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RESEARCH LETTER

Consistency of Cardiogenic Shock Subphenotypes and Their Association With Mortality

Cardiogenic shock (CS) manifests heterogeneous syndrome etiologies, severity, hemodynamics, and organ dysfunction.[1,2] Characterizing heterogeneity in CS and other critical illnesses may improve clinical care by facilitating individualized prognosis and treatment.[1,2] We and others have used the unsupervised machine learning partitioning method *k*-means clustering to identify 3 clinical subphenotypes of CS using the clinical and laboratory data.[2-4] These subphenotypes—which were labeled noncongested, cardiorenal, and hemometabolic by Zweck et al—stratify mortality risk, and facilitate prognostication.[2-4] Some have questioned the robustness of subphenotype derivation, and it remains uncertain how consistent these subphenotypes would be if derived using different statistical approaches.[2] We hypothesized that evaluating heterogeneity in CS using the alternative unsupervised machine learning approaches could support complementary derivation of clinically-relevant supbphenotyes in CS. Accordingly, we applied model-based latent class analysis (LCA) in a cohort of patients with CS to agnostically identify CS subphenotypes, determine consistency with prior groupings, and compare mortality between groups.

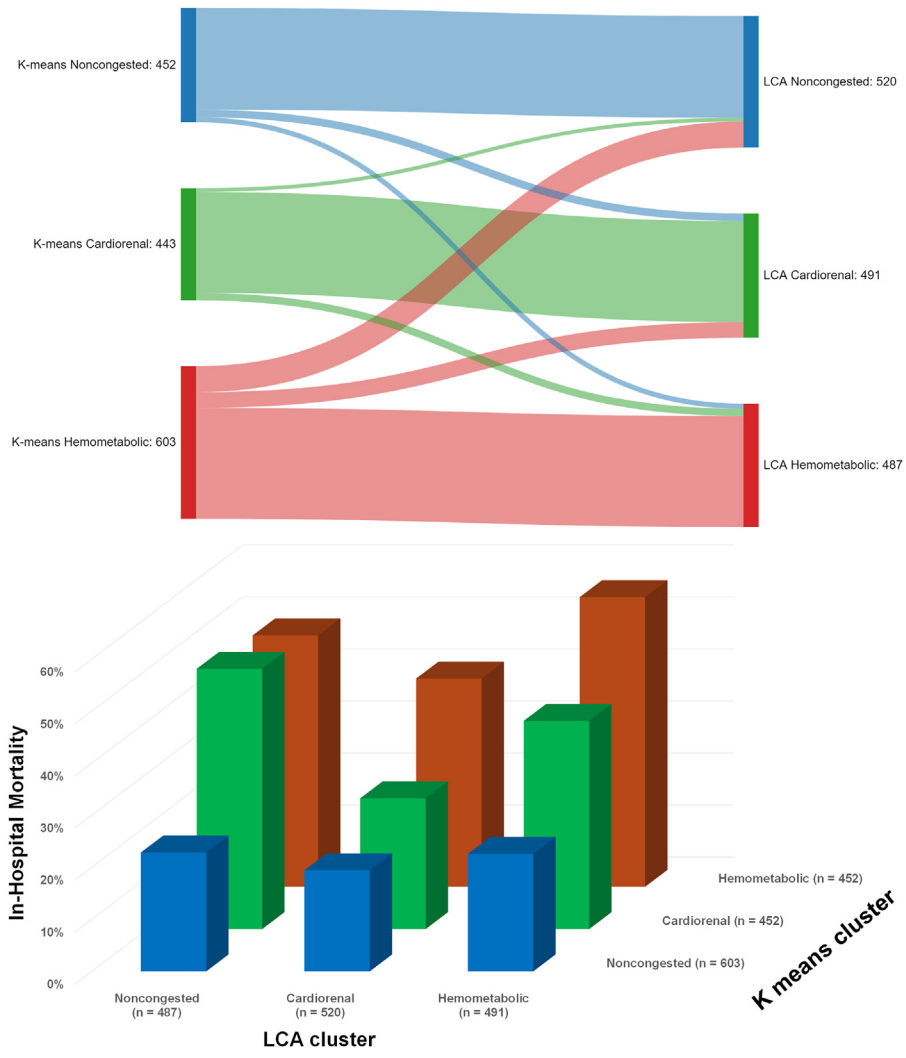
This study was approved by the Mayo Clinic Institutional Review Board as minimal risk to patients. We included consecutive unique patients admitted to the Mayo Clinic cardiac intensive care unit from 2007 to 2018 with an admission diagnosis of CS.[4] Congruous with prior clustering analyses in CS populations, we used 6 admission laboratory values (lactate, bicarbonate, white blood cell count, platelet count, alanine aminotransferase, and estimated glomerular filtration rate) as features after multiple imputation for missing values.[3,4] Prior to LCA, we categorized each feature variable into quartiles. The optimal number of clusters for LCA was empiric based on the lowest value of the Bayesian Information Criterion.[2] Groups were compared using analysis of variance for continuous variables and chi-square for categorical variables. The primary outcome was all in-hospital mortality, evaluated using logistic regression adjusted for age, comorbidities, cardiac arrest (CA), Acute Physiology and Chronic Health Evaluation-4 score, hemodynamic support and critical care therapies. Agreement between clustering algorithms was quantified using Cohen's unweighted kappa. Statistical analysis was performed using JMP Pro 14.1 (SAS Institute).

