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STATE-OF-THE-ART REVIEW

CRITICAL CARE CARDIOLOGY

Machine Learning Approaches for Phenotyping in Cardiogenic Shock and Critical Illness

Part 2 of 2

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ABSTRACT

Progress in improving cardiogenic shock (CS) outcomes may have been limited by failure to embrace the heterogeneity of pathophysiologic processes driving the underlying syndrome. To better understand the variability inherent to CS populations, recent algorithms for describing underlying CS disease subphenotypes have been described and validated. These strategies hope to identify specific patient subgroups with more favorable responses to standard therapies, as well as those who require novel treatment approaches. This paper is part 2 of a 2-part state-of-the-art review. In this second article, we present machine learning-based statistical approaches to identifying subphenotypes and discuss their strengths and limitations, as well as evidence from other critical illness syndromes and emerging applications in CS. We then discuss how staging and stratification may be considered in CS clinical trials and finally consider future directions for this emerging area of research. (JACC Adv 2022;1:100126) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cardiogenic shock (CS) remains associated with a high risk of short-term mortality despite a contemporary therapy.[1-4] CS is heterogeneous in its underlying etiologies, clinical manifestations, disease severity, and outcomes, yet traditional methods for stratification (eg, hemodynamic profiling using a pulmonary artery catheter) have not consistently improved outcomes.[1,3-7]

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AIC = Akaike information criterion

AMI = acute myocardial infarction

ARDS = acute respiratory distress syndrome

BIC = Bayesian information criterion

CA = cardiac arrest

CS = cardiogenic shock

CSWG = Cardiogenic Shock Working Group

HC = hierarchical clustering

HTE = heterogeneity of treatment effect

KMC = k-means clustering

LCA = latent class analysis

MCS = mechanical circulatory support

RCT = randomized controlled trial

SCAI = Society for Cardiovascular Angiography and Intervention

Randomized clinical trials (RCTs) enrolling CS patients may have failed to demonstrate incremental benefits due to an incomplete consideration of patient heterogeneity and diverse subgroups within the CS population.[2,8] The Society for Cardiovascular Angiography and Intervention (SCAI) Shock Classification is a streamlined approach for describing the severity of CS to facilitate clinical care and guide research.[5,6,9] The SCAI Shock Classification has demonstrated robust mortality risk stratification in patients with or at risk of CS, and "risk modifiers" have been identified that are independently associated with mortality across the spectrum of CS severity.[6,10-14] The heterogeneity of CS populations extends beyond illness severity and mortality risk factors, and a 3-axis model describing different aspects of CS patient presentations was proposed in the revised SCAI Shock Classification.[6,9] This model incorporates the different clinical phenotypes observed in patients with CS, which could provide insights into underlying disease mechanisms, targeted therapies, and individualized care.[15,16]

The limitations of traditional treatment approaches for improving outcomes in CS populations have spurred increased interest in personalized medicine, whereby subgroups in a population can be selectively targeted based on anticipated treatment response.[2] The terminology used to describe subgroups within a population has not been fully standardized.[17] Phenotypes broadly refer to clinically apparent traits that differ between groups, while subphenotypes imply a biological or mechanistic underpinning typically identified using biomarkers. Within CS populations, phenotypes have been defined clinically based on the triggering etiology or the pattern of ventricular dysfunction or congestion, while subphenotypes have been identified based on commonly available laboratory values.[4,14-16,18] When there is a specific biomarker profile implicating a disease pathway in a subphenotype that identifies a unique treatment response, this can be called a treatable trait.

In part 1 of this 2-part state-of-the-art review series, we reviewed the clinical context and rationale for staging and phenotyping in CS.[9] In part 2, we review the methodological considerations associated with using unsupervised machine learning (ML) algorithms to perform subphenotyping and then explore how these methods have been applied in patients with cardiovascular diseases and critical illnesses, including CS.

HIGHLIGHTS

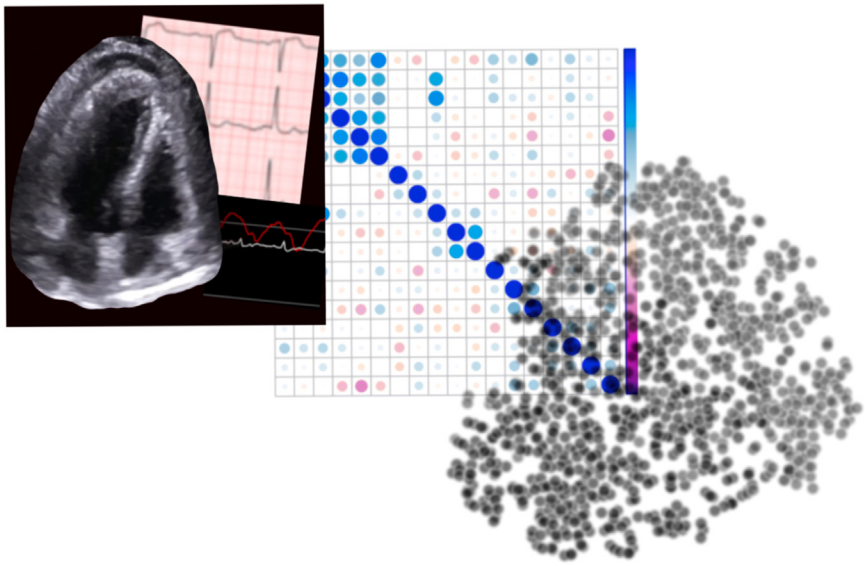
- Unsupervised machine learning can detect subgroups in heterogeneous syndromes.
- Hierarchical clustering, latent class analysis, and k-mean clustering are effective.
- Clustering can classify subphenotypes in critical illnesses including cardiogenic shock.
- Subphenotyping can facilitate precision medicine by matching treatment to patient.
- Heterogeneity of treatment effect may exist between subphenotypes in a population.

