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Identifying biomarker-driven subphenotypes of cardiogenic shock: analysis of prospective cohorts and randomized controlled trials



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Summary

Background Cardiogenic shock (CS) is a heterogeneous clinical syndrome, making it challenging to predict patient trajectory and response to treatment. This study aims to identify biological/molecular CS subphenotypes, evaluate their association with outcome, and explore their impact on heterogeneity of treatment effect (ShockCO-OP, NCT06376318).

Methods We used unsupervised clustering to integrate plasma biomarker data from two prospective cohorts of CS patients: CardShock (N = 205 [2010–2012, NCT01374867]) and the French and European Outcome reGistry in Intensive Care Units (FROG-ICU) (N = 228 [2011–2013, NCT01367093]) to determine the optimal number of classes. Thereafter, a simplified classifier (Euclidean distances) was used to assign the identified CS subphenotypes in three completed randomized controlled trials (RCTs) (OptimaCC, N = 57 [2011–2016, NCT01367743]; DOREMI, N = 192 [2017–2020, NCT03207165]; and CULPRIT-SHOCK, N = 434 [2013–2017, NCT01927549]) and explore heterogeneity of treatment effect with respect to 28-day mortality (primary outcome).

Findings Four biomarker-driven CS subphenotypes ('adaptive', 'non-inflammatory', 'cardiopathic', and 'inflammatory') were identified separately in the two cohorts. Patients in the inflammatory and cardiopathic subphenotypes had the highest 28-day mortality (p (log-rank test) = 0.0099 and 0.0055 in the CardShock and FROG-ICU cohorts, respectively). Subphenotype membership significantly improved risk stratification when

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added to traditional risk factors including the Society for Cardiovascular Angiography and Interventions (SCAI) shock stages (increase in Harrell's C-index by 4% ($p = 0.033$) and 6% ($p = 0.0068$) respectively in the CardShock and the FROG-ICU cohorts). The simplified classifier identified CS subphenotypes with similar biological/molecular and outcome characteristics in the three independent RCTs. No significant interaction was observed between treatment effect and subphenotypes.

Interpretation Subphenotypes with the highest concentration of biomarkers of endothelial dysfunction and inflammation (inflammatory) or myocardial injury/fibrosis (cardiopathic) were associated with mortality independently from the SCAI shock stages.

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Keywords: Cardiogenic shock; Unsupervised learning; Critical care; Heterogeneity of treatment effect; Precision medicine

Research in context

Evidence before this study

The contemporary clinical syndromic definition of cardiogenic shock (CS) fails to consider the heterogeneity and complexity of the underlying pathobiology (i.e., host response to myocardial injury and inflammation). This heterogeneity may have diluted the potential benefit of specific interventions and may have led to neutral results in CS trials (i.e., heterogeneity of treatment effect). Nonetheless, only scarce data exist regarding CS biological/molecular heterogeneity.

Added value of this study

We applied latent class analysis (i.e., unsupervised clustering) in a selected population of CS patients (CardShock and FROG-ICU prospective observational cohorts) and identified four biomarker-driven CS subphenotypes (labeled as 'adaptive', 'non-inflammatory', 'cardiopathic' and 'inflammatory'). When adjusting for traditional risk factors including the severity of illness (i.e., the Society for Cardiovascular Angiography and Interventions (SCAI) shock stages), the 'cardiopathic' and

'inflammatory' biological subphenotypes were independently associated with increased early mortality. This work is unique as we were able to derive and externally replicate in three independent randomized controlled trials (RCTs) (OptimaCC, DOREMI and CULPRIT-SHOCK) distinct clinically relevant molecular CS subphenotypes associated with different underlying pathobiology and adverse clinical outcomes across varying study designs and locations with more than 1000 CS patients with biomarker data.

Implications of all the available evidence

This work provides a new way in which we may think about classifying CS patients. These analyses may not only allow pathway and prognostic enrichment, but also support future RCTs of personalized interventions (e.g., mechanical circulatory support, host response modulation) in CS patients who are prospectively enrolled based on a biological/molecular pattern rather than the traditional inclusion of consecutive patients.

Introduction

Cardiogenic shock (CS) is associated with high mortality, with minimal improvement in survival over the last two decades; few therapies have been shown to decrease mortality in clinical trials.^{1,2} CS is a heterogeneous clinical syndrome, variable in its severity, aetiology, hemodynamic profile, associated complications, and underlying molecular pathways.³ Despite recent efforts to individualize CS trajectories with the Society for Cardiovascular Angiography and Interventions (SCAI) shock stages, the current clinical syndromic definition of CS fails to consider nuanced pathobiology, patient heterogeneity, and the complexity of the host response to myocardial injury and inflammation.⁴ Recent

translational research highlights the biological/molecular heterogeneity within the CS syndrome, which may have diluted the potential benefit of specific interventions and contributed to neutral clinical trial results.^{1,5} One approach to disentangle heterogeneity is to identify underlying subphenotypes (i.e., subclasses with distinct clinical/biological patterns) within the overall CS syndrome population.^{6,7} This approach has been applied to other heterogeneous critical illness syndromes (e.g., sepsis, acute respiratory distress syndrome [ARDS]) using circulating inflammatory markers to identify distinct subphenotypes that respond differently to specific interventions.⁸⁻¹⁰ Biomarker data may identify CS subphenotypes that are not apparent at the bedside, but that

have differing clinical outcomes and treatment responses.¹¹ Delineating these discrete subclasses may allow predictive enrichment in future CS clinical trials (i.e., identifying a sub-population that will have a greater treatment effect than occurs in an unselected population).⁶

