute, mean (SD)	97 (22)	97 (22)		96 (21)	96 (21)
Hemoglobin, g/dL, mean (SD)	12 (2)	12 (2)		12 (2)	12 (2)
INR, median [IQR]	1.3 [1.1 - 1.7]	1.3 [1.1 - 1.6]		1.3 [1.1 - 1.8]	1.2 [1.1 - 1.7]
Serum lactate mmol/L, median [IQR]	2 [1.3 - 3.7]	1.5 [1 - 2.4]		1.8 [1.2 - 3]	1.5 [1.0 - 2.3]
Oxygen Saturation, %, mean (SD)	94 [91 - 97]	94 [91 - 97]		94 [92 - 96]	94 [92 - 96]
PaO_2, mmHg, mean (SD)	123 (89)	109 (76)		116 (76)	102 (63)
Platelets, $x10^9$/L, median [IQR]	182 [124 - 251]	188 [130 - 256]		191 [134 - 258]	192 [134 - 260]
Respiratory rate, breaths per min, mean (SD)	22 (6)	22 (6)		22 (7)	22 (7)
Sodium, mEq/L, mean (SD)	137 (5)	137 (6)		137 (5)	137 (5)
Systolic Blood Pressure, mmHg, median [IQR]	110 [93 - 128]	110 [93 - 128]		110 [94 - 127]	110 [95 - 127]
Temperature, °C, mean (SD)	37.0 (1.0)	37.0 (1.0)		37.0 (0.9)	37.0 (0.9)
Troponin, ng/mL, median [IQR]	0.1 [0.04 - 0.1]	0.1 [0.04 - 0.1]		0.04 [0.04 - 0.1]	0.04 [0.04 - 0.1]
WBC count, $x10^9$/L, median [IQR]	10 [7 - 14]	10 [7 - 14]		10 [7 - 15]	10 [7 - 13]

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Summary statistics are shown from a random one of 11 datasets imputed

[c] Elixhauser is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 31

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation; WBC: white blood cell

eTable 9. Proportion of patients by phenotype in the SENECA derivation cohort (N=20,189) who had blood cultures or parenteral antibiotics administered first after presentation

Variable	α-type	ß-type	*y*-type	*∂*-type
No.	6,625	5,512	5.385	2,667
Blood culture as first body fluid culture after presentation, no. (%)	3,125 (47)	2,5151 (46)	2,593 (48)	1,250 (47)
Parenteral antibiotics as first antibiotic after presentation, no. (%)	5,050 (76)	4,269 (77)	4,826 (89)	2,492 (93)
Total days of any antibiotic during hospitalization, median [IQR]	3 [1 – 6]	4 [2 – 8]	6 [3 – 11]	6 [3 - 12[

eTable 10. Statistical output from latent class analysis in SENECA derivation cohort (N=20,189).

	Statistic			Class size					
Class number	**BIC**	**Entropy** [a]	**Median [IQR] probability of group membership**	**1**	**2**	**3**	**4**	**5**	**6**
2	2290364	0.927	99.9 [98.1 - 99.9]	8,018 (40%)	12,171 (60%)	.	.	.	.
3	2265815	0.898	99.3 [91.4 - 99.9]	6,628 (33%)	7,505 (37%)	6,056 (30%)	.	.	.
4	2251366	0.886	98.2 [86.8 - 99.9]	5,086 (25%)	6,148 (30%)	5,298 (26%)	3,657 (18%)	.	.
5	2238802	0.882	97.8 [84.0 - 99.9]	2,526 (13%)	4,917 (24%)	3,064 (15%)	5,135 (25%)	4,547 (23%)	.
6	2231214	0.877	96.4 [80.9 - 99.7]	3,831 (19%)	3,260 (16%)	3,814 (19%)	4,274 (21%)	2,537 (13%)	2,473 (12%)

[a] Entropy is a measure between 0 and 1 measures success of classification, where a value closer to 1 implies a better fit
Abbreviations: BIC: Bayesian information criteria; IQR: interquartile range

eTable 11. Clinical characteristics by phenotype derived using latent class analysis in the SENECA derivation cohort (N=20,189)

Variable [a, g]	Overall	α-type	ß-type	*y*-type	*∂*-type
No.	20,189	5,086 (25%)	6,148 (30%)	5,298 (26%)	3,657 (18%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	64 (17)	62 (18)	68 (15)	66 (17)	60 (17)
Male gender, no. (%)	10,022 (50%)	2,510 (49%)	2,915 (47%)	2,652 (50%)	1,945 (53%)
Race, no. (%) [b]					
White	15,640 (77%)	3,982 (78%)	4,848 (79%)	4,063 (77%)	2,747 (75%)
Black	2,428 (12%)	638 (13%)	756 (12%)	634 (12%)	400 (11%)
Other	2,121 (11%)	466 (9%)	544 (9%)	601 (11%)	510 (14%)
Elixhauser Comorbidity Index, mean (SD) [c]	1.8 (1.2)	1.6 (1.2)	2.1 (1.2)	1.8 (1.1)	1.7 (1.1)
Surgery, no. (%) [d]	2,727 (14%)	530 (10%)	853 (14%)	827 (16%)	517 (14%)
Max SIRS criteria within 24 hours, mean (SD) [e]	1.8 (1.2)	1.3 (1.0)	1.4 (1.1)	2.3 (1.1)	2.3 (1.1)
Max SOFA score within 24 hours, mean (SD) [f]	3.9 (2.4)	2.9 (1.3)	3.1 (1.4)	4.3 (2.4)	5.8 (3.5)
Inflammation					
Bands, %, median [IQR]	6 [2 - 14]	3 [1 - 8]	5 [2 - 11]	10 [4 - 18]	10 [4 - 21]
C-reactive protein, mg/L, median [IQR]	5 [2 - 16]	2 [0 - 5]	7 [3 - 16]	12 [4 - 28]	6 [2 - 26]
ESR, mm/hr, median [IQR]	46 [23 - 83]	26 [15 - 41]	69 [43 - 101]	63 [35 - 102]	27 [14 - 55]
Temperature, °C, mean (SD)	37.0 (1.0)	37.0 (0.9)	36.9 (0.8)	37.1 (1.1)	36.8 (1.3)
White blood cell count, $x10^9$/L, median [IQR]	10 [7 - 14]	9 [7 - 12]	9 [6 - 13]	11 [8 - 16]	10 [5 - 16]
Pulmonary					
Oxygen Saturation, %, median [IQR]	94 [91 - 97]	94 [91 - 97]	94 [91 - 97]	94 [90 - 97]	95 [91 - 97]
PaO_2, mmHg, mean (SD)	109 (76)	99 (63)	92 (52)	122 (85)	135 (98)
Respiratory rate, breaths per min, mean (SD)	22 (6)	20 (3)	20 (3)	26 (8)	24 (7)
Cardiovascular/Hemodynamic					
Bicarbonate, mEq/L, mean (SD)	25 (5)	26 (4)	26 (5)	25 (6)	22 (5)
Heart rate, beats per minute, mean (SD)	97 (22)	90 (18)	90 (17)	107 (24)	105 (24)
Serum lactate, mmol/L, median [IQR]	1.5 [1 - 2.5]	1.3 [0.9 - 1.9]	1.3 [0.9 - 1.9]	1.7 [1.1 - 2.7]	2.6 [1.6 - 4.6]
Systolic blood pressure, mmHg, median [IQR]	110 [93 - 128]	121 [106 - 137]	116 [100 - 133]	100 [83 - 118]	99 [82 - 116]
Troponin, ng/mL, median [IQR]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.2]	0.1 [0.1 - 0.8]
Renal					
BUN, mg/dL, median [IQR]	23 [15 - 38]	17 [12 - 24]	27 [18 - 43]	27 [17 - 45]	25 [14 - 43]

	Creatinine, mg/dL, median [IQR]	1.4 [1.0 - 2.2]	1.2 [0.9 - 1.5]	1.6 [1.2 - 2.7]	1.4 [1.0 - 2.4]	1.4 [0.9 - 2.3]
Hepatic						
	ALT, U/L, median [IQR]	31 [20 - 49]	31 [21 - 45]	28 [19 - 40]	27 [18 - 37]	70 [34 - 192]
	AST, U/L, median [IQR]	30 [20 - 55]	26 [19 - 40]	25 [18 - 39]	29 [21 - 43]	119 [55 - 265]
	Bilirubin, mg/dL, median [IQR]	0.8 [0.5 - 1.3]	0.7 [0.5 - 1.2]	0.8 [0.5 - 1.2]	0.7 [0.5 - 1.1]	1.5 [0.8 - 3.4]
Hematologic						
	Hemoglobin, g/dL, mean (SD)	12 (2)	13 (2)	11 (2)	11 (2)	11 (3)
	INR, median [IQR]	1.3 [1.1 - 1.6]	1.1 [1.0 - 1.2]	1.3 [1.1 - 1.8]	1.3 [1.1 - 1.6]	1.6 [1.3 - 2.6]
	Platelets, $x10^9$/L, median [IQR]	188 [130 - 257]	189 [138 - 249]	187 [127 - 256]	213 [154 - 284]	141 [75 - 221]
Neurological						
	Glasgow Coma Scale score, mean (SD)	12.9 (3.1)	12.5 (2.9)	14.8 (0.4)	12.0 (3.3)	11.4 (4.1)
Other						
	Albumin, g/dL, mean (SD)	2.9 (0.7)	3.5 (0.5)	2.9 (0.6)	2.6 (0.7)	2.7 (0.8)
	Chloride, mEq/L, mean (SD)	103 (7)	103 (4)	101 (5)	104 (9)	104 (7)
	Glucose, mg/dL, median [IQR]	130 [105 - 180]	122 [102 - 158]	125 [102 - 167]	144 [111 - 209]	138 [107 - 203]
	Sodium, mEq/L, mean (SD)	137 (6)	138 (3)	136 (4)	138 (8)	137 (6)
Outcomes						
	Days of mechanical ventilation, median [IQR] [d]	5 [2 - 10]	3 [2 - 8]	5 [2 - 10]	5 [3 - 12]	4 [2 - 10]
	Days of vasopressors, median [IQR] [d]	3 [2 - 5]	2 [2 - 4]	3 [2 - 5]	3 [2 - 5]	3 [2 - 5]
	Admitted to intensive care, no. (%) [d]	9,063 (45%)	1,026 (20%)	1,625 (26%)	3,799 (72%)	2,613 (71%)
	Inpatient mortality, no. (%)	2,082 (10%)	83 (2%)	251 (4%)	824 (16%)	924 (25%)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Chinese, Filipino, Hawaiian, American Indian/Alaskan, Asian, Hawaiian/Other Pacific Islander, Middle Eastern, Native American, Not specified, or Pacific Islander

[c] Elixhauser is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 31

[d] At any time during hospitalization

[e] SIRS criteria are a scoring system that measures the inflammatory response, ranging from 0 to 4 points

[f] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

[g] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all except days of vasopressors, $p=0.14$

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation; SIRS: systemic inflammatory response syndrome criteria; SOFA: sequential organ failure assessment score

eTable 12. Clinical characteristics by phenotype derived using consensus *k* means clustering in the SENECA validation cohort (N=43,086).