METHODS FOR IDENTIFYING DISEASE SUBTYPES

As with CS, the pathophysiology of other common critical illness syndromes (eg, acute respiratory distress syndrome [ARDS] or sepsis) is complex and incompletely understood, with substantial heterogeneity even among populations meeting standard syndrome criteria. Unsupervised ML enables the detection of patterns within multiple dimensions of data simultaneously to separate patients within a cohort into homogeneous groups based on similarity of features (**Figure 1**). Clustering approaches can use routine clinical and biological data or circulating markers (ie, "-omics") to identify subgroups with distinct mechanistic signatures portending different treatment responsiveness and outcomes.[17] The application of clustering techniques may ultimately be useful for understanding individuals within a heterogeneous population to facilitate individualized care in a precision medicine paradigm tailored to specific pathophysiologic mechanisms.[17]

Several unsupervised ML methods exist for data-driven subgroup identification by maximizing in-group similarities and between-group differences within a heterogeneous population, collectively referred to as clustering or partitioning algorithms (**Central Illustration**).[19-21] Clustering approaches define groups by minimizing the differences between group members (analogous to separating apples and

FIGURE 1 Patient Phenotype as Expressed in Data Form



Individual patient data, captured at a single timepoint, are translated into a data form. Parameters can be continuous such as physiologic parameters or nominal such as the presence or absence of a clinical finding. Typically, these data are normalized using an algorithm that retains the variability among measurements but scales the data to a consistent metric such that no one parameter will dominate based on the range of values.

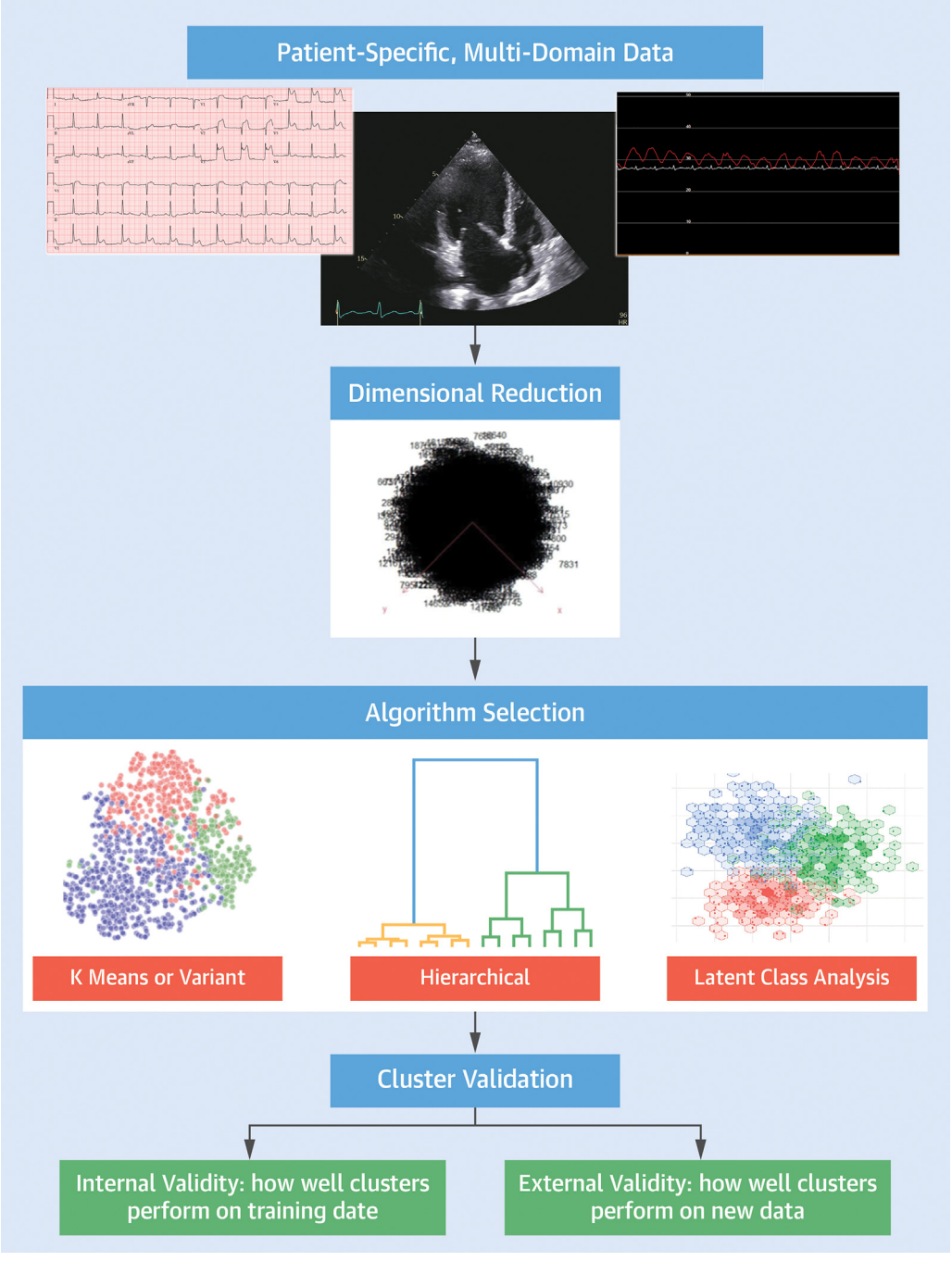
oranges); k-means clustering (KMC) and hierarchical clustering (HC) are 2 archetypal bottom-up clustering approaches.[19,21] Partitioning approaches generate a probability of belonging to each cluster for every individual based on overall distributions of features within a data set (analogous to slicing a pizza); latent class analysis (LCA) is the archetypal top-down partitioning approach.[20] These unsupervised ML approaches can augment or inform traditional and supervised ML methods for mortality risk stratification, as reviewed elsewhere.[22]

ANALYTICAL METHODS FOR CLUSTERING

K-MEANS CLUSTERING. KMC is the prototypical bottom-up clustering analysis approach.[19] Using a prespecified number of clusters (k), observations are assigned to the nearest cluster by distance, and cluster centers are then iteratively redefined using the mean of observations assigned to the cluster (**Figure 2A**). Each observation is assigned to a single cluster (hard assignment), and new observations can be easily assigned to clusters based on the distance to the established cluster centers.[19] KMC has low computational complexity, allowing clustering in larger populations with greater speed, and there are numerous variations of KMC that overcome some of the limitations of standard KMC.[19] Consensus KMC repeats the clustering in many bootstrapped samples from the population to determine to which cluster an individual is most often assigned and indicate the optimal number of clusters.[16,23] K-prototype is a variant of KMC that can incorporate both categorical and continuous variables.[24]