The primary goal was to identify novel biomarker-driven subphenotypes of CS using model-based clustering in prospective cohorts. Secondly, we sought to determine the association between these novel CS subphenotypes and short and long-term survival. Finally, we validated the existence of these novel subphenotypes in a more homogenized/selected CS population of independent RCTs and evaluated their impact on treatment effect.

Methods

Overview

This study involved two prospective observational cohorts and three independent RCTs including CS patients (The Shock and acute Conditions Outcomes Platform [ShockCO-OP], NCT06376318). A multistep statistical reanalysis approach was performed as previously reported in other critical care syndromes subphenotyping research^{8–10} (Fig. 1). Initially, biomarkers of host response and organ dysfunction collected at inclusion were used to derive and externally validate novel biomarker-driven CS subphenotypes in two independent observational cohorts (CardShock [derivation, NCT01374867] and FROG-ICU [validation, NCT01367093])^{12,13} using latent class analysis (LCA). LCA is a model-based clustering method used to identify unobserved subgroups within a heterogeneous population based on observed variables. Its main

assumption is local independence. It allows the determination of an optimal number of classes and individual subject assignment in one of the identified classes. In contrast to ‘hard’ clustering methods, in which each subject can only belong to a single class (e.g., k means clustering, hierarchical clustering), LCA is a ‘soft’ clustering method which provides for each subject a posterior probability of belonging to each of the classes (i.e., subjects are assigned to the class with the highest posterior probability). Soft clustering methods are probably more suitable for modelling the overlap/interplay between different pathophysiological mechanisms to identify distinct molecular subphenotypes in the heterogeneous CS population.¹⁴

Subsequently, the association between these newly derived CS-subphenotype classes with clinical outcomes was determined using regression-based models with adjustment for traditional risk factors (e.g., SCAI shock stages). Then, in the three CS RCTs (OptimaCC [NCT01367743], DOREMI [NCT03207165] and CULPRIT-SHOCK [NCT01927549]),^{15–17} a simplified approach to classify patients based on the nearest CardShock subphenotype centroid (i.e., data points that represent the centre of each subphenotype) was used. This classification approach is not based on cut-offs. Finally, their impact on treatment effect in the RCTs regarding outcome was explored.

Data sources and population

The design (inclusion criteria, primary outcome) and characteristics of the prospective observational cohorts and three RCTs were published elsewhere^{12,13,15–17} and are described/summarized in Table 1.

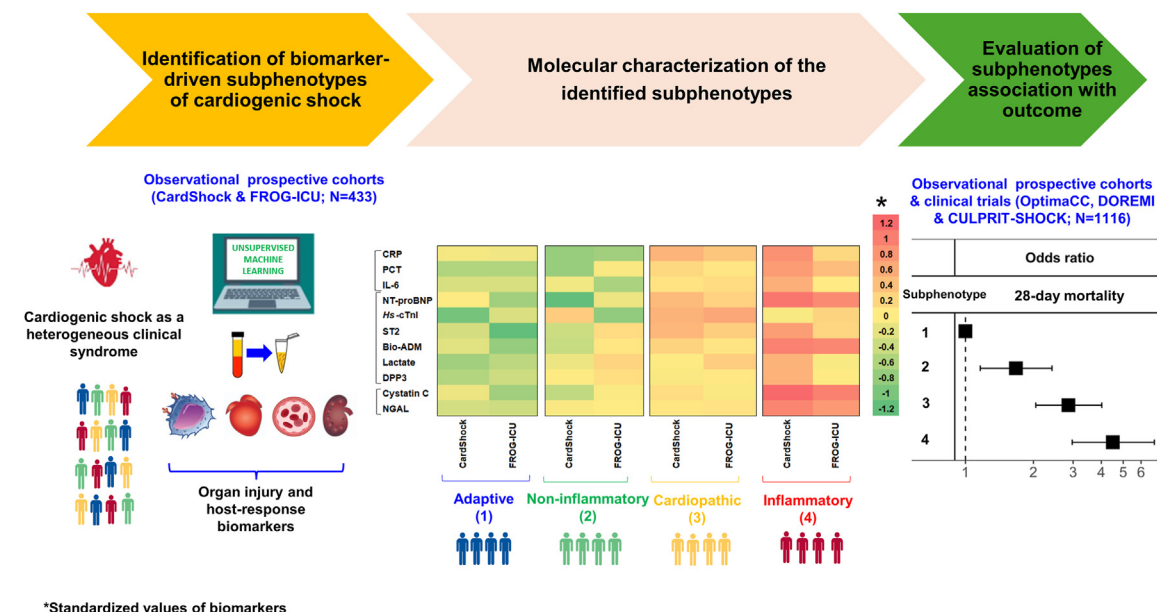


Fig. 1: Graphical schematic of study design.