Variable [a, g]	Overall	α-type	ß-type	*y*-type	*∂*-type
No.	43,086	12,485 (29%)	12,508 (29%)	12,121 (28%)	5,972 (14%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	67 (17)	68 (17)	72 (15)	63 (17)	66 (17)
Male gender, no. (%)	21,993 (51%)	7,201 (58%)	6,189 (49%)	5,892 (49%)	2,711 (45%)
Race, no. (%) [b]					
White	36,820 (85%)	10,794 (86%)	10,598 (85%)	10,615 (88%)	4,813 (81%)
Black	5,008 (12%)	1,418 (11%)	1,592 (13%)	1,208 (10%)	790 (13%)
Other	1,258 (3%)	273 (2%)	318 (3%)	298 (2%)	369 (6%)
Elixhauser Comorbidity Index, mean (SD) [c]	1.2 (1.2)	1.0 (1.0)	1.5 (1.2)	0.9 (1.0)	1.8 (1.4)
Surgery, no. (%) [d]	5,122 (12%)	946 (8%)	1,890 (15%)	1,375 (11%)	911 (15%)
Max SIRS criteria within 6 hours, mean (SD) [e]	1.4 (1.1)	0.9 (0.9)	1.3 (1.0)	1.8 (1.0)	2.2 (1.1)
Max SOFA score within 6 hours, mean (SD) [f]	3.6 (2.0)	3.1 (1.4)	3.6 (1.6)	3.0 (1.4)	5.9 (3.1)
Inflammation					
Bands, %, median [IQR]	5 [2 - 10]	3 [2 - 6]	5 [2 - 10]	5 [3 - 11]	10 [4 - 21]
C-reactive protein, mg/L, median [IQR]	7 [2 - 16]	1 [0 - 3]	13 [7 - 21]	11 [5 - 19]	8 [3 - 17]
ESR, mm/hr, median [IQR]	50 [27 - 84]	29 [17 - 47]	89 [61 - 109]	49 [30 - 74]	42 [21 - 69]
Temperature, °C, mean (SD)	37.0 (0.9)	36.8 (0.7)	36.9 (0.8)	37.4 (0.9)	36.9 (1.2)
White blood cell count, $x10^9$/L, median [IQR]	10 [7 - 13]	8 [6 - 11]	10 [8 - 14]	11 [8 - 14]	12 [9 - 17]
Pulmonary					
Oxygen Saturation, %, median [IQR]	94 [92 - 96]	95 [93 - 97]	95 [93 - 97]	93 [91 - 95]	94 [90 - 96]
PaO_2, mmHg, mean (SD)	102 (63)	106 (66)	107 (64)	82 (44)	122 (77)
Respiratory rate, breaths per min, mean (SD)	22 (7)	20 (4)	22 (5)	23 (7)	27 (9)
Cardiovascular/Hemodynamic					
Bicarbonate, mEq/L, mean (SD)	25 (5)	26 (4)	25 (5)	27 (5)	21 (5)
Heart rate, beats per minute, mean (SD)	96 (21)	86 (17)	92 (19)	103 (20)	108 (25)
Serum lactate, mmol/L, median [IQR]	1.5 [1.0 - 2.3]	1.4 [1.0 – 2.0]	1.3 [0.9 - 1.9]	1.5 [1.1 - 2.3]	2.9 [1.9 - 4.8]
Systolic blood pressure, mmHg, median [IQR]	110 [95 - 127]	118 [102 - 135]	110 [95 - 128]	110 [96 - 125]	92 [77 - 108]
Troponin, ng/mL, median [IQR]	0.0 [0.0 - 0.1]	0.0 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.0 [0.0 - 0.1]	0.1 [0.1 - 0.7]
Renal					
BUN, mg/dL, median [IQR]	23 [15 - 38]	20 [14 - 29]	38 [26 - 56]	16 [12 - 23]	32 [20 - 51]

	Creatinine, mg/dL, median [IQR]	1.3 [0.9 - 2.1]	1.1 [0.8 - 1.5]	2.1 [1.4 - 3.5]	1.0 [0.7 - 1.3]	1.7 [1.1 - 2.7]
Hepatic						
	ALT, U/L, median [IQR]	25 [17 - 40]	24 [17 - 36]	20 [15 - 29]	25 [18 - 39]	55 [28 - 145]
	AST, U/L, median [IQR]	26 [18 - 45]	24 [17 - 37]	23 [16 - 33]	25 [17 - 39]	86 [43 - 228]
	Bilirubin, mg/dL, median [IQR]	0.7 [0.4 - 1.1]	0.6 [0.4 - 0.9]	0.6 [0.4 - 0.9]	0.7 [0.5 - 1.2]	1.2 [0.6 - 2.5]
Hematologic						
	Hemoglobin, g/dL, mean (SD)	12 (2)	12 (2)	10 (2)	13 (2)	12 (2)
	INR, median [IQR]	1.2 [1.1 - 1.7]	1.2 [1.1 - 1.4]	1.3 [1.1 - 1.8]	1.2 [1.1 - 1.4]	1.7 [1.3 - 2.5]
	Platelets, $x10^9$/L, median [IQR]	192 [134 - 260]	167 [115 - 230]	212 [151 - 286]	206 [147 - 273]	168 [111 - 244]
Neurological						
	Glasgow Coma Scale score, mean (SD)	13.4 (2.8)	13.4 (2.6)	13.9 (2.0)	13.9 (2.0)	11.1 (4.1)
Other						
	Albumin, g/dL, mean (SD)	3.0 (0.6)	3.4 (0.5)	2.7 (0.6)	3.2 (0.5)	2.7 (0.6)
	Chloride, mEq/L, mean (SD)	103 (7)	105 (6)	103 (6)	99 (6)	105 (7)
	Glucose, mg/dL, median [IQR]	135 [107 - 188]	124 [102 - 164]	141 [110 - 199]	133 [108 - 184]	157 [118 - 224]
	Sodium, mEq/L, mean (SD)	137 (5)	140 (5)	137 (5)	135 (5)	138 (6)
Outcomes						
	Days of mechanical ventilation, median [IQR][d]	4 [2 - 8]	3 [2 - 6]	4 [2 - 9]	4 [2 - 8]	4 [2 - 9]
	Days of vasopressors, median [IQR] [d]	3 [2 - 5]	2 [2 - 4]	3 [2 - 4]	2 [1 - 4]	3 [2 - 5]
	Admitted to intensive care, no. (%) [d]	14,337 (33%)	2,409 (19%)	4,144 (33%)	3,320 (27%)	4,464 (75%)
	Inpatient mortality, no. (%)	2,666 (6%)	249 (2%)	588 (5%)	368 (3%)	1,461 (24%)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Chinese, Filipino, Hawaiian, American Indian/Alaskan, Asian, Hawaiian/Other Pacific Islander, Middle Eastern, Native American, Not specified, or Pacific Islander

[c] Elixhauser is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 31

[d] At any time during hospitalization

[e] SIRS criteria are a scoring system that measures the inflammatory response, ranging from 0 to 4 points

[f] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

[g] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all except days of vasopressors, $p=0.14$.

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; ESR: erythrocyte sedimentation rate; BUN: blood urea nitrogen; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation; SIRS: systemic inflammatory response syndrome criteria; SOFA: sequential organ failure assessment score

eTable 13. Clinical characteristics by phenotype in sensitivity analysis excluding variables with high missing data in the SENECA derivation data (N=20,189)

Variable [a, g]	Overall	α-type	ß-type	*y*-type	∂-type
No.	20,189	7,470 (37%)	6,564 (33%)	4,100 (20%)	2,055 (10%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	64 (17)	58 (18)	71 (15)	67 (16)	61 (17)
Male gender, no. (%)	10,022 (50%)	3,699 (50%)	3,154 (48%)	2,020 (49%)	1,149 (56%)
Race, no. (%) [b]					
White	15,640 (77%)	5,848 (78%)	5,077 (77%)	3,185 (78%)	1,530 (74%)
Black	2,428 (12%)	861 (12%)	900 (14%)	468 (11%)	199 (10%)
Other	2,121 (11%)	761 (10%)	587 (9%)	447 (11%)	326 (16%)
Elixhauser Comorbidity Index, mean (SD) [c]	1.8 (1.2)	1.5 (1.1)	2.3 (1.2)	1.6 (1.1)	1.8 (1.1)
Surgery, no. (%) [d]	2,727 (14%)	829 (11%)	934 (14%)	671 (16%)	293 (14%)
Max SIRS criteria within 24 hours, mean (SD) [e]	1.8 (1.2)	1.6 (1.1)	1.3 (1.0)	2.5 (1.0)	2.3 (1.2)
Max SOFA score within 24 hours, mean (SD) [f]	3.9 (2.4)	3.0 (1.4)	3.4 (1.7)	5.0 (2.8)	6.3 (3.8)
Inflammation					
Bands, %, median [IQR]	7 [3 - 15]	5 [2 - 12]	5 [2 - 12]	11 [5 - 21]	11 [4 - 22]
C-reactive protein, mg/L, median [IQR]	6 [2 - 16]	4 [1 - 12]	5 [2 - 14]	14 [5 - 30]	14 [4 - 32]
ESR, mm/hr, median [IQR]	48 [25 - 88]	40 [19 - 70]	59 [34 - 100]	63 [33 - 105]	35 [15 - 66]
Temperature, °C, mean (SD)	37.0 (1.0)	37.3 (0.9)	36.7 (0.8)	37.1 (1.1)	36.6 (1.2)
White blood cell count, $x10^9$/L, median [IQR]	10 [7 - 14]	9 [6 - 13]	9 [7 - 13]	12 [8 - 17]	12 [8 - 18]
Pulmonary					
Oxygen Saturation, %, median [IQR]	94 [91 - 97]	94 [91 - 96]	95 [92 - 97]	93 [89 - 96]	95 [91 - 97]
PaO_2, mmHg, mean (SD)	109 (77)	92 (59)	108 (72)	134 (95)	129 (91)
Respiratory rate, breaths per min, mean (SD)	22 (6)	21 (4)	20 (4)	28 (8)	23 (6)
Cardiovascular/Hemodynamic					
Bicarbonate, mEq/L, mean (SD)	25 (5)	27 (4)	25 (5)	23 (5)	22 (5)
Heart rate, beats per minute, mean (SD)	97 (22)	97 (19)	85 (16)	114 (23)	103 (22)
Serum lactate, mmol/L, median [IQR]	1.5 [1.0 - 2.4]	1.4 [1.0 – 2.0]	1.2 [0.9 - 1.8]	2.3 [1.4 - 3.7]	3.0 [1.8 - 5.3]
Systolic blood pressure, mmHg, median [IQR]	110 [93 - 128]	116 [102 - 132]	119 [102 - 137]	90 [76 - 105]	98 [82 - 115]
Troponin, ng/mL, median [IQR]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.1 - 0.3]	0.2 [0.1 - 1.1]
Renal					
BUN, mg/dL, median [IQR]	24 [15 - 38]	15 [10 - 20]	36 [26 - 51]	29 [19 - 44]	27 [17 - 46]

	Creatinine, mg/dL, median [IQR]	1.4 [1.0 - 2.2]	1.0 [0.8 - 1.3]	2.1 [1.5 - 3.5]	1.4 [1.0 - 2.2]	1.6 [1.0 - 2.7]
Hepatic						
	ALT, U/L, median [IQR]	30 [20 - 48]	31 [21 - 46]	26 [17 - 36]	27 [18 - 40]	129 [62 - 337]
	AST, U/L, median [IQR]	30 [20 - 53]	27 [19 - 43]	24 [17 - 36]	33 [22 - 53]	191 [112 - 429]
	Bilirubin, mg/dL, median [IQR]	0.8 [0.5 - 1.3]	0.8 [0.5 - 1.3]	0.6 [0.4 – 1.0]	0.8 [0.5 - 1.2]	2.3 [1.1 - 5.2]
Hematologic						
	Hemoglobin, g/dL, mean (SD)	12 (2)	12 (2)	11 (2)	11 (2)	11 (2)
	INR, median [IQR]	1.3 [1.1 - 1.6]	1.2 [1.1 - 1.4]	1.3 [1.1 - 1.6]	1.4 [1.2 - 1.9]	1.7 [1.4 - 2.7]
	Platelets, $x10^9$/L, median [IQR]	188 [130 - 256]	179 [124 - 249]	200 [143 - 263]	197 [136 - 271]	151 [96 - 228]
Neurological						
	Glasgow coma scale score, mean (SD)	12.8 (3.1)	13.1 (2.7)	13.6 (2.2)	11.5 (3.9)	11.8 (4.0)
Other						
	Albumin, g/dL, mean (SD)	2.9 (0.7)	3.3 (0.6)	3.0 (0.6)	2.4 (0.7)	2.6 (0.7)
	Chloride, mEq/L, mean (SD)	103 (7)	102 (5)	102 (6)	107 (8)	102 (8)
	Glucose, mg/dL, median [IQR]	130 [105 - 179]	120 [101 - 154]	133 [105 - 183]	150 [115 - 216]	141 [109 - 205]
	Sodium, mEq/L, mean (SD)	137 (6)	137 (5)	137 (5)	140 (7)	136 (6)
Outcomes						
	Days of mechanical ventilation, median [IQR] [d]	5 [2 - 10]	5 [2 - 11]	4 [2 - 9]	5 [3 - 12]	4 [2 - 9]
	Days of vasopressors, median [IQR] [d]	3 [2 - 5]	3 [2 - 5]	3 [2 - 4]	3 [2 - 5]	3 [2 - 5]
	Admitted to intensive care, no. (%) [d]	9,063 (45%)	2,054 (28%)	2,049 (31%)	3,442 (84%)	1,518 (74%)
	Inpatient mortality, no. (%)	2,082 (10%)	213 (3%)	329 (5%)	959 (23%)	581 (28%)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Chinese, Filipino, Hawaiian, American Indian/Alaskan, Asian, Hawaiian/Other Pacific Islander, Middle Eastern, Native American, Not specified, or Pacific Islander