KMC and its variants have been used to identify subgroups within populations of critically ill patients, including those with CS.[15,16] Elmer et al[24] performed k-prototypes clustering in 1,088 patients resuscitated from cardiac arrest (CA) using clinical variables, neurological examination, neuroimaging, and electroencephalogram findings. Patients were grouped into 5 clusters representing the spectrum of brain injury severity, and cluster assignment was strongly associated with survival and favorable neurological outcomes. The associations among targeted temperature management, goal mean arterial pressure, and coronary angiography with outcomes varied across clusters.[24] Applying this clustering approach to define the likelihood of a severe brain injury prospectively in patients with CS and CA could identify patients who are better candidates for certain therapies and guide RCT eligibility.[25] Seymour et al[23] defined 4

CENTRAL ILLUSTRATION **An Overview of Clustering Analyses**



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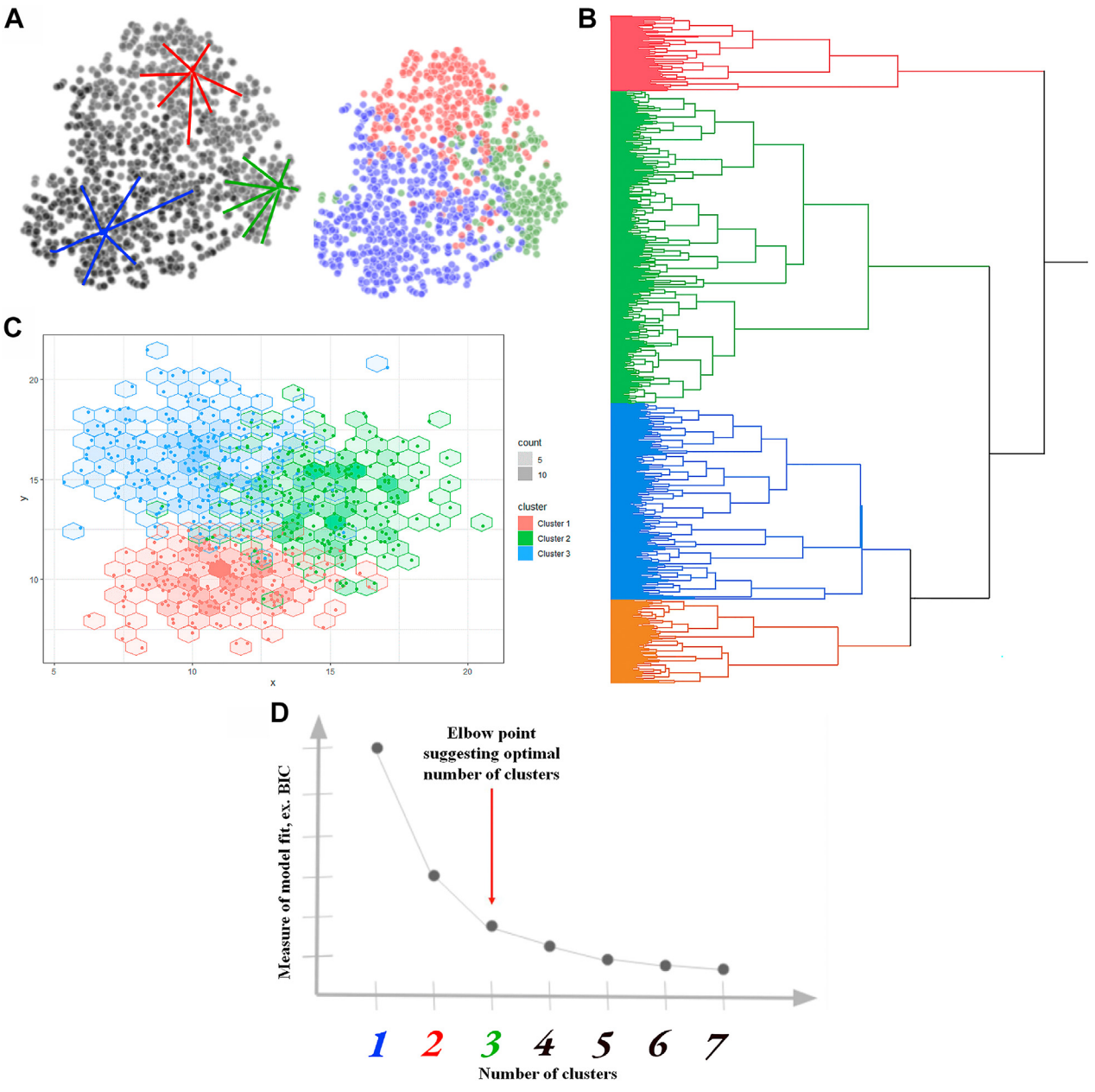
First, high-dimensionality data ideally representing different aspects of patient disease states are acquired. Next, it might be necessary in some cases to decrease the number of variables via dimensional reduction prior to clustering. Then, the preferred clustering algorithm is selected based on the clinical question, available data types, population size, and other factors, and clustering analysis is performed to identify subgroups. Finally, the derived clusters should be both internally and externally validated, including assessment of the clustering performance.

FIGURE 2 **Determining Cluster Membership and Optimal Number of Clusters**



For k-means clustering (KMC), **(A)** the distance between patients **(arrows)** defines the differences between separate clusters. For hierarchical clustering (HC), **(B)** the dendrogram shows individual patients with each linkage showing a layer of patient grouping; patients that are connected at higher levels are less similar than patients that are closely connected. For latent class analysis (LCA), **(C)** the shaded clouds surrounding individuals indicate the boundaries of similar observations within clusters and give a probability of class membership, with the individual assigned to the color-coded cluster with the highest probability. The elbow plot **(D)** shows a measure of model fit such as the Bayesian information criterion (BIC, with a lower value representing a better model fit) as a function of the number of clusters as clustering is repeated with increasing number of clusters; the bend demonstrates the optimal number of clusters.

subphenotypes of sepsis using consensus KMC based on routine clinical and biological data on admission, with subsequent validation using LCA and mapping post hoc onto several large prospective sepsis studies and RCTs. These subphenotypes were not correlated with traditional clinical variables and risk factors, but they were associated with different biomarker patterns and patient outcomes. Variable treatment

benefit was observed across the subphenotypes in RCT populations, and the distribution of subphenotypes within a hypothetical RCT population could influence the observed overall effect of the intervention.