All five studies were conducted in accordance with the Declaration of Helsinki. Reporting of the current reanalysis of the five studies was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and guidelines.¹⁸

Definition of cardiogenic shock

The definitions of CS in the CardShock (N = 205), OptimaCC (N = 57) and CULPRIT-SHOCK (N = 434) studies were aligned with their original inclusion criteria and met the SCAI definition of CS stage C, D and E (the SCAI classification was performed retrospectively)¹⁹ (Table 1). In the FROG-ICU cohort, the identification of CS patients was performed retrospectively based on the reported main cause for admission, clinical notes and clinical, biological and echocardiography data within the first 24 h after inclusion (Supplementary Fig. S1). The selected CS study population (N = 228) presented persistent hypotension and signs of hypoperfusion as inclusion criteria and met the SCAI definition of shock stage C, D and E. CS patients in the DOREMI trial (N = 192), met the SCAI stages B, C, D and E (original inclusion criteria) (Table 1).

Study outcomes

The primary outcome in the current study was all-cause mortality 28 days after inclusion. Secondary outcomes were all-cause one-year mortality and the use of organ support in the intensive care unit (ICU) (e.g., venoarterial extracorporeal membrane oxygenation (VA-ECMO), left ventricular assist device (LVAD), renal replacement therapy (RRT)).

Data collection and candidate biomarkers for phenotyping

Readily available clinical, biological, echocardiography and treatment data were recorded at inclusion and during ICU stay in the five studies. Severity scores were calculated at inclusion. Data collection details of the five studies are published elsewhere.^{12,15–17,20} In addition to routine laboratory data, host response and organ dysfunction circulating markers (e.g., inflammatory, cardiovascular, and renal biomarkers) were collected at inclusion and at different timepoints during ICU stay and measured centrally in the original CardShock and FROG-ICU studies (Supplementary Table S1). Details of the biomarkers and the methods used to perform the assays were previously published.^{12,20–23}

The list of biomarkers collected at inclusion to be included in LCA was determined *a priori* in the CardShock and FROG-ICU studies, which were classified as the derivation and validation cohorts respectively. Readily available laboratory data at inclusion as well as host response and organ dysfunction candidate circulating markers were preselected based on the prior published literature, their association with organ injury and outcome in CS, and their availability at inclusion in

both CardShock and FROG-ICU cohorts.^{11,21,22,24,25} Variables with more than 30% missing values were excluded from the selection process.^{9,26} The final selection of eight biomarker variables included in the LCA models (creatinine, N-terminal pro B-type natriuretic peptide [NT-proBNP], bio-adrenomedullin, c-reactive protein [CRP], lactate, Alanine transaminase [ALT], platelets and high-sensitive cardiac troponin T or I) (Supplementary Table S2) was made by consensus among three critical care cardiology experts: BL, VPH and AM. A more detailed description of the selection process is reported in Supplementary Table S3. For each variable, the first value within the first 24 h after inclusion was extracted. Biomarkers that were not included in the LCA were subsequently compared across the identified subphenotypes (i.e., subphenotypes molecular characterization).^{27,28}

Statistics

LCA was secondarily used (Latent Gold, v 6.0, Statistical Innovations, Arlington, MA)^{29,30} to identify classes of CS patients based on biomarker data at inclusion in the CardShock (derivation) and FROG-ICU (validation) cohorts separately. Subphenotype classification was conducted independently from outcomes. Missing values were handled by full-information maximum likelihood (FIML) methods implemented in the Latent GOLD software.²⁹

After evaluating correlation of class-defining variables using Spearman's rank-order statistics, highly correlated variables were excluded from the LCA ($|r| > 0.5$). Log transformation was used for non-normal data before standardization (Z score) and inclusion in the LCA model. We built distinct models consisting of one to six latent classes. The optimal number of classes was decided by considering the Bayesian Information Criteria (BIC) which is designed to assess the balance between accuracy and overfitting (lower values suggest model parsimony), followed by class interpretability (the extent to which additional classes provided clinically relevant information), and adequate class size (e.g., classes with at least 5% of the sample to improve replicability). Once the optimal n-class model was identified, CS patients were assigned in different classes based on the highest posterior probability (i.e., the probability [from 0 to 1] to belong to a given class).^{8,9}

The associations between subphenotype membership and 28-day mortality and secondary outcomes were analysed. Comparisons of baseline characteristics and circulating marker concentrations between subphenotypes were conducted within the first 24 h after inclusion. Continuous variables were expressed as median with interquartile range (IQR) and categorical variables were expressed as frequencies and percentages. Comparisons of participant characteristics were performed using Mann–Whitney or Kruskal–Wallis tests for continuous variables and Chi² test or Fisher–