[c] Elixhauser is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 31

[d] At any time during hospitalization

[e] SIRS criteria are a scoring system that measures the inflammatory response, ranging from 0 to 4 points

[f] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

[g] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation; SIRS: systemic inflammatory response syndrome criteria; SOFA: sequential organ failure assessment score

eTable 14. Clinical characteristics by phenotype in sensitivity analysis excluding variables with high correlation (Na, Hgb, BUN, and ALT) and high missingness (ESR, CRP, premature white cells (%bands)) in the SENECA derivation data (N=20,189).

Variable [a, g]	Overall	α-type	ß-type	*y*-type	*∂*-type
No.	20,189	4,756 (24%)	8,153 (40%)	4,276 (21%)	3,004 (15%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	64 (17)	54 (17)	71 (14)	63 (17)	65 (16)
Male gender, no. (%)	10,022 (50%)	2,678 (56%)	3,595 (44%)	2,154 (50%)	1,595 (53%)
Race, no. (%) [b]					
White	15,640 (77%)	3,610 (76%)	6,438 (79%)	3,333 (78%)	2,259 (75%)
Black	2,428 (12%)	583 (12%)	1,036 (13%)	478 (11%)	331 (11%)
Other	2,121 (11%)	563 (12%)	679 (8%)	465 (11%)	414 (14%)
Elixhauser Comorbidity Index, mean (SD) [c]	1.8 (1.2)	1.3 (1.0)	2.3 (1.2)	1.7 (1.1)	1.7 (1.1)
Surgery, no. (%) [d]	2,727 (14%)	637 (13%)	1,012 (12%)	608 (14%)	470 (16%)
Max SIRS criteria within 24 hours, mean (SD) [e]	1.8 (1.2)	1.5 (1.1)	1.2 (1.0)	2.5 (0.9)	2.5 (1.1)
Max SOFA score within 24 hours, mean (SD) [f]	3.9 (2.4)	3.6 (1.9)	3.0 (1.4)	3.9 (2.2)	6.4 (3.6)
Inflammation					
Bands, %, median [IQR]	7 [3 - 15]	6 [2 - 14]	4 [2 - 10]	9 [4 - 17]	13 [5 - 24]
C-reactive protein, mg/L, median [IQR]	6 [2 - 16]	4 [1 - 12]	4 [1 - 12]	14 [5 - 30]	14 [4 - 31]
ESR, mm/hr, median [IQR]	48 [25 - 88]	38 [17 - 69]	50 [29 - 88]	68 [38 - 107]	40 [16 - 80]
Temperature, °C, mean (SD)	37.0 (1.0)	37.1 (0.9)	36.8 (0.8)	37.5 (1.0)	36.5 (1.2)
White blood cell count, $x10^9$/L, median [IQR]	10 [7 - 14]	7 [5 - 10]	10 [7 - 13]	12 [8 - 17]	13 [8 - 18]
Pulmonary					
Oxygen Saturation, %, median [IQR]	94 [91 - 97]	96 [94 - 98]	94 [91 - 96]	92 [88 - 95]	95 [91 - 97]
PaO_2, mmHg, mean (SD)	109 (77)	108 (74)	98 (64)	102 (68)	152 (104)
Respiratory rate, breaths per min, mean (SD)	22 (6)	20 (3)	20 (3)	28 (8)	24 (7)
Cardiovascular/Hemodynamic					
Bicarbonate, mEq/L, mean (SD)	25 (5)	25 (4)	27 (5)	25 (5)	20 (5)
Heart rate, beats per minute, mean (SD)	97 (22)	93 (17)	86 (16)	117 (20)	106 (23)
Serum lactate, mmol/L, median [IQR]	1.5 [1.0 - 2.4]	1.4 [1.0 – 2.0]	1.2 [0.9 - 1.7]	1.8 [1.2 - 2.8]	3.3 [2.0 - 5.6]
Systolic blood pressure, mmHg, median [IQR]	110 [93 - 128]	113 [100 - 128]	121 [106 - 139]	98 [82 - 113]	90 [76 - 106]
Troponin, ng/mL, median [IQR]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.2 [0.1 - 1.3]
Renal					

	BUN, mg/dL, median [IQR]	24 [15 - 38]	16 [11 - 25]	27 [18 - 42]	21 [14 - 33]	34 [21 - 55]
	Creatinine, mg/dL, median [IQR]	1.4 [1.0 - 2.2]	1.1 [0.8 - 1.5]	1.6 [1.2 - 2.6]	1.2 [0.8 - 1.7]	1.9 [1.3 - 3.2]
Hepatic						
	ALT, U/L, median [IQR]	30 [20 - 48]	32 [21 - 52]	27 [19 - 38]	29 [20 - 45]	47 [26 - 119]
	AST, U/L, median [IQR]	30 [20 - 53]	34 [22 - 59]	23 [17 - 34]	29 [20 - 46]	85 [42 - 200]
	Bilirubin, mg/dL, median [IQR]	0.8 [0.5 - 1.3]	1.2 [0.7 - 2.1]	0.6 [0.4 - 0.9]	0.7 [0.5 - 1.1]	1.2 [0.7 - 2.5]
Hematologic						
	Hemoglobin, g/dL, mean (SD)	12 (2)	12 (3)	12 (2)	11 (2)	11 (2)
	INR, median [IQR]	1.3 [1.1 - 1.6]	1.2 [1.1 - 1.5]	1.2 [1.1 - 1.5]	1.3 [1.1 - 1.6]	1.8 [1.4 - 2.8]
	Platelets, $x10^9$/L, median [IQR]	188 [130 - 256]	128 [77 - 186]	210 [154 - 273]	215 [157 - 289]	174 [114 - 247]
Neurological						
	Glasgow coma scale score, mean (SD)	12.8 (3.1)	13.1 (2.8)	13.5 (2.3)	12.8 (3.0)	10.6 (4.4)
Other						
	Albumin, g/dL, mean (SD)	2.9 (0.7)	3.1 (0.7)	3.1 (0.6)	2.7 (0.7)	2.5 (0.7)
	Chloride, mEq/L, mean (SD)	103 (7)	103 (6)	102 (6)	102 (7)	106 (8)
	Glucose, mg/dL, median [IQR]	130 [105 - 179]	114 [97 - 143]	131 [105 - 178]	140 [112 - 198]	157 [118 - 231]
	Sodium, mEq/L, mean (SD)	137 (6)	137 (5)	137 (5)	137 (6)	138 (7)
Outcomes						
	Days of mechanical ventilation, median [IQR] [d]	5 [2 - 10]	5 [2 - 11]	4 [2 - 9]	6 [3 - 13]	4 [2 - 9]
	Days of vasopressors, median [IQR] [d]	3 [2 - 5]	3 [2 - 5]	3 [2 - 4.5]	3 [2 - 5]	3 [2 - 5]
	Admitted to intensive care, no. (%) [d]	9,063 (45%)	1,569 (33%)	2,030 (25%)	2,870 (67%)	2,594 (86%)
	Inpatient mortality, no. (%)	2,082 (10%)	240 (5%)	280 (3%)	560 (13%)	1,002 (33%)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Chinese, Filipino, Hawaiian, American Indian/Alaskan, Asian, Hawaiian/Other Pacific Islander, Middle Eastern, Native American, Not specified, or Pacific Islander

[c] Elixhauser is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 31

[d] At any time during hospitalization

[e] SIRS criteria are a scoring system that measures the inflammatory response, ranging from 0 to 4 points

[f] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

[g] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation; SIRS: systemic inflammatory response syndrome criteria; SOFA: sequential organ failure assessment score

eTable 15. Clinical characteristics by phenotype using a 12-hour window of EHR data in the SENECA validation data (N=43,086)

Variable [a, g]	Overall	α-type	ß-type	*y*-type	∂-type
No.	43,086	14,605 (34%)	13,229 (31%)	9,594 (22%)	5,658 (13%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	67 (17)	67 (17)	71 (15)	64 (17)	65 (17)
Male gender, no. (%)	21,993 (51%)	7,955 (54%)	6,573 (50%)	4,961 (52%)	2,504 (44%)
Race, no. (%) [b]					
White	36,820 (85%)	12,760 (87%)	11,115 (84%)	8,281 (86%)	4,624 (82%)
Black	5,008 (12%)	1,544 (11%)	1,757 (13%)	999 (10%)	708 (13%)
Other	1,258 (3%)	301 (2%)	317 (2%)	314 (3%)	326 (6%)
Elixhauser Comorbidity Index, mean (SD) [c]	1.2 (1.2)	0.9 (1.0)	1.5 (1.2)	1.0 (1.1)	1.7 (1.4)
Surgery, no. (%) [d]	5,122 (12%)	1,122 (8%)	1,860 (14%)	1,329 (14%)	811 (14%)
Max SIRS criteria within 6 hours, mean (SD) [e]	1.7 (1.2)	1.2 (1.0)	1.5 (1.1)	2.3 (1.1)	2.3 (1.1)
Max SOFA score within 6 hours, mean (SD) [f]	4.1 (2.4)	3.2 (1.5)	3.9 (1.8)	4.3 (2.6)	6.4 (3.5)
Inflammation					
Bands, %, median [IQR]	5 [2 - 12]	3 [1 - 7]	5 [2 - 11]	8 [4 - 16]	10 [4 - 20]
C-reactive protein, mg/L, median [IQR]	7 [2 - 15]	2 [1 - 5]	11 [6 - 19]	10 [4 - 18]	8 [3 - 17]
ESR, mm/hr, median [IQR]	47 [26 - 79]	29 [15 - 45]	85 [60 - 105]	46 [28 - 72]	39 [21 - 63]
Temperature, °C, mean (SD)	37.2 (0.8)	37.0 (0.7)	37.1 (0.7)	37.5 (1.0)	37.2 (1.1)
White blood cell count, x 10^9/L, median [IQR]	10 [7 - 13]	8 [6 - 11]	10 [7 - 13]	11 [8 - 15]	11 [8 - 16]
Pulmonary					
Oxygen Saturation, %, median [IQR]	93 [91 - 95]	94 [92 - 96]	94 [92 - 96]	92 [90 - 94]	93 [90 - 95]
PaO_2, mmHg, mean (SD)	101 (59)	102 (60)	101 (57)	95 (55)	112 (67)
Respiratory rate, breaths per min, mean (SD)	23 (7)	21 (4)	22 (5)	27 (9)	27 (9)
Cardiovascular/Hemodynamic					
Bicarbonate, mEq/L, mean (SD)	25 (5)	26 (4)	25 (5)	26 (5)	23 (5)
Heart rate, beats per minute, mean (SD)	98 (21)	90 (17)	93 (18)	111 (22)	108 (24)
Serum lactate, mmol/L, median [IQR]	1.5 [1.0 - 2.3]	1.3 [1.0 – 2.0]	1.3 [0.9 - 1.9]	1.7 [1.1 - 2.7]	2.5 [1.6 - 4.3]
Systolic blood pressure, mmHg, median [IQR]	106 [92 - 122]	114 [100 - 129]	108 [94 - 125]	98 [83 - 112]	93 [77 - 108]
Troponin, ng/mL, median [IQR]	0.0 [0.0 - 0.1]	0.0 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.1 - 0.7]
Renal					
BUN, mg/dL, median [IQR]	23 [15 - 37]	18 [12 - 25]	35 [23 - 53]	19 [13 - 29]	27 [17 - 44]