HIERARCHICAL CLUSTERING. HC is another bottom-up clustering approach where each observation is grouped progressively into a cluster with its nearest neighbors based on distance metrics, forming an inverted tree pattern (agglomerative HC).[19] Each observation is assigned to a single group (hard assignment), and the further a linkage from the base, the greater the degree of difference between clusters. HC trees (dendrograms) clearly visualize the linkages between the clusters, and the ease of visualization is a relative strength of HC (**Figure 2B**). HC differs from KMC in that each branch on the dendrogram is a subdivision of the tree above it (ie, each side branch is independent), so the number of clusters can be changed post hoc based on where the hierarchy is cut without repeating the analysis; by contrast, in KMC, a change in the number of clusters entails deriving clusters entirely anew.

Recently, HC has been used to define subgroups in populations of patients with critical illnesses or cardiovascular diseases. Shah et al[26] performed agglomerative HC in 397 heart failure with preserved ejection fraction patients and identified 3 clusters with different clinical characteristics and long-term outcomes. Davenport et al[27] quantified peripheral blood leukocyte gene expression in septic shock patients and used HC to identify 2 sepsis response signatures that were associated with immune function, prognosis, and the response to corticosteroids. Geri et al[28] combined clinical and echocardiographic variables to define 5 hemodynamic sepsis subphenotypes using the principal components analysis followed by HC, which they proposed could be used to guide resuscitation strategies. Toma et al[29] used HC to cluster patients with acute myocardial infarction (AMI) based on leukocyte genomic expression patterns, identifying hyperinflammatory and prothrombotic subphenotypes.

LATENT CLASS ANALYSIS. LCA is a top-down partitioning approach that assumes that observed patterns of variables result from the superimposed distributions within the underlying clusters (ie, latent classes).[20] Clusters are assigned through iterative generation of an estimated probability of membership in each of a prespecified number of clusters via mixture modeling (**Figure 2C**). Considering that individuals may have characteristics of more than 1 cluster, the ability to provide a probability of membership in each cluster (soft assignment) is an advantage of partitioning approaches (ie, LCA) vs clustering approaches (ie, KMC and HC). There are many variations of LCA including latent profiles analysis that allow flexibility to handle mixed data.[20] Due to a higher computational load, LCA cannot handle very large data sets with a practical maximum of approximately 25,000 observations.[20]

LCA has been used to identify subgroups in populations of patients with critical illnesses or cardiovascular diseases. Segar et al[30] used a penalized LCA variant to separate 1,767 patients who had heart failure with preserved ejection fraction from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) RCT into 3 subgroups, demonstrating divergent clinical profiles with differences in prognosis. LCA using molecular biomarkers in patients with sepsis demonstrated differences in acute kidney injury, early and late outcomes, and treatment responses.[31,32] Soussi et al[32] used LCA to identify 2 subgroups of patients with sepsis with distinct biomarker profiles; these subgroups had differences in 1-year mortality after adjusting for severity of illness. Calfee et al reanalyzed ARDS RCTs using LCA based on clinical, mechanical ventilation, and biomarker data to identify 2 ARDS subphenotypes: a hyperinflammatory subphenotype that was associated with excess inflammation and worse outcomes and a hypoinflammatory subphenotype with lower illness severity and better outcomes.[33-35] The hyperinflammatory ARDS subphenotype was generally associated with a better response to the assessed treatments in these RCTs.[33-35] Two equivalent subphenotypes were identified within populations with ARDS due to COVID-19 infection, and the benefit of corticosteroids appeared greater in the hyperinflammatory subphenotype.[36]

PRACTICAL CONSIDERATIONS WHEN PERFORMING CLUSTERING ANALYSES

DATA QUALITY CONSIDERATIONS. As with conventional statistical approaches, clustering algorithms can be sensitive to missing data, particularly when data are not missing completely at random (**Table 1**).[22] KMC, HC, and many LCA models require complete data, which often necessitates imputation in clinical data sets. Some LCA variants can allow missing data, but they assume missingness is completely at random, which is often not the case in clinical data sets. Therefore, features with high missingness (ie, >20%-25%) are often excluded from clustering analysis.[37]

As with all traditional and ML statistical approaches, clustering algorithms only work as well as

the quality of the data fed into the algorithms, necessitating careful selection of included variables to ensure that the generated subgroups reflect clinically meaningful differences.[22,37] The maximum number of variables that can be used in clustering is limited by the sample size; the Formann formula specifies that clustering analysis should include at least 2^n (ideally $5 * 2^n$) individuals, where n is the number of variables.[16] Preselection of candidate variables may be necessary (sometimes referred to as "semi-supervised" clustering), which requires a combination of clinical judgement and statistical methods as with any model-building approach.[22] Variables that reflect underlying disease mechanisms and pathophysiological processes are ideal to include; selecting variables based on their association with outcomes of interest risks identifying clusters based on outcomes rather than pathophysiology.[16]

Highly correlated data can pose a challenge for KMC and LCA, which assume that model variables are uncorrelated and will overweight highly correlated variables (correlation coefficient >0.6).[19,20] The "best" of several correlated variables can be selected for inclusion based on clinical judgement, association with outcomes, or representation of distinct pathways; alternatively, dimension-reduction techniques such as principal components analysis can be performed prior to clustering.[22,28] Standard KMC does not handle categorical data or a mix of categorical and continuous data although k-prototypes can.[19] LCA and HC are better able to handle categorical data or a mixture of categorical and continuous data.[20] Skewed data can adversely affect all clustering algorithms, so log transformation and standardization to a z-scale are typically performed before clustering.[20,37]

TABLE 1 Practical Considerations for Performing Clustering Algorithms

Data Problem	Potential Solutions
Missing data	Single value imputation Multiple imputation Model-based imputation Use LCA variants that handle missing data, such as FIML
Excessive number of candidate features	Preselection of features ("semi-supervised clustering") • Association with outcomes of interest • Known to be clinically relevant (even if not associated with an outcome) • Association with disease mechanisms • Least missingness Principal components analysis before clustering Larger sample size will allow more features
Correlated features	Select the "best" from among correlated features • Association with outcomes of interest • Known to be clinically relevant (even if not associated with an outcome) • Association with disease mechanisms • Least missingness Reduce weights of correlated features if both are included
Mixed data types (eg, continuous and categorical)	Use LCA variants that handle mixed data types Use of k-prototypes or hierarchical clustering Categorize continuous variables for LCA (not ideal) • Dichotomization by cut points • Quantiles
Skewed distribution/outliers	Log-transformation Standardization Use LCA variants instead of k-means

FIML = full information maximum likelihood; LCA = latent class analysis.