Study (population size)	Design	Enrolment period	Inclusion criteria	Compared treatment	Primary outcome
CardShock cohort (n = 205 over 219) ^a	Prospective multicentre cohort study	2010–2012	<ul style="list-style-type: none"> - Age ≥18 years - Inclusion ≤6 h from the identification of CS - Acute cardiac cause with SBP <90 mmHg for 30 min OR vasopressor therapy to maintain SBP >90 mmHg - AND signs of hypoperfusion (AMS, cold periphery, oliguria <0.5 ml/kg/h (6 h), lactate >2 mmol/l). 	NA	All-cause in-hospital mortality
FROG-ICU cohort (n = 228 over 2087) ^b	Prospective multicentre cohort study	2011–2013	<ul style="list-style-type: none"> - Age ≥18 years - Invasive mechanical ventilation OR treatment with vasopressors ≥24 h. - The main ICU admitting diagnosis is CS OR CA with cardiac cause. - AND signs of hypoperfusion at inclusion (AMS, UO <720 ml/24 h, lactate >2 mmol/l) that requires an initial set of interventions (inotropes, vasopressor, mechanical support) to restore perfusion. 	NA	One-year mortality
OptimaCC trial (n = 57)	Randomized controlled trial	2011–2016	<ul style="list-style-type: none"> - Age ≥18 years - CS due to AMI successfully revascularized by using PCI and fulfilling the following criteria: <ol style="list-style-type: none"> 1) SBP <90 mm Hg OR MAP <65 mm Hg without a vasopressor agent OR need for vasopressor therapy to correct hypotension. 2) CI <2.2 l/min/m² in the absence of vasopressor or inotrope therapy. 3) Pulmonary artery occlusion pressure >15 mm Hg OR echocardiographic evidence of high pressure. 4) Echocardiographic ejection fraction <40% without inotrope support. 5) At least one evidence of tissue hypoperfusion (e.g., skin mottling, oliguria, elevated lactate level, altered consciousness); AND 6) An inserted pulmonary artery catheter. 	Epinephrine vs. Norepinephrine	Cardiac index evolution, and the occurrence of refractory CS.
DOREMI trial (n = 192)	Randomized controlled trial	2017–2020	<ul style="list-style-type: none"> - Age ≥18 years, admitted to the cardiac intensive care unit (ICU), AND - Had cardiogenic shock meeting the SCAI definition of CS stage B, C, D, or E. 	Milrinone vs. Dobutamine	Composite outcome of: in-hospital death from any cause, resuscitated CA, receipt of a cardiac transplant or MCS, nonfatal MI, transient ischemic attack or stroke, or initiation of RRT.
CULPRIT-SHOCK trial (n = 434 over 706) ^c	Randomized controlled trial	2013–2017	<ul style="list-style-type: none"> - Acute myocardial infarction with multivessel disease and cardiogenic shock. - Cardiogenic shock criteria: SBP <90 mmHg OR the use of catecholamine therapy to maintain SBP ≥90 mmHg, clinical signs of pulmonary congestion AND signs of impaired organ perfusion (altered mental status, or cold limbs, or oliguria with UO <30 ml/h, or arterial lactate level ≥2 mmol/l) 	PCI of the culprit lesion only vs. immediate multivessel PCI	Composite outcome of death or severe renal failure leading to RRT within 30 days after randomization.

Abbreviations: RCT, randomized controlled trial; ICU, intensive care unit; SBP, systolic blood pressure; AMS, altered mental status, UO, urine output; MAP, mean arterial pressure; CI, cardiac index; SCAI, Society for Cardiovascular Angiography and Interventions; CA, cardiac arrest; MCS, mechanical circulatory support; MI, myocardial infarction; RRT, renal replacement therapy; PCI, percutaneous coronary intervention. ^aPatients who died within the first 24 h after admission were not included in the current reanalysis of the CardShock cohort. ^bOnly patients with CS criteria were included in the current reanalysis of the FROG-ICU cohort. ^cOnly patients with biomarker data were included in the current reanalysis of the CULPRIT-SHOCK trial.

Table 1: Characteristics of the reanalysed cohorts and trials.

Freeman-Halton test for categorical variables as appropriate. To examine the impact of class membership on 28-day mortality, survival curves were generated by the

Kaplan–Meier estimator and compared using log-rank test. Multivariable survival analysis was performed using a Cox proportional hazards regression model and

adjusted hazard ratios (HR) with 95% confidence intervals (CI) were reported. Subphenotype membership at inclusion and traditional mortality risk factors were included in the Cox regression model (i.e., age, comorbidities, severity of shock, ischemic origin of CS and prior cardiac arrest). Variables with collinearity were excluded from the regression models (variance inflation factor >5). A rule of a minimum of 5–10 events for each predictor variable was considered.³¹ Inference was combined from the sets of 20 imputed samples using Rubin's rules. Cox models' discriminations were assessed using Harrell's C-statistic analysis. To assess the improvement in discrimination of adding the identified subphenotypes to a Cox regression model with traditional predictors of early mortality (e.g., SCAI shock stages), the difference in the Harrell C-statistic between the aforesaid prediction models was assessed.³² The individual variables used in the LCA to determine the subphenotypes were also examined to select the best linear combination of three of them that maximised the C-index. These variables were then used in Cox models to evaluate whether adding the subphenotypes as a variable further improved the C-index. For internal validation, a bootstrap resampling (2000 samples) was used to quantify any optimism within the different models.