	Creatinine, mg/dL, median [IQR]	1.3 [0.9 – 2.0]	1.0 [0.7 - 1.4]	1.9 [1.3 - 3.2]	1.0 [0.8 - 1.5]	1.4 [1.0 - 2.3]
Hepatic						
	ALT, U/L, median [IQR]	24 [17 - 40]	24 [17 - 35]	20 [15 - 30]	25 [17 - 39]	70 [34 - 193]
	AST, U/L, median [IQR]	26 [17 - 46]	23 [16 - 35]	23 [16 - 35]	26 [17 - 43]	104 [51 - 270]
	Bilirubin, mg/dL, median [IQR]	0.7 [0.4 - 1.1]	0.6 [0.4 - 1.0]	0.6 [0.4 - 1.0]	0.6 [0.4 - 1.1]	1.4 [0.7 - 3.3]
Hematologic						
	Hemoglobin, g/dL, mean (SD)	11 (2)	12 (2)	10 (2)	12 (2)	11 (2)
	INR, median [IQR]	1.3 [1.1 - 1.8]	1.2 [1.1 - 1.4]	1.3 [1.2 - 2]	1.2 [1.1 - 1.6]	1.6 [1.3 - 2.4]
	Platelets, $x10^9$/L, median [IQR]	190 [133 - 257]	173 [123 - 235]	206 [147 - 280]	209 [153 - 279]	162 [101 - 230]
Neurological						
	Glasgow coma scale score, mean (SD)	13.3 (2.8)	13.7 (2.3)	14.1 (1.8)	12.7 (3.3)	11.6 (4.0)
Other						
	Albumin, g/dL, mean (SD)	3.0 (0.6)	3.4 (0.5)	2.7 (0.6)	3.0 (0.6)	2.8 (0.6)
	Chloride, mEq/L, mean (SD)	104 (6)	105 (6)	103 (6)	104 (7)	106 (7)
	Glucose, mg/dL, median [IQR]	139 [109 - 199]	126 [103 - 170]	145 [111 - 212]	148 [115 - 211]	154 [116 - 220]
	Sodium, mEq/L, mean (SD)	138 (5)	139 (5)	137 (5)	138 (6)	138 (6)
Outcomes						
	Days of mechanical ventilation, median [IQR] [d]	4 [2 - 8]	3 [2 - 6]	4 [2 - 8]	4 [2 - 9]	4 [2 - 9]
	Days of vasopressors, median [IQR] [d]	3 [2 - 5]	2 [2 - 4]	3 [2 - 5]	2 [2 - 4]	3 [2 - 5]
	Admitted to intensive care, no. (%) [d]	14,337 (33%)	2,214 (15%)	3,752 (28%)	4,640 (48%)	3,731 (66%)
	Inpatient mortality, no. (%)	2,666 (6%)	243 (2%)	527 (4%)	763 (8%)	1,133 (20%)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Chinese, Filipino, Hawaiian, American Indian/Alaskan, Asian, Hawaiian/Other Pacific Islander, Middle Eastern, Native American, Not specified, or Pacific Islander

[c] Elixhauser is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 31

[d] At any time during hospitalization

[e] SIRS criteria are a scoring system that measures the inflammatory response, ranging from 0 to 4 points

[f] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

[g] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; EHR: electronic health record; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation; SIRS: systemic inflammatory response syndrome criteria; SOFA: sequential organ failure assessment score

eTable 16. Clinical characteristics by phenotype in the GenIMS cohort study (N=583)

Variable [a, d]	All patients	α-type	ß-type	*y*-type	∂-type
No.	583	118 (20%)	162 (28%)	192 (33%)	111 (19%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	67 (17)	58 (17)	76 (12)	62 (18)	70 (16)
Male gender, no. (%)	329 (56%)	60 (51%)	99 (61%)	96 (50%)	74 (67%)
Race, no. (%) [b]					
White	493 (85%)	99 (84%)	148 (91%)	153 (80%)	93 (84%)
Black	74 (13%)	15 (13%)	8 (5%)	33 (17%)	18 (16%)
Other	16 (3%)	4 (3%)	6 (4%)	6 (3%)	0 (0%)
Charlson Comorbidity Index, mean (SD) [c]	2.3 (2.5)	1.4 (2.1)	3.1 (3.0)	2.0 (2.3)	2.5 (2.3)
Inflammation					
Temperature, °C, mean (SD)	37.9 (1.1)	37.7 (1.0)	37.5 (0.9)	38.4 (1.1)	37.8 (1.2)
White blood cell count, $x10^9$/L, median [IQR]	13 [9 - 17]	11 [8 - 15]	12 [9 - 16]	14 [10 - 19]	16 [11 - 20]
Pulmonary					
Oxygen Saturation, %, median [IQR]	90 [86 - 94]	91 [88 - 95]	92 [88 - 94]	88 [82 - 92]	91 [86 - 95]
PaO_2, mmHg, mean (SD)	85 (64)	65 (17)	76 (47)	69 (25)	128 (105)
Respiratory rate, breaths per min, mean (SD)	28 (8)	24 (4)	24 (4)	31 (8)	32 (8)
Cardiovascular/Hemodynamic					
Heart rate, beats per minute, mean (SD)	109 (23)	104 (17)	93 (16)	119 (20)	117 (26)
Serum lactate, mmol/L, median [IQR]	2.1 [1.6 - 4.1]	3.1 [3.1 - 3.1]	1.6 [1.4 - 3.9]	1.9 [1.3 – 2.0]	4.6 [4.1 - 6.3]
Systolic blood pressure, mmHg, median [IQR]	109 [93 - 125]	123 [109 - 139]	115 [101 - 132]	104 [90 - 117]	90 [75 - 102]
Renal					
BUN, mg/dL, median [IQR]	23 [16 - 34]	14 [11 - 18]	33 [24 - 45]	19 [14 - 27]	31 [22 - 46]
Creatinine, mg/dL, median [IQR]	1.2 [0.9 - 1.7]	0.9 [0.7 - 1.1]	1.5 [1.2 - 2.5]	1.0 [0.8 - 1.3]	1.5 [1.2 - 2.2]
Hepatic					
Bilirubin, mg/dL, median [IQR]	0.6 [0.4 - 0.9]	0.6 [0.5 - 0.8]	0.6 [0.3 - 0.8]	0.5 [0.3 - 0.8]	0.9 [0.5 - 1.7]
Hematologic					
Hemoglobin, g/dL, mean (SD)	13 (2)	14 (2)	12 (2)	12 (2)	13 (2)
INR, median [IQR]	1.2 [1.0 - 1.6]	1.1 [1.0 - 1.2]	1.1 [1.0 - 1.5]	1.2 [1.0 - 1.6]	1.3 [1.1 - 2.2]
Platelets, $x10^9$/L, median [IQR]	249 [193 - 323]	261 [204 - 324]	242 [187 - 321]	262 [205 - 337]	226 [161 - 315]
Neurological					
Glasgow Coma Scale score, mean (SD)	14.3 (2.0)	14.7 (1.0)	14.7 (0.8)	14.8 (0.9)	12.5 (3.8)

Other						
	Albumin, g/dL, mean (SD)	3.3 (0.6)	3.8 (0.5)	3.4 (0.7)	3.1 (0.6)	3.1 (0.6)
	Glucose, mg/dL, median [IQR]	126 [105 - 160]	121 [101 - 139]	132 [109 - 181]	125 [105 - 155]	132 [108 - 176]
	Sodium, mEq/L, mean (SD)	137 (5)	137 (5)	137 (5)	135 (5)	139 (6)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Asian, Oriental, Pacific Islander, Hispanic origin, Other, or Unknown from case report form

[c] Charlson is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24

[d] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all except race, $p=0.08$

Abbreviations: BUN: blood urea nitrogen; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation

eTable 17. Clinical characteristics by phenotype in the ACCESS randomized trial (N=1,706)

Variable [a, d]	All patients	α-type	ß-type	*y*-type	*∂*-type
No.	1,706	466 (27%)	473 (28%)	471 (28%)	296 (17%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	66 (15)	63 (16)	72 (11)	63 (16)	65 (16)
Male gender, no. (%)	1,003 (59%)	286 (61%)	290 (61%)	246 (52%)	181 (61%)
Race, no. (%) [b]					
White	1,360 (80%)	378 (81%)	365 (77%)	379 (80%)	238 (80%)
Black	105 (6%)	19 (4%)	37 (8%)	32 (7%)	19 (6%)
Other	241 (14%)	69 (15%)	71 (15%)	60 (13%)	41 (13%)
Charlson Comorbidity Index, mean (SD) [c]	2.6 (2.5)	1.8 (2.0)	4.1 (2.7)	2.0 (2.0)	2.3 (2.5)
Inflammation					
Bands, %, median [IQR]	16 [7 - 28]	10 [7 - 20]	13 [6 - 24]	25 [14 - 33]	24 [12 - 31]
Temperature, °C, mean (SD)	37.3 (1.2)	37.3 (1.1)	36.9 (1.1)	37.7 (1.1)	37.0 (1.4)
Pulmonary					
Respiratory rate, breaths per min, mean (SD)	22 (8)	20 (6)	20 (6)	26 (11)	24 (7)
Cardiovascular/Hemodynamic					
Bicarbonate, mEq/L, mean (SD)	18 (5)	21 (5)	18 (5)	18 (5)	15 (4)
Heart rate, beats per minute, mean (SD)	103 (22)	96 (19)	92 (19)	115 (20)	111 (22)
Systolic blood pressure, mmHg, median [IQR]	110 [97 - 125]	116 [102 - 132]	114 [100 - 129]	104 [93 - 116]	104 [91 - 118]
Renal					
BUN, mg/dL, median [IQR]	13 [8 - 19]	9 [6 - 11]	19 [14 - 26]	10 [7 - 14]	15 [12 - 21]
Creatinine, mg/dL, median [IQR]	1.8 [1.1 - 2.7]	1.2 [0.8 - 1.7]	2.7 [2.0 - 3.7]	1.3 [0.9 – 2.0]	2.4 [1.7 - 3.4]
Hepatic					
ALT, U/L, median [IQR]	32 [18 - 70]	32 [20 - 53]	24 [14 - 44]	24 [15 - 41]	194 [96 - 646]
AST, U/L, median [IQR]	53 [29 - 123]	46 [27 - 84]	40 [23 - 74]	44 [28 - 72]	347 [180 - 1134]
Bilirubin, mg/dL, median [IQR]	0.7 [0.4 - 1.3]	0.6 [0.4 - 1.1]	0.5 [0.3 - 0.9]	0.7 [0.4 - 1.2]	1.3 [0.7 - 2.6]
Hematologic					
Hemoglobin, g/dL, mean (SD)	11 (2)	12 (2)	10 (2)	10 (2)	11 (2)
Platelets, $x10^9$/L, median [IQR]	181 [115 - 258]	180 [121 - 249]	201 [132 - 271]	200 [123 - 311]	127 [77 - 185]
Other					
Albumin, g/dL, mean (SD)	2.3 (0.6)	2.7 (0.5)	2.3 (0.6)	2.0 (0.5)	2.2 (0.6)
Chloride, mEq/L, mean (SD)	106 (8)	106 (8)	106 (8)	105 (7)	106 (7)