DETERMINING THE OPTIMAL NUMBER OF CLUSTERS. An optimal number of clusters should produce good separation, resulting in extensive similarities within clusters while producing clusters of an adequate size to be clinically relevant. With HC, the number of clusters can be easily selected post hoc by altering the depth of the tree to select a specific number of clusters. For KMC and LCA, the number of clusters is assigned a priori, and the analysis is repeated across a range of k clusters; model fit metrics such as the Akaike information criterion (AIC) or Bayesian information criterion (BIC) are used to determine the optimal value of k.[20] While a higher number of clusters typically will have a lower AIC or BIC value representing better model fit, the incremental improvement in model fit decreases with a higher number of clusters.[20] A simple way to select the optimal number of clusters is to plot the AIC or BIC as a function of the number of clusters (called an "elbow plot"), with the inflection point defining the optimal number of clusters (**Figure 2D**).[20] Fewer clusters are typically preferred in the absence of a compelling reason that a more complex model is appropriate. Clustering algorithms may find subgroups within a population even if no true subgroups exist, and the identified subgroups may not be clinically meaningful.[19] It is important to ensure that the identified clusters do not simply represent different levels of the variables (ie, low, intermediate, and high values).

SELECTION OF A CLUSTERING ALGORITHM AND DETERMINING CLUSTER VALIDITY. Understanding the strengths and limitations of each method (including potential sources of bias) is important when evaluating the suitability of a method to the clinical problem (**Table 2**). When all variables are numerical and have a relatively parametric distribution, KMC and its variants will often work well, and this approach is preferred with very large data sets.[19] When variables are of mixed type, categorical, and/or have a nonparametric distribution, LCA may be a better solution assuming the sample size is not very large.[20] An ordering points to identify the clustering structure (OPTICS) algorithm can determine which method better fits the data structure.[23] For LCA and KMC, it is difficult to visualize and communicate

TABLE 2 Strengths and Weaknesses of Common Unsupervised Clustering Methods

Technique	Strengths	Weaknesses
K-means	• Fast and intuitive • Widely used in clinical research • Scales to very large data sets	• No probability of membership • Not well-suited to categorical or non-normally distributed data • Cannot handle missing data
Latent class analysis	• Generates probabilistic estimates of cluster membership • Handles mixed data types • Tolerates non-normal data • Some models tolerate missing data	• Slow • Does not scale well to very large data sets (more than roughly 25,000 patients)
Hierarchical clustering	• Intuitive visualization • Simultaneously generates different options for number of clusters	• Splitting decisions may be suboptimal and nonmodel or data-driven • Order of splitting can significantly impact results • Sensitive to outliers • Does not scale well to large data sets

TABLE 3 Characteristics of the 3 Phenotypes Proposed by Zweck et al

Characteristic	Noncongested	Cardiorenal	Hemometabolic
Age	Younger	Older	Intermediate
Comorbidities	Few	Many (DM, CKD)	Few
Blood pressure	Low	Low	Very low
Congestion	None	Left-sided	Right-sided
Heart rate	Normal	Normal	Elevated
Hemoglobin	Normal	Low	Normal
WBC count	Mildly elevated	Mildly elevated	Very elevated
Transaminases	Mildly elevated	Mildly elevated	Very elevated
Lactate	Mildly elevated	Normal	Very elevated
Kidney function	Normal	Very low	Low

CKD = chronic kidney disease; DM = diabetes mellitus; WBC = white blood cell.

how clusters differ and how assignments to the clusters were generated. By contrast, HC is more transparent regarding how clusters are separated and may be preferred when exploring the relationships between similar individuals is the most important goal. Correlation of the cluster assignments using multiple clustering methods is conceptually appealing, but without a gold standard, it is difficult to interpret the results when the 2 methods assign individuals to different clusters.[23]

PHENOTYPING IN CS POPULATIONS

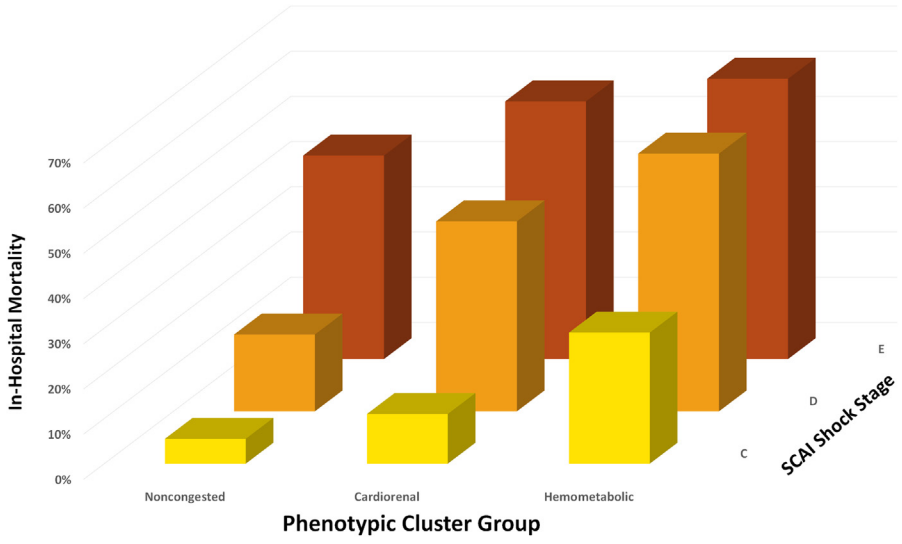
INITIAL SUBPHENOTYPING ANALYSIS. Clustering algorithms have recently been applied for subphenotyping in CS populations. An analysis by Zweck et al[16] employed unsupervised clustering to identify and characterize 3 distinct CS subphenotypes in multiple contemporary data sets. This study examined 1,959 patients from 2 international registries: the Cardiogenic Shock Working Group (CSWG) Registry (including separate AMI-CS and HF-CS cohorts)[14] and the Danish Retroshock MI Registry,[38] which included patients with AMI-CS. Paralleling the approach taken by Seymour et al[23] in patients with sepsis, consensus KMC was used to identify subgroups based on 6 admission laboratory variables (white blood cell count, platelet count, estimated glomerular filtration rate, alanine aminotransferase, lactate, bicarbonate). These variables were selected based on their strong associations with in-hospital mortality.[16]

The CSWG AMI-CS cohort was used as the derivation cohort, with internal validation in the CSWG HF-CS cohort and external validation in the Danish Retroshock MI Registry cohort. An optimal cluster number of 3 was determined, and the clusters were labeled as "noncongested," "cardiorenal," and "cardiometabolic" subphenotypes based on their clinical characteristics (Table 3).[16] The noncongested cluster included young patients with few comorbidities and overall lower illness severity including fewer laboratory abnormalities and more favorable hemodynamics. The cardiorenal cluster included older patients with more comorbidities, anemia, severe kidney dysfunction, and left-sided (pulmonary) congestion. The hemometabolic cluster included patients with the highest illness severity including extensive laboratory abnormalities, multiorgan dysfunction, and poor hemodynamics with right-sided (systemic) congestion.