In the three RCTs, missing data for class-defining variables were presented in [Supplementary Table S4](#). Missing values were handled by multiple imputation by chained equations (R-package 'mice'). A total of 20 imputed datasets were generated using all covariates and the primary outcome. Log transformation was performed for non-normal data and the available class-defining variables were standardized. In each of the imputed datasets, subphenotype membership was predicted separately by calculating the Euclidean distances using the available class-defining variables in individual patients to the centroid of each subphenotype from the CardShock derivation cohort. Thereafter, final subphenotype assignment in the different RCTs was the one selected in the most imputed datasets (i.e., majority vote in the 20 imputed datasets). The subphenotypes description was based on the final class assignment and the original dataset (with missing values).^{8,9} To explore the heterogeneity of treatment effect, the association between the different interventions and clinical outcomes by subphenotypes was assessed (odds ratios [ORs] with 95% CI).³³ Logistic regression models with a test for interaction of the subphenotype classes with the tested interventions (i.e., their product as predictor) were also used.^{34,35} A significance level of 0.10 was used for interaction *p* values.³⁶

Two-sided tests were applied with $p \leq 0.05$ considered statistically significant. The analyses were performed using Latent GOLD software (v 6.0, Statistical Innovations, Arlington, MA) for LCA and SPSS 24.0 statistical software (IBM Corp., Armonk, NY, USA) and

the R statistical software on R Studio (<https://www.r-project.org/>).

Ethics

The reanalyses of the five studies were performed in compliance with their original local ethics committee's approval.^{9,12,13,15–17} The current study was performed in compliance with Unity Health Toronto (Toronto, Ontario, Canada) Research Ethics Board (n° 19–138).

Role of funding source

The funders of this research project had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Patient characteristics across the different prospective cohorts and RCTs are summarized in [Supplementary Table S5](#). The rates of CS of ischemic origin ranged from 34% (N = 65/192, DOREMI) to 100% (N = 434, CULPRIT-SHOCK). Across the different studies, the 28-day mortality rates ranged from 26% (N = 59/228, FROG-ICU) to 47% (N = 198/434, CULPRIT-SHOCK) ([Supplementary Table S5](#)).

Identification of cardiogenic shock subphenotypes in the derivation and validation cohorts

In both CardShock and FROG-ICU cohorts, a four-class LCA model was selected as the optimal fit clustering solution. A summary of the model fits for one to six classes for the derivation and validation cohorts is provided in the [Supplementary Tables S6 and S7](#). The missing data per biomarker variable included in the LCA models in both CardShock and FROG-ICU cohorts are presented in [Supplementary Table S2](#). The class-defining biomarker variables correlations are summarized in [Supplementary Fig. S2](#). Patient assignments to the distinct subphenotypes in the derivation and validation cohorts are presented in [Tables 2 and 3](#).

Clinical and host-response biomarker patterns in cardiogenic shock subphenotypes

Baseline, clinical/biological characteristics and outcomes across subphenotypes in the derivation and validation cohorts are summarized in [Tables 2 and 3](#) and [Supplementary Tables S8 and S9](#). Standardized mean difference plots of class-defining variables of the two cohorts are shown in [Fig. 2A](#). Overall, the four identified classes of CS patients using LCA in the CardShock and FROG-ICU cohorts presented similar clinical and biological characteristics. Patients with the adaptive subphenotype 1 had less comorbidity and organ dysfunction with lower circulating concentrations of creatinine and lactate on ICU admission. Patients with the non-inflammatory subphenotype 2 had less organ dysfunction and a lower circulating concentration of