	Glucose, mg/dL, median [IQR]	139 [108 - 187]	139 [114 - 180]	141 [108 - 196]	130 [103 - 173]	144 [106 - 205]
	Sodium, mEq/L, mean (SD)	139 (7)	140 (7)	140 (7)	138 (6)	140 (6.3)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to Asian non-Japanese, Japanese, and Other from care report form

[c] Charlson is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24

[d] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all except race, $p=0.28$ and chloride, $p=0.75$

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; SD: standard deviation

eTable 18. Clinical characteristics by phenotype in the PROWESS randomized trial (N=1,690)

Variable [a, d]	All patients	α-type	ß-type	*y*-type	∂-type
No.	1,690	496 (29%)	445 (26%)	498 (29%)	251 (15%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	61 (17)	55 (18)	69 (12)	59 (16)	59 (17)
Male gender, no. (%)	964 (57%)	302 (61%)	256 (58%)	252 (51%)	154 (61%)
Race, no. (%) [b]					
White	1,384 (82%)	416 (84%)	380 (85%)	394 (80%)	194 (77%)
Black	131 (8%)	28 (6%)	33 (7%)	43 (9%)	27 (11%)
Other	175 (10%)	52 (10%)	32 (7%)	61 (12%)	30 (12%)
Total Comorbidity, mean (SD) [c]	1.3 (1.2)	0.9 (1.1)	2.0 (1.2)	1.0 (1.0)	1.1 (1.1)
Inflammation					
Bands, %, median [IQR]	1 [1 - 3]	1 [0 - 1]	1 [0 - 2]	2 [1 - 4]	2 [1 - 4]
Temperature, °C, mean (SD)	38.2 (1.7)	38.2 (1.5)	37.5 (1.9)	38.7 (1.4)	38.4 (1.8)
White blood cell count, $x10^3$/L, median [IQR]	14 [9 - 20]	11 [7 - 16]	13 [8 - 20]	17 [10 - 24]	16 [10 - 23]
Pulmonary					
Oxygen Saturation, %, median [IQR]	95 [91 - 97]	95 [91 - 97]	96 [92 - 98]	93 [89 - 96]	95 [92 - 98]
PaO_2, mmHg, mean (SD)	94 (66)	87 (54)	107 (80)	79 (38)	114 (88)
Respiratory rate, breaths per min, mean (SD)	31 (12)	29 (12)	26 (11)	36 (12)	33 (12)
Cardiovascular/Hemodynamic					
Heart rate, beats per minute, mean (SD)	130 (28)	127 (25)	115 (30)	143 (21)	135 (28)
Systolic blood pressure, mmHg, median [IQR]	80 [70 - 95]	90 [75 - 113]	80 [70 - 96]	77 [66 - 88]	75 [64 - 88]
Renal					
BUN, mg/dL, median [IQR]	10 [6 - 15]	6 [4 - 9]	16 [12 - 23]	9 [6 - 12]	15 [10 - 20]
Creatinine, mg/dL, median [IQR]	1.3 [0.9 – 2.0]	0.9 [0.7 - 1.2]	1.9 [1.4 – 3.0]	1.1 [0.8 - 1.6]	2.0 [1.3 - 3.3]
Hepatic					
ALT, U/L, median [IQR]	28 [16 - 55]	26 [17 - 45]	20 [13 - 33]	25 [16 - 40]	149 [82 - 424]
AST, U/L, median [IQR]	43 [24 - 93]	37 [23 - 66]	31 [21 - 52]	43 [26 - 71]	277 [145 - 702]
Bilirubin, mg/dL, median [IQR]	0.7 [0.4 - 1.3]	0.7 [0.4 - 1.1]	0.6 [0.4 – 1.0]	0.6 [0.4 - 1.1]	1.4 [0.6 - 3.2]
Hematologic					
Hemoglobin, g/dL, mean (SD)	11 (2)	12 (2)	10 (2)	10 (2)	11 (2)
Platelets, $x10^9$/L, median [IQR]	168 [105 - 240]	159 [106 - 225]	182 [125 - 269]	186 [123 - 264]	107 [60 - 180]
Neurological					

	Glasgow Coma Scale score, mean (SD)	12.8 (3.1)	12.5 (3.3)	12.9 (2.9)	13.4 (2.6)	11.8 (3.5)
Other						
	Albumin, g/dL, mean (SD)	2.0 (0.6)	2.4 (0.6)	2.0 (0.6)	1.7 (0.5)	2.0 (0.6)
	Chloride, mEq/L, mean (SD)	106 (7)	106 (7)	106 (8)	106 (7)	107 (8)
	Glucose, mg/dL, median [IQR]	146 [115 - 198]	139 [115 - 178]	159 [119 - 220]	144 [112 - 198]	150 [114 - 222]
	Sodium, mEq/L, mean (SD)	139 (6)	139 (6)	139 (7)	138 (6)	140 (7)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Other race corresponds to East/Southeast Asian, Western Asian, Hispanic, or Other from care report form

[c] Comorbidities were categorized from the case report form and approximated to the categories of the Charlson comorbidity index. Charlson is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24

[d] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all except chloride, $p=0.02$, and race, $p=0.01$

Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; PaO_2: partial pressure of oxygen; SD: standard deviation

eTable 19. Clinical characteristics by phenotype in the ProCESS randomized trial (N=1,341)

Variable [a, d]	All patients	α-type	ß-type	*y*-type	∂-type
No.	1,341	430 (32%)	340 (25%)	353 (26%)	218 (16%)
Demographics and Burden of Organ Dysfunction					
Age, years, mean (SD)	61 (16)	57 (16)	66 (14)	58 (15)	63 (15)
Male gender, no. (%)	748 (56%)	225 (52%)	208 (61%)	186 (53%)	129 (59%)
Race, no. (%) [b]					
White	916 (68%)	310 (72%)	231 (68%)	239 (68%)	136 (62%)
Black	333 (25)	88 (6%)	92 (27%)	84 (24%)	69 (32%)
Other	92 (7%)	32 (7%)	17 (5%)	30 (8%)	13 (6%)
Charlson Comorbidity Index, mean (SD) [c]	2.7 (2.6)	1.8 (2.0)	4.1 (3.0)	2.4 (2.4)	2.6 (2.5)
Inflammation					
Bands, %, mean (SD)	12 [4 - 22]	6 [1 - 16]	8 [1.6 - 18]	15 [7 - 25]	20 [10 - 32]
Temperature, °C, mean (SD)	37.4 (1.6)	37.5 (1.4)	36.8 (1.6)	38.0 (1.3)	36.8 (1.8)
White blood cell count, $x10^9$/L, mean (SD)	14 [8 - 20]	13 [8 - 18]	15 [9 - 21]	15 [9 - 21]	15 [10 - 22]
Pulmonary					
Oxygen Saturation, %, mean (SD)	97 [94 - 99]	97 [95 - 99]	98 [95 - 100]	96 [92 - 98]	97 [92 - 100]
PaO_2, mmHg, mean (SD)	118 (93)	98 (68)	122 (104)	99 (66)	160 (116)
Respiratory rate, breaths per min., mean (SD)	23 (7)	21 (5)	20 (5)	25 (8)	25 (9)
Cardiovascular/Hemodynamic					
Heart rate, beats per minute, mean (SD)	111 (24)	112 (23)	95 (21)	123 (21)	116 (23)
Serum lactate, mmol/L, mean (SD)	4.4 [2.5 – 6.0]	4.2 [2.1 - 5.3]	3.6 [1.9 – 5.0]	4.2 [2.5 - 5.8]	6.9 [4.9 - 9.6]
Systolic blood pressure, mmHg, mean (SD)	94 [81 - 116]	106 [88 - 132]	88 [79 - 106]	91 [78 - 110]	90 [76 - 110]
Renal					
BUN, mg/dL, mean (SD)	27 [18 - 44]	18 [13 - 24]	47 [33 - 68]	24 [17 - 32]	40 [27 - 57]
Creatinine, mg/dL, mean (SD)	1.6 [1.1 - 2.7]	1.1 [0.9 - 1.5]	3.0 [1.9 - 5.1]	1.4 [1.0 – 2.0]	2.3 [1.6 - 3.3]
Hepatic					
Bilirubin, mg/dL, mean (SD)	0.9 [0.5 - 1.5]	0.8 [0.5 - 1.3]	0.7 [0.4 - 1.3]	0.8 [0.6 - 1.4]	1.4 [0.8 - 3.2]
Hematologic					
Hemoglobin, g/dL, mean (SD)	12 (3)	13 (2)	11 (2)	11 (2)	12 (3)
Platelets, $x10^9$/L, mean (SD)	212 [139 - 293]	204 [154 - 278]	220 [138 - 319]	229 [147 - 323]	175 [98 - 279]
Neurological					
Glasgow Coma Scale score, mean (SD)	13.6 (2.9)	14.1 (2.2)	14.0 (2.2)	14.2 (2.0)	10.9 (4.7)

Other						
	Albumin, g/dL, mean (SD)	3.1 (0.9)	3.7 (0.7)	3.0 (0.8)	2.7 (0.7)	2.6 (0.9)
	Chloride, mEq/L, mean (SD)	100 (8)	100 (6)	100 (9)	99 (7)	103 (9)
	Glucose, mg/dL, mean (SD)	129 [99 - 182]	128 [105 - 168]	126 [100 - 183]	124 [96 - 177]	146 [94 - 210]
	Sodium, mEq/L, mean (SD)	136 (6)	137 (5)	135 (7)	134 (5)	139 (8)

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3
[b] Other race corresponds to Asian, American Indian, Native Alaskan, Native Hawaiian, Other Pacific islander, Unknown, Other from case report form
[c] Charlson is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24
[d] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes, $p<0.01$ for all except gender, $p=0.04$, race, $p=0.19$, and glucose, $p=0.18$
Abbreviations: BUN: blood urea nitrogen; PaO_2: partial pressure of oxygen; SD: standard deviation

eTable 20. Biomarkers measured at baseline in the GenIMS cohort study by phenotype

Variable	All patients	α-type	ß-type	*y*-type	∂-type	P-Value[a]
No.	583	118 (20%)	162 (28%)	192 (33%)	111 (19%)	
Biomarkers						
Antithrombin III, mg/mL, median [IQR]	85 [74 - 97]	91 [84 - 102]	92 [80 - 98]	82 [71 - 95]	79 [62 - 90]	<.01
D-Dimer, ng/mL, median [IQR]	850 [414 - 1621]	444 [253 - 1060]	1093 [616 - 1708]	850 [411 - 1841]	920 [539 - 1725]	<.01
Factor IX, %, median [IQR]	122 [87 - 150]	120 [96 - 143]	123 [95 - 153]	123 [79 - 148]	122 [75 - 151]	0.66
IL-6, pg/mL, median [IQR]	80 [25 - 248]	41 [19 - 150]	52 [20 - 136]	94 [38 - 271]	204 [67 - 541]	<.01
IL-10, pg/mL, median [IQR]	18 [9 - 43]	24 [8 - 56]	13 [9 - 27]	17 [9 - 36]	25 [9 - 65]	0.15
PAI-1, ng/mL, median [IQR]	9 [4 - 19]	9 [4 - 22]	7 [3 - 13]	9 [4 - 15]	13 [7 - 28]	0.03
PCT, ng/mL, median [IQR]	0.40 [0.17 - 2.24]	0.21 [0.15 - 0.69]	0.27 [0.15 - 0.99]	0.59 [0.23 - 2.72]	1.65 [0.43 - 5.72]	<.01
TAT complex, µg/dL, median [IQR]	5.1 [2.4 - 10.8]	3.5 [2.5 - 6.8]	6.7 [2.4 - 14.4]	4.2 [2.3 - 9.6]	8.1 [2.1 - 14.0]	0.14
TNF, pg/mL, median [IQR]	9.8 [6.5 - 18]	7.7 [5.6 - 12.3]	8.8 [7.0 - 17.3]	11.1 [6.3 - 19.2]	12.9 [8.6 - 19.7]	0.01