In-hospital mortality varied substantially across the 3 clusters in each cohort.[16] The SCAI Shock Classification was assigned based on the maximum number of vasoactive drugs and temporary mechanical circulatory support (MCS) devices during hospitalization.[14] The noncongested cluster had lower shock severity, and the hemometabolic cluster had higher shock severity. Patients in the SCAI Shock stage C had the lowest mortality, and patients in the SCAI Shock stage E had the highest mortality in each subphenotype, but the 3 subphenotypes demonstrated differences in mortality within each SCAI Shock stage (Figure 3). Both SCAI Shock stage and subphenotype were independently associated with in-hospital mortality, suggesting that the subphenotype is a risk modifier when added to the SCAI Shock Classification.

An important strength of this analysis is the derivation of subphenotypes in patients with AMI-CS with validation in patients with HF-CS, suggesting conservation across etiologies of CS. Subphenotypes were assigned based on characteristics at the time of admission, facilitating prospective application. The use of commonly obtained admission laboratory values enhances the generalizability, while the lack of mechanistic biomarkers limits inferences regarding

FIGURE 3 **In-Hospital Mortality According to the SCAI Shock Classification and CS Phenotype in the 3 Combined Cohorts From the Analysis by Zweck et al[15]**



Just as higher SCAI Shock stages are associated with increased mortality in each CS phenotype, the CS phenotypes are associated with different mortality risks at each SCAI Shock stage. CS = cardiogenic shock; SCAI = Society for Cardiovascular Angiography and Intervention.

the underlying pathophysiology. The maximum SCAI Shock stage during hospitalization was determined instead of the admission SCAI Shock stage, which precludes us from knowing whether the subphenotype determined the severity of CS or vice versa.[14] Preselection of variables based on their association with in-hospital mortality, followed by validation of clusters using in-hospital mortality, does not guarantee identifying subphenotypes with unique disease mechanisms.

SUBSEQUENT CONFIRMATORY ANALYSIS. External validation studies are valuable to distinguish conserved subphenotypes from idiosyncratic clusters that are unique to a specific cohort. For this reason, Jentzer et al performed simple KMC using the same 6 admission laboratory variables to assign 1,498 Mayo Clinic cardiac intensive care unit patients with CS of diverse etiologies to 3 clusters as defined by Zweck et al.[15,16] This study population included acute coronary syndrome (ACS) patients forming 57% and patients with CA forming 34%; SCAI Shock stage was assigned on admission. The distribution of clusters was as follows: noncongested, 40%; cardiorenal, 30%; and hemometabolic, 30%. The characteristics of these groups predominantly resembled those described by Zweck et al.[15,16] Although the cardiorenal cluster had a lower prevalence of ACS and CA, the overall severity of illness and shock was similar between the noncongested and cardiorenal clusters. The hemometabolic cluster had greater severity of CS with the majority of SCAI Shock stage E patients and higher illness severity including the poorest renal function, highest transaminases, and the worst lactic acidosis. Although left ventricular ejection fraction was the same across clusters, other echocardiographic findings differed between clusters, suggesting that cardiac function may differ between subphenotypes. Patients in the hemometabolic cluster had the lowest systemic flow and worst RV function, while the noncongested group had the lowest estimated filling pressures.

A gradient of in-hospital mortality was observed across the clusters, being highest in the hemometabolic cluster and comparable in the noncongested and cardiorenal clusters.[15] After adjustment, the hemometabolic cluster remained associated with higher in-hospital mortality while the noncongested and cardiorenal clusters did not differ. Differences in mortality between clusters were observed up to 1 year, with hospital survivors in the noncongested cluster having lower postdischarge mortality. The hemometabolic cluster exhibited higher mortality when patients were stratified by the presence of ACS or CA, SCAI Shock stage, or illness severity, suggesting that the subphenotype assignment captured novel prognostic information. Although these

differences were not significant, mortality varied across the clusters according to the use of temporary MCS, and only noncongested patients who received an intra-aortic balloon pump appeared to have lower mortality.

FUTURE DIRECTIONS. These studies illustrate that separating CS patients based on 6 standard admission laboratory variables via KMC produces 3 subgroups with consistent characteristics across populations that display clinically relevant differences beyond the clustering variables.[15,16] These clusters portend substantially different prognosis during and after hospitalization, with a higher risk observed in the severely ill hemometabolic cluster. If equivalent clusters are observed in other CS populations, then these clusters likely represent true disease subphenotypes. It will be essential to link these clusters to distinct disease mechanisms based on novel biomarkers reflecting the underlying physiologic processes.[21] Future studies using larger, prospective CS registries incorporating data on treatment course should determine whether 3 is the optimal number of clusters to characterize the CS population and whether different clustering variables would produce a more robust set of subgroups. Repeating the clustering using serial laboratory values from different time points during hospitalization will clarify whether these subphenotypes evolve or converge over time and whether these subphenotypes represent distinct disease states or merely different time points on a single disease continuum. For example, if undertreated CS with persistent hypoperfusion can develop from another profile into the hemometabolic subphenotype, then early hemodynamic support might prevent this transition.[39] Defining these clusters retrospectively in RCT cohorts may shed light on treatment-subphenotype interactions. If one or more subphenotype is linked to a specific underlying disease mechanism, then that might represent a treatable trait, and treatments targeting that mechanism could be explored. Identification of subphenotypes may enhance development of selective treatment strategies in clinically distinct subsets of CS and facilitate targeted patient enrollment in RCTs.