	Subphenotype 1 (Adaptive) (n = 49)	Subphenotype 2 (Non-Inflammatory) (n = 56)	Subphenotype 3 (Cardiopathic) (n = 73)	Subphenotype 4 (Inflammatory) (n = 27)	p
Demographics					
Age, years ^a	65 (58–74)	66 (57–73)	67 (61–76)	67 (57–75)	0.79
Sex, male, n (%)	33 (67%)	43 (79%)	56 (77%)	19 (70%)	0.61
BMI, kg/m ^{2a}	26 (23–28)	26 (24–31)	26 (24–28)	26 (24–30)	0.56
Past medical history^a					
Previous myocardial infarction, n (%)	13 (26%)	8 (14%)	20 (27%)	6 (22%)	0.31
Previous PCI, n (%)	6 (12%)	6 (11%)	12 (16%)	3 (11%)	0.77
Previous CABG, n (%)	2 (4%)	2 (4%)	5 (7%)	6 (22%)	0.013
Previous stroke or transient ischemic attack, n (%)	6 (12%)	6 (11%)	6 (8%)	3 (11%)	0.90
Chronic kidney disease, n (%)	2 (4%)	2 (4%)	3 (4%)	12 (44%)	<0.0001
Chronic heart failure, n (%)	14 (29%)	1 (2%)	8 (11%)	9 (33%)	<0.0001
Peripheral arterial disease, n (%)	5 (10%)	7 (12%)	6 (8%)	3 (11%)	0.88
COPD, n (%)	9 (18%)	3 (5%)	5 (7%)	5 (18%)	0.057
Diabetes mellitus, n (%)	13 (26%)	16 (29%)	21 (29%)	7 (26%)	0.98
Severity of illness					
Charlson age-comorbidity index ^a	4 (2–5)	3 (1–4)	4 (2–5)	5 (3–7)	0.019
APACHE II ^a	12 (9–19)	19 (12–24)	20 (12–25)	27 (15–28)	<0.0001
SCAI shock stage, n (%) ^a					<0.0001
C	19 (39%)	7 (12%)	23 (31%)	1 (4%)	
D	23 (47%)	20 (36%)	35 (48%)	21 (78%)	
E	7 (14%)	29 (52%)	15 (20%)	5 (18%)	
Admission diagnoses^c					
ACS	27 (55%)	53 (95%)	70 (96%)	15 (56%)	<0.0001
Cardiac arrest	6 (12%)	30 (54%)	16 (22%)	5 (18%)	<0.0001
OHCA (n = 204)	1 (2%)	7 (12%)	5 (7%)	1 (4%)	0.17
ICU stay and organ support					
Duration of ICU stay, days	5 (2–7)	5 (2–10)	5 (2–11)	8 (3–14)	0.43
Mechanical ventilation, n (%) ^a (n = 204)	27 (55%)	40 (71%)	32 (44%)	14 (54%)	0.020
Vasopressors/inotropes use, n (%) ^a (n = 203)	46 (94%)	54 (96%)	67 (94%)	27 (100%)	0.58
RRT, n (%) ^b (n = 204)	4 (8%)	5 (9%)	11 (15%)	14 (52%)	<0.0001
IABP, n (%) ^b (n = 204)	26 (53%)	39 (70%)	40 (56%)	15 (56%)	0.28
LVAD/V-A ECMO, n (%) ^b (n = 203)	1 (2%)	3 (5%)	0 (0%)	0 (0%)	0.14
Outcomes					
28-day mortality, n (%)	7 (14%)	18 (32%)	27 (37%)	13 (48%)	0.011
Composite outcome of in-ICU mortality, receipt of VA-ECMO/LVAD or RRT initiation, n (%)	8 (17%)	22 (39%)	27 (37%)	20 (74%)	<0.0001
One-year mortality, n (%)	12 (24%)	20 (36%)	33 (45%)	17 (63%)	0.0070

Continuous variables are expressed as medians (IQR) and categorical variables as numbers (%). Comparisons across all 4 phenotypes were performed using Kruskal–Wallis test for continuous variables and χ^2 test or Fisher–Freeman–Halton test for categorical variables as appropriate. Abbreviations: ICU, intensive care unit; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary-artery bypass grafting; COPD, Chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation; SCAI, Society for cardiovascular angiography and interventions; ACS, acute coronary syndrome; OHCA, out-of-hospital cardiac arrest; RRT, renal replacement therapy; IABP, Intra-aortic balloon pump; LVAD, Left ventricular assist device; V-A ECMO, Veno-arterial extracorporeal membrane oxygenation; IQR, interquartile range. ^aAt inclusion. ^bDuring ICU stay. ^cNot mutually exclusive.

Table 2: Baseline characteristics and outcomes by subphenotype in the CardShock derivation cohort (n = 205).

CRP. Patients with the cardiopathic subphenotype 3 had higher heart rate and higher circulating concentrations of cardiac biomarkers (High-sensitivity Troponin I and T and NT-proBNP). Patients with the inflammatory subphenotype 4 had more comorbidities, higher severity scores and higher circulating concentrations of creatinine, lactate, and CRP (Fig. 2A, Supplementary Tables S8 and S9).

To ascertain that CS subphenotypes represent classes of patients with distinct underlying mechanistic signatures, host-response circulating markers reflecting organ injury/dysfunction and inflammation were analysed and compared across the distinct LCA-derived classes. Patients in the adaptive subphenotype had the lowest concentration of Dipeptidyl peptidase 3 (DPP3), an active circulating marker that modulates the renin-