[a] Kruskal-Wallis, ANOVA, or chi-square p-value, as appropriate, comparing across all 4 phenotypes
Abbreviations: IL: interleukin; IQR: interquartile range; PAI: plasminogen activator inhibitor; PCT: procalcitonin; TAT: thrombin-antithrombin; TNF: tumor necrosis factor

eTable 21. Biomarkers measured at baseline in the ACCESS trial by phenotype

Variable		All patients	α-type	ß-type	*y*-type	*∂*-type	P-Value[a]
No.		1,706	466	473	471	296	
Biomarkers							
	IL-1b, pg/mL, med [IQR]	1.6 [1.6 - 3.3]	1.6 [1.6 - 1.6]	1.6 [1.6 - 1.6]	1.6 [1.6 - 4.3]	1.6 [1.6 - 4.2]	<.01
	IL-6, pg/mL, med [IQR]	1346 [298 - 8789]	604 [189 - 3146]	786 [205 - 6236]	2962 [533 - 10001]	4620 [820 - 100001]	<.01
	IL-8, pg/mL, med [IQR]	299 [116 - 1010]	157 [67 - 502]	236 [98 - 588]	401 [163 - 1980]	665 [299 - 4180]	<.01
	IL-10, pg/mL, med [IQR]	1153 [326 - 4472]	625 [173 - 2077]	770 [231 - 2753]	1506 [461 - 5791]	3887 [1464 - 10001]	<.01
	IL-12, pg/mL, med [IQR]	1.6 [1.6 - 12]	1.6 [1.6 - 12]	1.6 [1.6 - 14]	1.6 [1.6 - 12]	1.6 [1.6 - 11]	>.99
	TNF, pg/mL, med [IQR]	67 [30 - 179]	40 [18 - 102]	70 [34 - 183]	72 [37 - 182]	134 [50 - 300]	<.01
	PCT, ng/mL, med [IQR]	21 [5 - 59]	10 [2 - 36]	20 [4 - 59]	25 [7 - 57]	42 [14 - 104]	<.01

[a] Kruskal-Wallis, ANOVA, or chi-square p-value, as appropriate, comparing across all 4 phenotypes
Abbreviations: IL: interleukin; IQR: interquartile range; PCT: procalcitonin; TNF: tumor necrosis factor

eTable 22. Biomarkers measured at baseline in the PROWESS randomized trial by phenotype

Variable	All patients	α-type	ß-type	*y*-type	*∂*-type	P-Value[a]
No.	1,690	496 (29%)	445 (26%)	498 (29%)	251 (15%)	
Biomarkers						
Antithrombin, mg/mL, median [IQR]	0.59 [0.44 - 0.75]	0.65 [0.52 - 0.80]	0.61 [0.47 - 0.77]	0.56 [0.42 - 0.71]	0.49 [0.35 - 0.66]	<.01
D-dimer, µg/mL, median [IQR]	4.2 [2.2 - 8.3]	3.1 [1.7 - 6.1]	4.4 [2.3 - 7.6]	4.2 [2.4 - 8.2]	8.1 [3.9 - 16.5]	<.01
Factor V, % of normal, median [IQR]	84 [62 - 105]	91 [75 - 111]	86 [62 - 91]	73 [60 - 116]	46 [44 - 85]	0.32
IL-1b, pg/mL, median [IQR]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	10 [10 - 10]	0.40
IL-6, pg/mL, median [IQR]	492 [144 - 2574]	299 [107 - 1445]	415 [124 - 1707]	720 [199 - 3792]	910 [203 - 7350]	<.01
IL-8, pg/mL, median [IQR]	50 [50 - 227]	50 [50 - 155]	50 [50 - 127]	50 [50 - 296]	175 [50 - 1657]	<.01
IL-10, pg/mL, median [IQR]	10 [10 - 41]	10 [10 - 30]	10 [10 - 27]	10 [10 - 41]	38 [10 - 88]	<.01
PAI-1, AU/mL, median [IQR]	34 [20 - 64]	24 [16 - 41]	25 [17 - 40]	38 [24 - 76]	78 [38 - 90]	<.01
Plasminogen activity, %, median [IQR]	61 [49 - 75]	69 [57 - 83]	62 [49 - 80]	58 [48 - 68]	50 [39 - 65]	<.01
Protein C activity, %, median [IQR]	0.48 [0.31 - 0.65]	0.55 [0.39 - 0.71]	0.49 [0.34 - 0.69]	0.45 [0.29 - 0.62]	0.37 [0.24 - 0.50]	<.01
Protein S activity, %, median [IQR]	0.36 [0.22 - 0.57]	0.46 [0.28 - 0.65]	0.35 [0.20 - 0.57]	0.35 [0.22 - 0.55]	0.31 [0.17 - 0.50]	<.01
Prothrombin time, seconds, median [IQR]	19 [17 - 22]	18 [16 - 20]	19 [16 - 21]	19 [17 - 22]	22 [18 - 27]	<.01
Prothrombin fragment 1-2, nmol/L, median [IQR]	1.8 [1.1 - 2.6]	1.5 [1.0 - 2.2]	1.9 [1.2 - 2.9]	1.7 [1.1 - 2.5]	2.2 [1.3 - 3.4]	<.01
TAT complex, µg/dL, median [IQR]	11 [7 - 20]	10 [7 - 18]	11 [7 - 17]	11 [7 - 18]	20 [13 - 33]	<.01
TNF, pg/mL, median [IQR]	21 [10 - 52]	10 [10 - 34]	24 [10 - 42]	24 [10 - 65]	49 [10 - 115]	<.01

[a] Kruskal-Wallis, ANOVA, or chi-square p-value, as appropriate, comparing across all 4 phenotypes
Abbreviations: IL: interleukin; IQR: interquartile range; PAI: plasminogen activator inhibitor, TAT: thrombin-antithrombin; TNF: tumor necrosis factor

eTable 23. Biomarkers measured at baseline in the ProCESS randomized trial by phenotype

Variable	All patients	α-type	ß-type	*y*-type	*∂*-type	P-Value[a]
No.	1,341	430 (32%)	340 (25%)	353 (26%)	218 (16%)	
Biomarkers						
C-Reactive Protein, mg/L, median [IQR]	111 [38 - 221]	82 [10 - 176]	132 [71 - 216]	93 [38 - 230]	97 [68 - 232]	0.22
COL-4, ng/mL, median [IQR]	9.9 [3.7 - 24.2]	6.3 [2.3 - 15.8]	11.6 [3.8 - 28.4]	11.2 [4.3 - 30.2]	18.2 [8.7 - 69.5]	<.01
D-Dimer, µg/mL, median [IQR]	0.5 [0.5 - 1.0]	0.5 [0.5 - 1.0]	0.5 [0.5 - 1.0]	0.5 [0.5 - 1.0]	1 [0.5 - 2]	<.01
E-Selectin, ng/mL, median [IQR]	91 [56 - 200]	107 [67 - 299]	64 [44 - 163]	111 [61 - 269]	86 [63 - 155]	0.01
ICAM, ng/mL, median [IQR]	524 [339 - 876]	422 [292 - 602]	450 [282 - 615]	673 [419 - 1102]	582 [388 - 1182]	<.01
IGFBP-7, ng/mL, median [IQR]	100 [49 - 194]	88 [47 - 184]	91 [47 - 173]	109 [54 - 199]	119 [60 - 232]	<.01
IL-6, pg/mL, median [IQR]	243 [50 - 2366]	131 [34 - 1203]	121 [36 - 771]	456 [102 - 4957]	1091 [180 - 8919]	<.01
IL-10, pg/mL, median [IQR]	19 [13 - 79]	13 [13 - 63]	13 [13 - 44]	32 [13 - 105]	49 [18 - 237]	<.01
KIM-1, ng/mL, median [IQR]	1.7 [0.6 - 3.8]	0.9 [0.4 - 2.4]	2.1 [0.8 - 3.7]	2.6 [0.8 - 4.8]	1.9 [1.1 - 4.5]	<.01
PAI-1, ng/mL, median [IQR]	14 [6 - 28]	14 [5 - 27]	11 [7 - 20]	19 [9 - 34]	22 [9 - 59]	0.03
Prothrombin Fragment 1-2, pmol/L, median [IQR]	324 [194 - 674]	330 [194 - 779]	302 [183 - 549]	445 [268 - 894]	296 [164 - 536]	0.48
P-Selectin, ng/mL, median [IQR]	79 [53 - 119]	76 [57 - 142]	78 [46 - 105]	78 [56 - 119]	91 [64 - 121]	0.37
TAT complex, µg/dL, median [IQR]	12 [5 - 29]	11 [5 - 29]	10 [5 - 26]	12 [6 - 27]	17 [10 - 33]	<.01
TIMP-2, ng/mL, median [IQR]	6.9 [3.6 - 14.3]	5.3 [2.6 - 10.0]	8.2 [3.7 - 18.2]	7.0 [3.9 - 14.8]	9.6 [5.5 - 22.7]	<.01
TNF, pg/mL, median [IQR]	28 [28 - 36]	28 [20 - 28]	28 [28 - 33]	28 [28 - 56]	28 [28 - 86]	<.01
VCAM, ng/mL, median [IQR]	1988 [1076 - 4138]	1371 [820 - 2805]	2066 [1082 - 3629]	2538 [1266 - 4681]	3006 [1582 - 5078]	<.01

[a] Kruskal-Wallis, ANOVA, or chi-square p-value, as appropriate, comparing across all 4 phenotypes
Abbreviations: COL: collagen; ICAM: intercellular adhesion molecule; IGFBP: insulin-like growth factor-binding protein; IL: interleukin; IQR: interquartile range; KIM: kidney injury molecule; PAI: Plasminogen activator inhibitor; TAT: thrombin-antithrombin; TIMP: tissue inhibitor of metalloproteinases; TNF: tumor necrosis factor; VCAM: vascular adhesion molecule

eTable 24. Primary and secondary outcomes by study

Variable	SENECA derivation [a]	SENECA validation [a]	GenIMS	ACCESS	ProWess	ProCESS
Hospital Utilization						
Admitted to ICU, no. (%)	9,063/20,189 (45%)	14,337/43,086 (33%)	224/583 (38%)	1,687/1,706 (99%)	1,679/1,690 (99%)	1,175/1341 (88%)
Days of Mechanical Ventilation, mean (SD)	9 (12)	7 (9)	6 (5)	11 (9)	14 (11)	7 (9)
Days of Vasopressors, mean (SD)	4 (5)	4 (5)	3 (2)	6 (6)	9 (11)	3 (2)
Outcomes						
Inpatient Mortality, no. (%)	2,082/20,189 (10%)	2,666/43,086 (6%)	83/583 (14%)	-	-	259/1,341 (19%)
28-Day Mortality, no. (%)	2,776/16,652 (17%)	3,892/31,160 (12%)	80/583 (14%)	458/1,706 (27%)	469/1,690 (28%)	302/1,341 (23%)
365-Day Mortality, no. (%)	5,771/16,652 (35%)	9,661/31,160 (31%)	-	726/1,706 (43%)	687/1,690 (41%)	0
α-type						
Hospital Utilization						
Admitted to ICU, no. (%)	1,644/6,625 (25%)	2,409/12,485 (19%)	29/118 (25%)	459/466 (99%)	493/496 (99%)	345/430 (80%)
Days of Mechanical Ventilation, mean (SD)	7 (10)	5 (6)	5 (4)	11 (8)	11 (11)	6 (8)
Days of Vasopressors, mean (SD)	3 (4)	3 (3)	3 (2)	5 (5)	5 (9)	2 (1)
Outcomes						
Inpatient Mortality, no. (%)	126/6,625 (2%)	249/12,485 (2%)	7/118 (6%)	-	-	29/430 (7%)
28-Day Mortality, no. (%)	287/5,691 (5%)	837/9,427 (9%)	6/118 (5%)	71/466 (15%)	77/496 (16%)	34/430 (8%)
365-Day Mortality, no. (%)	1,022/5,691 (18%)	2,632/9,427 (28%)	-	130/466 (28%)	121/496 (24%)	94/430 (22%)
β-type						
Hospital Utilization						
Admitted to ICU, no. (%)	1,778/5,512 (32%)	4,144/12,508 (33%)	53/162 (33%)	468/473 (99%)	439/445 (99%)	303/340 (89%)
Days of Mechanical Ventilation, mean (SD)	8 (13)	7 (9)	6 (6)	11 (9)	14 (11)	6 (10)
Days of Vasopressors, mean (SD)	4 (4)	4 (4)	3 (2)	6 (6)	9 (11)	3 (2)
Outcomes						
Inpatient Mortality, no. (%)	286/5,512 (5%)	588/12,508 (5%)	22/162 (14%)	-	-	76/340 (22%)
28-Day Mortality, no. (%)	561/4,420 (13%)	923/8,242 (11%)	20/162 (12%)	130/473 (27%)	149/445 (33%)	94/340 (28%)
365-Day Mortality, no. (%)	1,575/4,420 (36%)	2,487/8,242 (30%)	-	227/473 (48%)	227/445 (51%)	163/340 (48%)