USING SUBPHENOTYPING APPROACHES TO PERSONALIZE CARE

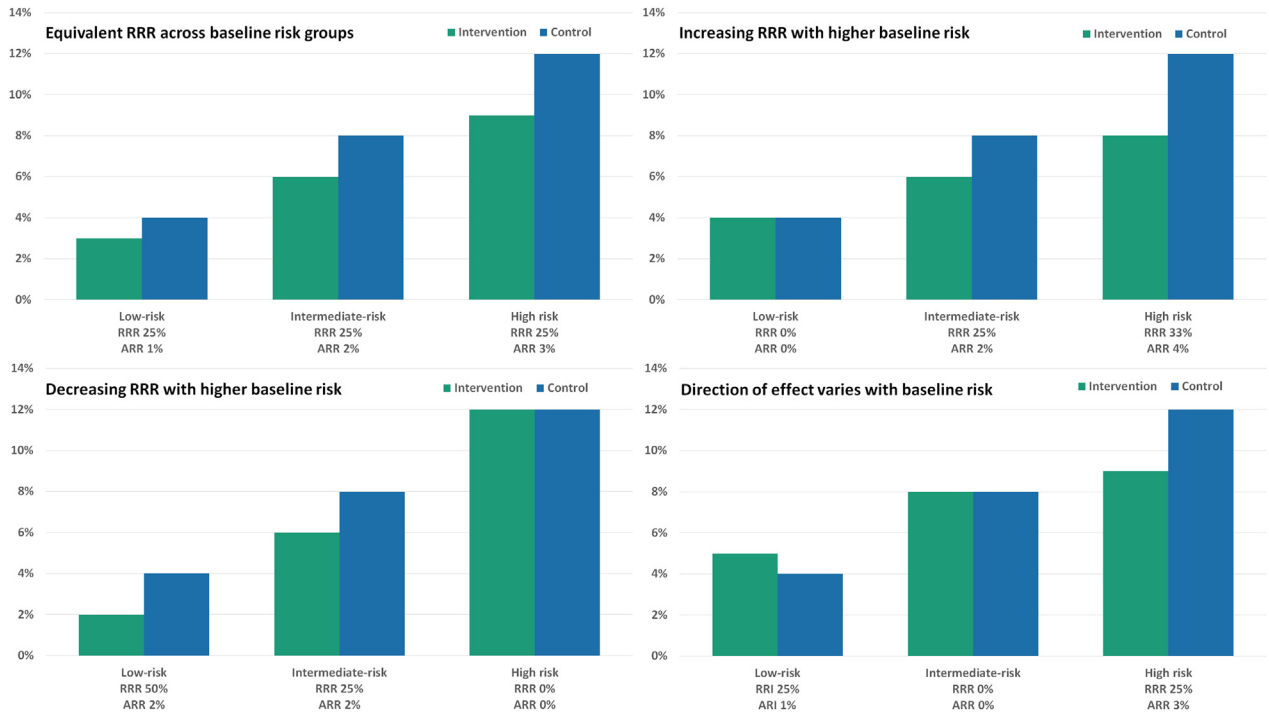
HETEROGENEITY OF TREATMENT EFFECT. The increasing recognition of heterogeneity within the CS population is an initial step toward developing more effective, personalized treatments for CS. Disease heterogeneity may imply heterogeneity of treatment effect (HTE), whereby treatments may have a differential risk-benefit profile based on the underlying disease stage or subphenotype.[40,41] Approaches to RCT design that rely on staging and subphenotyping may accommodate HTE, resulting in smaller sample sizes, less exposure to risks in patients unlikely to benefit, and a higher overall likelihood of identifying effective treatments.

Identifying HTE based on subphenotypes is considered "predictive," whereby a patient is selected for a treatment based on a higher predicted likelihood of response to the treatment (ie, presence of a treatable trait). Identifying HTE based on risk is considered "prognostic," whereby a patient is selected for a treatment based on their likelihood of having the outcome modified by the treatment. Either subphenotyping or staging can identify high-risk patients for prognostic enrichment, while subphenotyping is well-suited for identifying patients with different underlying disease mechanisms for predictive enrichment.

PREDICTIVE ENRICHMENT IN CLINICAL TRIALS. RCTs using predictive enrichment to selectively enroll patients whose underlying disease mechanism is targeted by the tested therapy are common within the field of oncology, resulting in an individualized medicine approach to many common tumors based on molecular profiling. Preliminary data suggest that it may be possible to take an equivalent approach in critical illness syndromes, as exemplified by the secondary analysis of the HARP-2 (Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction-2) trial in which only the hyperinflammatory ARDS subphenotype appeared to derive benefits from simvastatin.[33] Given that the putative mechanism of action of simvastatin in ARDS is by suppressing inflammation, these post hoc findings may support a new RCT of simvastatin that would enroll only patients with the hyperinflammatory subphenotype (predictive enrichment).[42] Insofar as varying inflammatory subphenotypes may exist in AMI and CS, this may present an underlying biologic pattern to support predictive enrichment.[29,43-45] If the proposed CS subphenotypes have different response profiles to certain interventions, they could guide predictive enrichment in future RCTs.

PROGNOSTIC ENRICHMENT IN CLINICAL TRIALS. Prognostic enrichment involves selectively enrolling patients into RCTs with a higher likelihood of the outcome being studied. Most non-ST-segment elevation ACS RCTs are enriched with high-risk patients to increase the control group event rate and resulting statistical power. The relative risk reduction

FIGURE 4 Theoretical RCT Results Demonstrating HTE



Each panel represents simulated data from a hypothetical RCT including low-risk, intermediate-risk, and high-risk subgroups with a different pattern of risk-benefit interaction for the intervention. When the relative risk reduction (RRR) is stable across risk groups **(top left)**, the absolute risk reduction (ARR) increases linearly with baseline risk. When the RRR increases with baseline risk **(top right)**, the ARR is magnified in the high-risk group. When the RRR decreases with baseline risk **(bottom left)**, the ARR decreased in the high-risk group. When the magnitude and direction of the RRR change with baseline risk **(bottom right)**, a benefit in the high-risk group could be masked by harm in the low-risk group. Knowing the pattern of HTE across risk categories can facilitate prognostic enrichment during RCT enrollment.
HTE = heterogeneity of treatment effect; RCT = randomized controlled trial.