	Subphenotype 1 (Adaptive) (n = 72)	Subphenotype 2 (Non-Inflammatory) (n = 35)	Subphenotype 3 (Cardiopathic) (n = 75)	Subphenotype 4 (Inflammatory) (n = 46)	p
Demographics					
Age, years ^a	53 (48–68)	63 (47–74)	65 (56–74)	64 (53–75)	<0.0001
Sex, male, n (%)	49 (68.1%)	21 (60.0%)	52 (69.3%)	31 (67.4%)	0.80
BMI, kg/m ^{2a}	25 (22–27)	27 (23–34)	26 (23–29)	27 (24–29)	0.30
Past medical history^a					
Coronary artery disease, n (%)	9 (12%)	4 (11%)	13 (17%)	10 (22%)	0.48
Previous myocardial infarction, n (%)	6 (8%)	1 (3%)	8 (11%)	4 (9%)	0.59
Previous revascularization, n (%)	5 (7%)	4 (11%)	10 (13%)	4 (9%)	0.61
Previous stroke or transient ischemic attack, n (%)	5 (7%)	0 (0%)	7 (9%)	4 (9%)	0.32
Chronic kidney disease, n (%)	1 (1%)	5 (14%)	7 (9%)	16 (35%)	<0.0001
Chronic heart failure, n (%)	1 (1%)	5 (14%)	6 (8%)	9 (20%)	0.006
Peripheral arterial disease, n (%)	5 (10%)	7 (12%)	6 (8%)	3 (11%)	0.79
COPD, n (%)	5 (7%)	3 (9%)	5 (7%)	4 (9%)	0.96
Diabetes mellitus, n (%)	4 (6%)	10 (29%)	13 (17%)	13 (28%)	0.0030
Severity of illness					
Charlson age-comorbidity index ^a	1 (1–3)	4 (1–5)	3 (1–4)	5 (1–6)	<0.0001
SAPS II ^a	57 (48–65)	56 (48–64)	69 (51–78)	64 (49–78)	<0.0001
SCAI shock stage, n (%) ^a					<0.0001
C	62 (86%)	26 (74%)	46 (61%)	19 (41%)	
D	4 (6%)	2 (6%)	18 (24%)	14 (30%)	
E	6 (8%)	7 (20%)	11 (15%)	13 (28%)	
Admission diagnoses^c					
ACS, n (%)	28 (39%)	10 (29%)	38 (51%)	15 (33%)	0.099
Cardiac arrest, n (%)	44 (61%)	7 (20%)	43 (57%)	10 (22%)	<0.0001
OHCA, n (%)	42 (58%)	3 (9%)	37 (49%)	5 (11%)	<0.0001
ICU stay and organ support					
Duration of ICU stay, days	6 (5–9)	8 (4–19)	9 (5–13)	11 (5–19)	0.0020
Mechanical ventilation, n (%) ^a	67 (93%)	28 (80%)	68 (91%)	39 (85%)	0.17
Vasopressors/inotropes use, n (%) ^a	59 (82%)	30 (86%)	67 (89%)	43 (93%)	0.28
RRT, n (%) ^b	3 (4%)	4 (11%)	18 (24%)	22 (48%)	<0.0001
IABP, n (%) ^b	4 (6%)	1 (3%)	8 (11%)	3 (6%)	0.43
LVAD/VA-ECMO, n (%) ^b	4 (6%)	4 (11%)	8 (11%)	11 (24%)	0.022
Outcomes					
28-day mortality, n (%)	8 (11%)	9 (26%)	25 (33%)	17 (37%)	0.0040
Composite outcome of in-ICU mortality, receipt of VA-ECMO/LVAD or RRT initiation, n (%)	14 (19%)	11 (31%)	39 (52%)	31 (67%)	<0.0001
One-year mortality, n (%)	9 (12%)	14 (40%)	32 (43%)	28 (61%)	<0.0001

Abbreviations: ICU, intensive care unit; BMI, body mass index; COPD, Chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiologic Score; SCAI, Society for cardiovascular angiography and interventions; ACS, acute coronary syndrome; OHCA, out-of-hospital cardiac arrest; RRT, renal replacement therapy; IABP, Intra-aortic balloon pump; LVAD, Left ventricular assist device; V-A ECMO, Veno-arterial extracorporeal membrane oxygenation; IQR, interquartile range. Continuous variables are expressed as medians (IQR) and categorical variables as numbers (%). Comparisons across all 4 phenotypes were performed using Kruskal-Wallis test for continuous variables and χ^2 test or Fisher-Freeman-Halton test for categorical variables as appropriate. ^aAt inclusion. ^bDuring ICU stay. ^cNot mutually exclusive.

Table 3: Baseline characteristics and outcomes by subphenotype in the FROG-ICU validation cohort (n = 228).

angiotensin-aldosterone system (RAAS). Patients classified as non-inflammatory had the lowest level of biomarkers of inflammation (procalcitonin and interleukin-6 [IL-6]). Patients in the cardiopathic subphenotype had the highest concentration of soluble form of suppression of tumorigenicity 2 (ST2), a circulating marker of myocardial fibrosis and adverse remodelling. Patients in the inflammatory subphenotype presented

with a higher concentration of circulating markers of renal injury (Neutrophil gelatinase associated lipocalin (NGAL) and Cystatin C), endothelial dysfunction (bio-adrenomedullin) and inflammation (IL-6) (Fig. 2B). Differences in host response biomarker concentrations between subphenotypes persisted after subgroup analysis stratified by age terciles, Charlson age-comorbidity index terciles, severity of shock (SCAI shock stages) and the