γ-type							
Hospital Utilization							
	Admitted to ICU, no. (%)	3,381/5,385 (63%)	3,320/12,121 (27%)	90/192 (47%)	466/471 (99%)	496/498 (99%)	321/353 (91%)
	Days of Mechanical Ventilation, mean (SD)	11 (14)	7 (8)	8 (6)	11 (9)	15 (11)	7 (10)
	Days of Vasopressors, mean (SD)	5 (5)	3 (3)	3 (3)	6 (6)	9 (11)	2 (2)
Outcomes							
	Inpatient Mortality, no. (%)	818/5,385 (15%)	368/12,121 (3%)	22/192 (11%)	-	-	69/353 (20%)
	28-Day Mortality, no. (%)	1,031/4,318 (24%)	854/9,151 (9%)	22/192 (11%)	134/471 (28%)	138/498 (28%)	78/353 (22%)
	365-Day Mortality, no. (%)	1,944/4,318 (45%)	2,588/9,151 (28%)	-	208/471 (44%)	210/498 (42%)	151/353 (43%)
δ-type							
Hospital Utilization							
	Admitted to ICU, no. (%)	2,260/2,667 (85%)	4,464/5,972 (75%)	52/111 (47%)	294/296 (99%)	251/251 (100%)	206/218 (95%)
	Days of Mechanical Ventilation, mean (SD)	8 (9)	8 (11)	5 (4)	9 (9)	18 (11)	8 (9)
	Days of Vasopressors, mean (SD)	4 (5)	4 (6)	3 (2)	5 (5)	13 (12)	3 (2)
Outcomes							
	Inpatient Mortality, no. (%)	852/2,667 (32%)	1,461/5,972 (24%)	32/111 (29%)	-	-	85/218 (39%)
	28-Day Mortality, no. (%)	897/2,223 (40%)	1,278/4,340 (29%)	32/111 (29%)	123/296 (42%)	105/251 (42%)	96/218 (44%)
	365-Day Mortality, no. (%)	1,230/2,223 (55%)	1,954/4,340 (45%)	-	161/296 (54%)	129/251 (51%)	125/218 (57%)

[a] Fixed time point mortality rates derived from unique patients in SENECA derivation (N=16,552) and validation (N=31,160)

eTable 25. Primary and secondary outcomes by phenotype.

Outcome	All	α-type	ß-type	*y*-type	*∂*-type
In-hospital Mortality, no. (%)					
SENECA derivation	2,082/20,189 (10%)	126/6,625 (2%)	286/5,512 (5%)	818/5,385 (15%)	852/2,667 (32%)
SENECA validation	2,666/43,086 (6%)	249/12,485 (2%)	588/12,508 (5%)	368/12,121 (3%)	1,461/5,972 (24%)
GenIMS	83/583 (14%)	7/118 (6%)	22/162 (14%)	22/192 (11%)	32/111 (29%)
ACCESS	-	-	-	-	-
PROWESS	-	-	-	-	-
ProCESS [a]	259/1,341 (19%)	29/430 (7%)	76/340 (22%)	69/353 (20%)	85/218 (39%)
28-Day Mortality, no. (%) [b]					
SENECA derivation	2,776/16,652 (17%)	287/5,691 (5%)	561/4,420 (13%)	1,031/4,318 (24%)	897/2,223 (40%)
SENECA validation	3,892/31,160 (12%)	837/9,427 (9%)	923/8,242 (11%)	854/9,151 (9%)	1,278/4,340 (29%)
GenIMS	80/583 (14%)	6/118 (5%)	20/162 (12%)	22/192 (11%)	32/111 (29%)
ACCESS	458/1,706 (27%)	71/466 (15%)	130/473 (27%)	134/471 (28%)	123/296 (42%)
PROWESS	469/1,690 (28%)	77/496 (16%)	149/445 (33%)	138/498 (28%)	105/251 (42%)
ProCESS	302/1,341 (23%)	34/430 (8%)	94/340 (28%)	78/353 (22%)	96/218 (44%)
365-Day Mortality, no. (%) [b]					
SENECA derivation	5,771/16,652 (35%)	1,022/5,691 (18%)	1,575/4,420 (36%)	1,944/4,318 (45%)	1,230/2,223 (55%)
SENECA validation	9,661/31,160 (31%)	2,632/9,427 (28%)	2,487/8,242 (30%)	2,588/9,151 (28%)	1,954/4,340 (45%)
GenIMS	-	-	-	-	-
ACCESS	726/1,706 (43%)	130/466 (28%)	227/473 (48%)	208/471 (44%)	161/296 (54%)
PROWESS	687/1,690 (41%)	121/496 (24%)	227/445 (51%)	210/498 (42%)	129/251 (51%)
ProCESS	533/1,341 (40%)	94/430 (22%)	163/340 (48%)	151/353 (43%)	125/218 (57%)
Admission to Intensive Care Unit, no. (%)					
SENECA derivation	9,063/20,189 (45%)	1,644/6,625 (25%)	1,778/5,512 (32%)	3,381/5,385 (63%)	2,260/2,667 (85%)
SENECA validation	14,337/43,086 (33%)	2,409/12,485 (19%)	4,144/12,508 (33%)	3,320/12,121 (27%)	4,464/5,972 (75%)
GenIMS	224/583 (38%)	29/118 (25%)	53/162 (33%)	90/192 (47%)	52/111 (47%)
ACCESS	1,687/1,706 (99%)	459/466 (99%)	468/473 (99%)	466/471 (99%)	294/296 (99%)
PROWESS	1,679/1,690 (99%)	493/496 (99%)	439/445 (99%)	496/498 (99%)	251/251 (100%)
ProCESS	1,175/1,341 (88%)	345/430 (80%)	303/340 (89%)	321/353 (91%)	206/218 (95%)
Days of Mechanical Ventilation, mean (SD) [c]					
SENECA derivation	9 (12)	7 (10)	8 (13)	11 (14)	8 (9)
SENECA validation	7 (9)	5 (6)	7 (9)	7 (8)	8 (11)
GenIMS	6 (5)	5 (4)	6 (6)	8 (6)	5 (4)
ACCESS	11 (9)	11 (8)	11 (9)	11 (9)	9 (9)
PROWESS	14 (11)	11 (11)	14 (11)	15 (11)	18 (11)
ProCESS	7 (9)	6 (8)	6 (10)	7 (10)	8 (9)

Days of Vasopressors, mean (SD) [c]						
	SENECA derivation	4 (5)	3 (4)	4 (4)	5 (5)	4 (5)
	SENECA validation	4 (5)	3 (3)	4 (4)	3 (3)	4 (6)
	GenIMS	3 (2)	3 (2)	3 (2)	3 (3)	3 (2)
	ACCESS	6 (6)	5 (5)	6 (6)	6 (6)	5 (5)
	PROWESS	9 (11)	5 (9)	9 (11)	9 (11)	13 (12)
	ProCESS	3 (2)	2 (1)	3 (2)	2 (2)	3 (2)

[a] In-hospital mortality corresponds to 60-day inpatient mortality for the ProCESS trial
[b] Fixed time point mortality rates among unique SENECA derivation (N=16,554) and validation (N=31,160)
[c] Day of organ support truncated at first 28d for PROWESS trial and first 7d for ProCESS

eTable 26. Baseline characteristics of trial populations at the upper limits of the simulation in ACCESS trial (N=1,706)

Variable	Original	Scenario with ∂ = 44%	Scenario with α = 100%
Age, years, mean (SD)	66 (15)	66 (16)	63 (16)
Male gender, no. (%)	1,003 (59%)	992 (58%)	1,062 (62%)
Charlson Comorbidity Index score, mean (SD)[a]	2.6 (2.5)	2.7 (2.5)	1.8 (2.0)
Vitals and laboratory values			
Systolic blood pressure, mean (SD)	112 (22)	109 (22)	118 (23)
Respiratory rate, mean (SD)	22 (8)	23 (9)	20 (6)

[a] Charlson is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24

Abbreviations: SD: standard deviation; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment

Interpretive example: In simulated changes of the ACCESS trial population to the frequency of ∂- and α –types, the mean baseline characteristics modestly change and are within the range seen in many contemporary RCTs in sepsis, such as LeoPARDS, VANISH, and ADRENAL trials.[16,18,19]

eTable 27. Baseline characteristics of trial populations at the upper limits of the simulation in PROWESS trial (N=1,690)

Variable	Original	Scenario with ∂ = 44%	Scenario with α = 100%
Age, years, mean (SD)	61 (17)	62 (15)	56 (18)
Male gender, no. (%)	964 (57%)	967 (57%)	1,026 (61%)
Total comorbidities, mean (SD)	1.3 (1.2)	1.4 (1.2)	0.9 (1.1)
SIRS criteria at baseline, mean (SD)[a]	3.6 (0.5)	3.6 (0.5)	3.6 (0.5)
SOFA score at baseline, mean (SD)[b]	7.8 (2.8)	8.6 (2.9)	6.5 (2.5)
Vitals and laboratory values			
Systolic blood pressure, mean (SD)	88 (32)	81 (25)	102 (40)
Respiratory rate, mean (SD)	32 (12)	31 (12)	29 (12)

[a] SIRS criteria are a scoring system that measures the inflammatory response, ranging from 0 to 4 points

[b] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

Abbreviations: SD: standard deviation; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment

Interpretive example: In simulated changes of the PROWESS trial population to the frequency of ∂- and α –types, the mean baseline characteristics modestly change and are within the range seen in many contemporary RCTs in sepsis, such as LeoPARDS, VANISH, and ADRENAL trials.[16,18,19]

eTable 28. Baseline characteristics of trial populations at the upper limits of the simulation in ProCESS trial (N=895)

Variable	Original	Scenario with ∂ = 44%	Scenario with α = 100%
Age, years, mean (SD)	61 (16)	62 (16)	58 (17)
Male gender, no. (%)	496 (55%)	527 (59%)	480 (54%)
Charlson Comorbidity Index score, mean (SD)[a]	2.7 (2.6)	3.1 (2.8)	1.8 (2.0)
SOFA score at baseline, mean (SD)[b]	7.2 (3.6)	8.6 (3.6)	5.2 (2.9)
Vitals and laboratory values			
Serum lactate, mean (SD)	4.8 (3.2)	5.9 (3.9)	4.1 (2.2)
Systolic blood pressure, mean (SD)	100 (29)	96 (26)	114 (31)
Respiratory rate, mean (SD)	23 (7)	24 (7)	22 (6)

[a] Charlson is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24

[b] SOFA score corresponds to the severity of organ dysfunction, reflecting six organ systems each with a score range of 0 to 4 points (cardiovascular, hepatic, hematologic, respiratory, neurological, renal), with a total score range of 0 to 24 points

Abbreviations: SD: standard deviation; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment

Interpretive example: In simulated changes of the PROWESS trial population to the frequency of ∂- and α –types, the mean baseline characteristics modestly change and are within the range seen in many contemporary RCTs in sepsis, such as LeoPARDS, VANISH, and ADRENAL trials.[16,18,19]

eTable 29. Control group mortality rate for changes in phenotype distributions shown in Figure 5.