associated with a treatment is often assumed to be constant across the spectrum of risk such that higher-risk patients will necessarily have a higher absolute risk reduction. However, the relative risk reduction may vary according to baseline risk, reflecting an interaction such that high-risk or low-risk patients might have a magnified or mitigated absolute risk reduction (**Figure 4**). For example, only higher-risk non-ST-segment elevation ACS patients appeared to benefit from early coronary angiography in the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial.[46] In addition, in the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial of activated drotrecogin alfa (recombinant human activated protein C) in patients with severe sepsis, a post hoc analysis showed a beneficial treatment effect only at higher baseline predicted mortality risk, with greater separation between the groups as baseline predicted mortality increased.[47] However, a subsequent larger RCT enrolling septic shock patients with high illness severity failed to demonstrate a benefit of drotrecogin alfa in any subgroup, underscoring the need to be cautious when interpreting post hoc analyses of RCTs.[48]

The efficacy of temporary MCS devices in patients with CS might vary based on the severity of CS.[49] If RCTs examining temporary MCS devices enrolled patients with average CS severity exceeding the capability of the tested MCS device, then this might explain why the device failed to improve survival, as could have occurred in the IABP-SHOCK-II (Intra-aortic Balloon Pump in Cardiogenic Shock-II) study.[49-52] In this way, the SCAI Shock Classification could be used for prognostic enrichment in future RCTs to identify patients with a severity of CS that matches the hemodynamic efficacy of the tested intervention.[53] Additionally, the highest-risk CS patients often have CA, and outcomes in CA patients may be driven by nonmodifiable brain injury more than modifiable cardiovascular factors; inclusion of large numbers of CA patients in RCTs may therefore

potentially bias these studies toward the null hypothesis.[2,25,54] Higher-risk CS patients (especially those with CA) may be less likely to benefit from a hemodynamic intervention may explain the neutral findings of the IMPRESS (IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK) study, which enrolled primarily CS patients with CA and demonstrated a high rate of death due to brain injury.[51] Using a combination of predictive and prognostic enrichment could increase the likelihood of demonstrating a favorable effect by identifying a CS population that has a high-enough risk to benefit yet is likely to respond to the tested intervention.

ALTERNATIVE CLINICAL TRIAL DESIGNS. Beyond the conventional 2-arm parallel-group RCT designs, emerging adaptive RCT approaches may offer advantages that better account for HTE.[55] Adaptive clinical trials may employ group sequential stopping designs which allow the RCT to reach separate conclusions based on observed treatment effects in predefined subgroups sequentially, potentially accelerating evidence dissemination. For example, a hypothetical single adaptive RCT could enroll patients with ST-segment elevation myocardial infarction and multivessel coronary disease with or without CS, randomizing them to a strategy of culprit-only revascularization or complete revascularization. This hypothetical RCT could specify adaptive stopping groups based on the presence or absence of CS, allowing the RCT to prospectively test independent conclusions in these subgroups. The recent ATTACC/ACTIV-4a/REMAP-CAP (Antithrombotic Therapy to Ameliorate Complications of Covid-19/A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19/Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) multiplatform RCT evaluating therapeutic heparin compared with usual care thromboprophylaxis in hospitalized patients with COVID-19 used an adaptive group sequential design.[56] The trial tested conclusions independently for critically ill and noncritically ill patients, and noncritically ill patients were stratified based on D-dimer levels.[56-59] The trial reached a futility conclusion in the critically-ill patient group first.[58] One month later, a superiority conclusion in the noncritically ill group was reached.[57] This stratified design which prospectively incorporated principles of both clinical staging and predictive HTE enabled precise, reliable treatment effects to be observed and disseminated in a timely manner. If the critically ill and noncritically ill patients had been comingled together with a plan for post hoc subgroup analyses, then perhaps the main study finding would have been neutral, thus invalidating the subgroup analyses. Such adaptive designs may be well-suited to heterogeneous conditions such as CS and could leverage prospective phenotyping to test the efficacy of a specific therapy in different subgroups.

PHENOTYPING IN CLINICAL PRACTICE AND TRIALS. There are several potential uses of phenotyping for the care of CS patients in clinical practice, including prognostication, standard treatment decision-making (including the initiation and weaning of vasoactive drugs and temporary MCS), and the use of novel treatments (eg, anti-inflammatory therapies in hyperinflammatory disease phenotypes). The ultimate goal of these strategies is to pivot from the current era of empiric therapy to a precision medicine approach guided by a deeper understanding of disease mechanisms that allow the personalization of treatments to each individual.[60] For phenotyping to be effective in clinical practice, the requisite clustering algorithms will require timely clinical access to information, which will be initially the easiest to apply on routinely available data. If the underlying biomarker profiles of common disease subphenotypes in CS patients can be identified and these subphenotypes can be separated effectively based on a limited number of biomarkers, then subphenotyping can be implemented by measuring these biomarkers at the bedside with point-of-care multimarker devices such as mobile enzyme-linked immunoadsorbent assays.[61,62] The use of a mobile enzyme-linked immunoadsorbent assay device which assigns the subphenotype automatically by integrating a simplified clustering algorithm could facilitate an actionable clinical staging and subphenotyping framework in real time.

FUTURE RESEARCH APPLICATIONS OF PHENOTYPING. Subphenotyping in CS is currently in its infancy, using limited a number of commonly available laboratory tests to identify groups without extensive insights into the underlying disease mechanisms or possible treatable traits.[15,16] An essential next step is the integration of a multibiomarker or the "-omics" approach to understand the differences in the underlying pathophysiology that separate these clinical subphenotypes. Incorporation of other clinical data including cardiac imaging (eg, electrocardiogram, echocardiography, angiography) might aid in identifying differences in underlying disease states.[28] For example, applying artificial intelligence methods to the standard 12-lead electrocardiogram has enabled

identification of the underlying left ventricular dysfunction in CICU patients, with prognostic implications; incorporating this ubiquitous noninvasive test might potentially improve phenotyping.[63,64]

CONCLUSIONS

With the increasing recognition that CS is a heterogeneous clinical syndrome, numerous techniques have emerged to stratify patients into clinically relevant subgroups based on the severity of CS, associated clinical features, and underlying subphenotypes. The use of unsupervised ML clustering to identify occult subphenotypes in critically ill populations has been applied to CS, allowing recognition of preserved subphenotypes that have prognostic implications. Deep phenotyping to understand the underlying disease mechanisms that separate these subphenotypes could permit translation into treatable traits to facilitate individualized precision medicine for patients with CS. This is a burgeoning field offering innumerable opportunities for future basic science, clinical and translational research.

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