We included 1,498 patients with CS with a mean age of 68 ± 14 years (37% females); acute coronary syndrome (ACS) was present in 57% and CA was present in 34%. *K*-means assigned patients to the following clusters: noncongested (n = 603, 40%), cardiorenal (n = 452, 30%), hemometabolic (n = 443, 30%) using the nomenclature of Zweck et al.[3]

LCA determined that a 3-cluster model had the lowest Bayesian Information Criterion and assigned patients to the following clusters, which we labeled based on biomarker characteristics as the noncongested (n = 487, 32%), cardiorenal (n = 520, 35%), hemometabolic (n = 491, 33%) groups. Using LCA cluster assignment, patients in the noncongested and hemometabolic clusters predominantly had ACS (68% and 60%) and frequently had CA (37% and 44%), while patients in the cardiorenal cluster less frequently had ACS (44%) or CA (22%). Most (83%) patients were assigned to the same cluster by both LCA and *k*-means methods (**Figure 1**, top) (kappa 0.74 [95% CI: 0.71-0.77] for agreement between cluster assignment methods).

In-hospital mortality was significantly higher in the hemometabolic (50.5%), vs noncongested (25.5%) and cardiorenal (24.4%) clusters (both $P < 0.001$). When patients were stratified by both LCA and *k*-means cluster, a gradient of mortality was observed, with the *k*-means clustering groups demonstrating a stronger association with in-hospital mortality than the LCA group (**Figure 1**, bottom). Patients assigned to the hemometabolic cluster by either *k*-means (adjusted odds ratio [OR]: 2.60; 95% CI: 1.92-3.53; $P < 0.001$) or LCA (adjusted OR: 2.10; 95% CI: 1.55-2.85; $P < 0.001$) had higher in-hospital mortality. Patients assigned to the hemometabolic cluster by

FIGURE 1 Subphenotype Assignment According to K-Means Clustering and LCA and In-Hospital Mortality



Sankey diagram demonstrating agreement among clusters **(top)** and the in-hospital mortality observed as a function of cluster assignment by each method **(bottom)**. Note that non-agreement groups generally had small numbers of patients, and mortality estimates should be interpreted with caution. LCA = latent class analysis.

both algorithms had the highest mortality (55.6%, adjusted OR: 2.72; 95% CI: 1.94-3.80; $P < 0.001$).

This analysis extends prior findings in several important ways. First, we validated 3 as the optimal number of subgroups in this population via a different clustering approach.[2-4] Second, both methods agreed on the cluster assignment in more than 80% of patients, suggesting that these clusters may represent conserved biological phenotypes. Patients labeled as hemometabolic by either method had more than 2-fold higher risk of adjusted in-hospital mortality. Finally, these findings highlight the wide gradient in patient outcomes with CS across subphenotypes.[1]

Relevant limitations of our study include retrospective cohort design, substantial missingness of certain laboratory values prior to imputation (eg, lactate and alanine aminotransferase) such that only 47.8% of patients had complete data, and inclusion of a mixed CS cohort spanning more than a decade.

Among several LCA variants, we used one that requires categorical variables as features so we used quartiles to categorize the continuous variables; another LCA variant or use of a different approach to categorization could have yielded different findings. We were unable to evaluate changes in CS subphenotype during hospitalization.

In conclusion, we confirmed the presence of 3 distinct subphenotypes of CS that differ in clinical characteristics and outcomes, offering insights into the heterogeneity within the CS population. Differing statistical methods produced consistent cluster assignments, supporting the potential robustness of these groups. Future research should seek to explain the underlying mechanistic differences between these subphenotypes (ie, potential biological targets), whether subphenotypes can converge or evolve from one another over time, and how the subphenotype may influence treatment responses to permit predictive enrichment in future clinical trials.

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