Simulation	Average mortality rate (%) in 10,000 iterations		
	ACCESS [placebo arm]	**PROWESS [placebo arm]**	**ProCESS [usual care arm]**
α-type frequency (%)			
0	31.6	38.9	26.7
24	28.5	31.2	20.3
Baseline	26	30.9	18.8
46	24.1	22	16.4
100	15.2	13.7	8.6
∂-type frequency (%)			
0	15.2	13.7	8.6
5	23.3	17.5	11.7
Baseline	26	30.9	18.8
23	27.1	33.4	20.2
44	31.6	38.9	25.9

Interpretive example: In 3 large RCTs, a simulated increase in *∂*-type and decrease in α-type had modest effects on outcomes rates of the control group. For example, when *∂*-type was doubled to 44% of the trial population in ProCESS, the usual care arm mortality increased from 19% to 26%. The changes in control group outcomes rates were more substantial when simulations decreased *∂*-type or increased α-type from the baseline frequency in the trial. All changes are within the range of control group mortality rates seen in many contemporary RCTs.[15-19]

eTable 30. Site of infection by phenotype in the ACCESS trial (N=1,706)

Variable	All patients	α-type	ß-type	*y*-type	*∂*-type	P-Value[a]
No.	1,706	466 (27%)	473 (28%)	471 (28%)	296 (17%)	
Number of infected sites, mean (SD)	1.2 (0.4)	1.1 (0.3)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	<.01
Site of infection, no. (%)						
Lung	849 (50%)	278 (60%)	211 (45%)	253 (54%)	107 (36%)	<.01
Primary bloodstream	52 (3%)	11 (2%)	9 (2%)	14 (3%)	18 (6%)	0.01
Genitourinary	364 (21%)	77 (17%)	152 (32%)	72 (15%)	63 (21%)	<.01
Abdomen	394 (23%)	61 (13%)	104 (22%)	121 (26%)	108 (36%)	<.01
Skin/Soft tissue	146 (9%)	28 (6%)	44 (9%)	47 (10%)	27 (9%)	0.14
Central nervous system	41 (2%)	29 (6%)	1 (0.2%)	6 (1%)	5 (2%)	<.01
Cather-related bacteremia	38 (2%)	8 (2%)	13 (3%)	14 (3%)	3 (1%)	0.23
Other	99 (6%)	18 (4%)	28 (6%)	34 (7%)	19 (6%)	0.16

[a] Kruskal-Wallis, ANOVA, or chi-square p-value, as appropriate
Abbreviations: SD: standard deviation

eTable 31. Clinical characteristics by quartile of APACHE 3 score at enrollment in the ProCESS randomized trial (N=1,341)

Variable [a]	All patients	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value [b]
No.	1,341	359 (27%)	332 (25%)	331 (25%)	319 (24%)	
Demographics and Burden of Organ Dysfunction						
Age, years, mean (SD)	61 (16)	56 (16)	58 (15)	63 (14)	66 (15)	<0.01
Male gender, no. (%)	748 (56%)	198 (55%)	183 (55%)	196 (59%)	171 (54%)	0.51
Race, no. (%) [c]						0.20
White	916 (68%)	252 (70%)	223 (67%)	236 (71%)	205 (64%)	
Black	333 (25)	77 (22%)	87 (26%)	73 (22%)	96 (30%)	
Other	92 (7%)	30 (8%)	22 (7%)	22 (7%)	18 (6%)	
Charlson Comorbidity Index, mean (SD) [d]	2.7 (2.6)	2.0 (2.2)	2.3 (2.6)	2.8 (2.6)	3.6 (2.9)	<0.01
Inflammation						
Bands, %, median [IQR]	12 [4 - 22]	10 [2 - 23]	12 [4 - 22]	14 [4 - 23]	14 [5 - 22]	0.23
Temperature, °C, mean (SD)	37.4 (1.6)	37.5 (1.2)	37.4 (1.4)	37.4 (1.4)	37.1 (2.2)	0.27
White blood cell count, $x10^9$/L, median [IQR]	14 [8 - 20]	14 [9 - 20]	15 [9 - 21]	14 [8 - 19]	14 [8 - 21]	0.25
Pulmonary						
Oxygen Saturation, %, median [IQR]	97 [94 - 99]	97 [94 - 99]	97 [95 - 99]	97 [94 - 99]	97 [92 - 100]	0.84
PaO_2, mmHg, mean (SD)	118 (93)	106 (80)	108 (74)	108 (80)	140 (113)	0.03
Respiratory rate, breaths per min, mean (SD)	23 (7)	23 (6)	22 (6)	22 (7)	24 (8)	0.01
Cardiovascular/Hemodynamic						
Heart rate, beats per minute, mean (SD)	111 (24)	110 (22)	110 (22)	111 (24)	114 (28)	0.02
Serum lactate, mmol/L, median [IQR]	4.4 [2.5 – 6.0]	4.2 [2.1 - 5.4]	4.1 [2.1 - 5.6]	4.4 [2.8 - 5.8]	5.0 [3.5 - 7.7]	<0.01
Systolic blood pressure, mmHg, median [IQR]	94 [81 - 116]	99 [85 - 124]	90 [81 - 112]	92 [80 - 111]	96 [78 - 118]	<0.01
Renal						
BUN, mg/dL, median [IQR]	27 [18 - 44]	22 [15 - 37]	26 [18 - 41]	28 [19 - 44]	33 [21 - 52]	<0.01
Creatinine, mg/dL, median [IQR]	1.6 [1.1 - 2.7]	1.4 [1.0 - 2.2]	1.7 [1.1 - 2.7]	1.6 [1.1 - 2.8]	1.9 [1.2 – 3.0]	<0.01
Hepatic						
Bilirubin, mg/dL, median [IQR]	0.9 [0.5 - 1.5]	0.8 [0.5 - 1.4]	0.8 [0.5 - 1.4]	1.0 [0.6 - 1.5]	0.9 [0.5 - 1.9]	0.02
Hematologic						
Hemoglobin, g/dL, mean (SD)	12 (3)	12 (3)	12 (2)	11 (3)	11 (3)	<0.01
Platelets, $x10^9$/L, median [IQR]	212 [139 - 293]	216 [158 - 290]	202 [140 - 279]	216 [136 - 314]	211 [119 - 309]	0.31
Neurological						

	Glasgow Coma Scale score, mean (SD)	13.6 (2.9)	14.5 (1.3)	14.6 (1.2)	14.1 (2.0)	11.0 (4.5)	<0.01
Other							
	Albumin, g/dL, mean (SD)	3.1 (0.9)	3.4 (0.8)	3.2 (0.9)	3.0 (0.8)	2.7 (0.9)	<0.01
	Chloride, mEq/L, mean (SD)	100 (8)	99 (7)	100 (8)	100 (8)	102 (9)	<0.01
	Glucose, mg/dL, median [IQR]	129 [99 - 182]	129 [104 - 186]	128 [99 - 176]	128 [98 - 172]	132 [94 - 195]	0.70
	Sodium, mEq/L, mean (SD)	136 (6)	136 (6)	136 (6)	135 (6)	137 (8)	0.17
Outcomes							
	Admitted to intensive care, no. (%) [e]	1,175 (88%)	277 (77%)	294 (89%)	300 (91%)	304 (95%)	<0.01
	60-day Inpatient Mortality, no. (%)	259 (19%)	38 (11%)	36 (11%)	64 (19%)	121 (38%)	<0.01
	365-Day Mortality, no. (%)	533 (40%)	88 (25%)	97 (29%)	138 (42%)	210 (66%)	<0.01

[a] Corresponds to minimum or maximum value, as appropriate, within 6 hours of presentation, variables log transformed for modeling as shown in eTable 3

[b] Kruskal-Wallis, ANOVA, or chi-square p-value as appropriate comparing across all four phenotypes

[c] Other race corresponds to Asian, American Indian, Native Alaskan, Native Hawaiian, Other Pacific islander, Unknown, Other from case report form

[d] Charlson is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, ranging from 0 to 24

[e] At any time during hospitalization

Abbreviations: BUN: blood urea nitrogen; PaO_2: partial pressure of oxygen; SD: standard deviation

eTable 32. Biomarkers of the host immune response by quartile of APACHE 3 score at enrollment in the ProCESS randomized trial (N=1,341)

Variable	All patients	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-Value[a]
No.	1,341	430 (32%)	340 (25%)	353 (26%)	218 (16%)	
Biomarkers						
D-Dimer, µg/mL, median [IQR]	0.5 [0.5 - 1.0]	0.5 [0.5 - 1.0]	0.5 [0.5 - 1.0]	0.5 [0.5 - 1.0]	0.5 [1.0 - 2.0]	<0.01
E-Selectin, ng/mL, median [IQR]	91 [56 - 200]	118 [56 - 255]	107 [53 - 248]	89 [59 - 194]	77 [54 - 153]	0.38
ICAM, ng/mL, median [IQR]	524 [339 - 876]	516 [324 - 684]	458 [297 - 935]	528 [354 - 732]	558 [351 - 928]	0.87
IL-6, pg/mL, median [IQR]	243 [50 - 2366]	130 [34 - 679]	273 [41 - 3003]	307 [59 - 5136]	386 [89 - 3783]	<0.01
IL-10, pg/mL, median [IQR]	19 [13 - 79]	13 [13 - 53]	13 [13 - 69]	20 [13 - 134]	36 [13 - 145]	<0.01
PAI-1, ng/mL, median [IQR]	14 [6 - 28]	14 [7 - 24]	10 [5 - 22]	17 [7 - 28]	17 [9 - 53]	0.02
Prothrombin Fragment 1-2, pmol/L, median [IQR]	324 [194 - 674]	476 [268 - 834]	307 [183 - 548]	277 [111 - 639]	357 [242 - 722]	0.21
P-Selectin, ng/mL, median [IQR]	79 [53 - 119]	98 [60 - 129]	72 [48 - 98]	78 [53 - 122]	81 [57 - 122]	0.19
TAT complex, µg/dL, median [IQR]	12 [5 - 29]	11 [5 - 28]	10 [5 - 27]	11 [5 - 28]	16 [9 - 37]	<0.01
TNF, pg/mL, median [IQR]	28 [28 - 36]	28 [20 - 28]	28 [28 - 33]	28 [28 - 56]	28 [28 - 86]	<.01
C-Reactive Protein, mg/L, median [IQR]	111 [38 - 221]	107 [30 - 238]	151 [65 - 219]	86 [28 - 221]	105 [46 - 259]	0.61
VCAM, ng/mL, median [IQR]	1988 [1076 - 4138]	1810 [908 - 2990]	1735 [1058 - 3467]	1890 [1332 - 4138]	3006 [1082 - 5198]	0.05

[a] Kruskal-Wallis, ANOVA, or chi-square p-value, as appropriate, comparing across quartiles
Abbreviations: ICAM: intercellular adhesion molecule; IL: interleukin; PAI: plasminogen activator inhibitor; TAT: thrombin-antithrombin; TNF: tumor necrosis factor; VCAM: vascular adhesion molecule

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