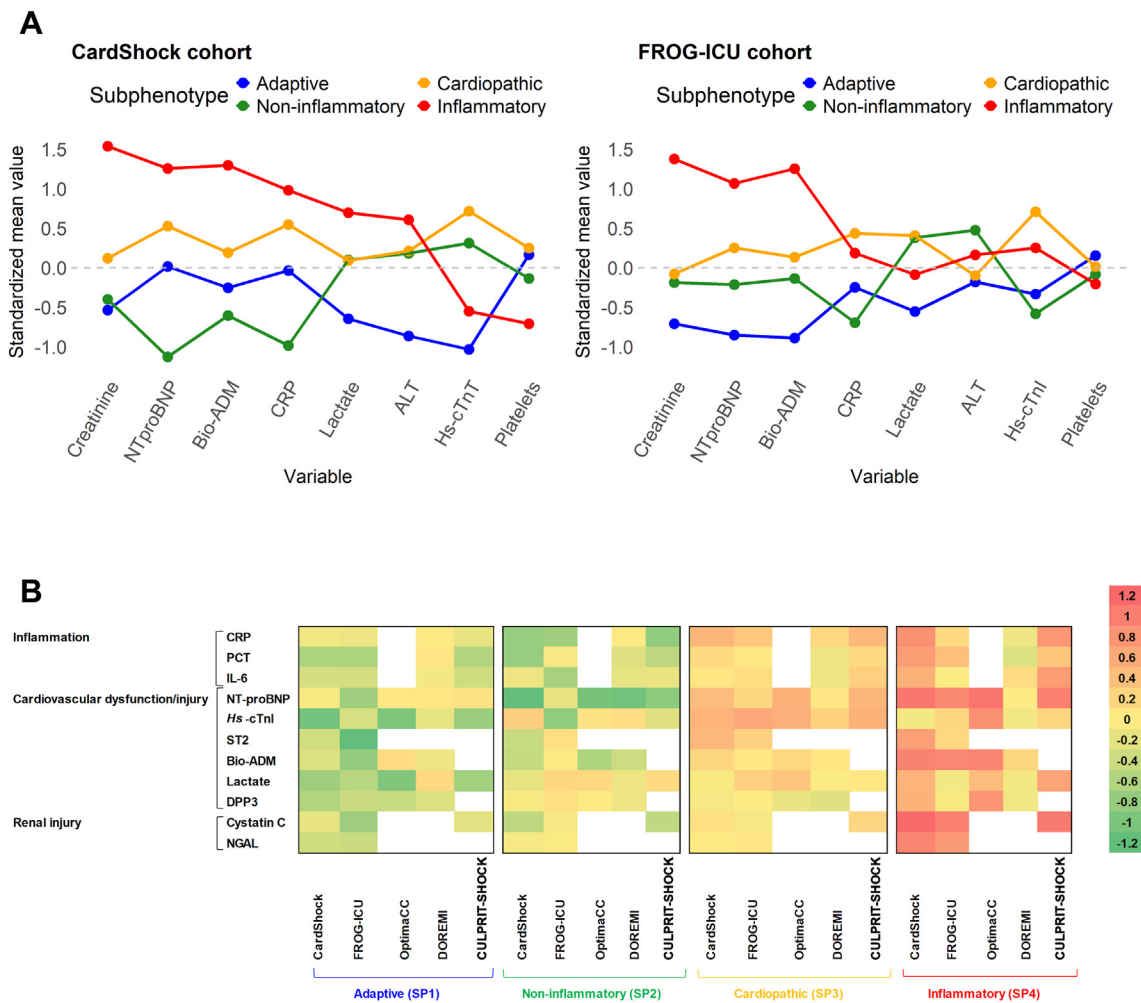


Fig. 2: (A) Comparison of class-defining variables using latent class analysis at inclusion in the CardShock cohort and the FROG-ICU cohort. Description: continuous variables were plotted after natural log transformation. Every normalized variable was standardized such that all means are scaled to 0 and SDs to 1. Group means of standardized values are shown by subphenotypes. A value of +1 for the standardized variable (y-axis) indicates that the mean value for a given subphenotype was one SD higher than the mean value in a whole cohort. Subphenotype classes sizes at inclusion (n): CardShock cohort: adaptive subphenotype N = 49, non-inflammatory subphenotype N = 56, cardiopathic subphenotype N = 73, inflammatory subphenotype N = 27; FROG-ICU cohort: adaptive subphenotype N = 72, non-inflammatory subphenotype N = 35, cardiopathic subphenotype N = 75, inflammatory subphenotype N = 46. **(B)** Biomarker heatmap across the different subphenotypes in the analysed studies. The heatmap shows the standardized median values of host response and organ dysfunction circulating markers (i.e., inflammation, endothelial dysfunction, myocardial injury and fibrosis, cardiac congestion and renal injury). Green colour represents lower standardized median values in a given subphenotype compared with the median of the whole study while red colour represents a higher value compared with the standardized median of the whole study. White cells represent biomarkers that were not measured/available. Abbreviations: SD, standard deviations; LCA, latent class analysis; CRP, C-reactive protein; PCT, Procalcitonin; IL6, Interleukin-6; NT-proBNP, N-terminal pro B-type natriuretic peptide; ALT, Alanine transaminase; Hs-cTnT, *high-sensitive cardiac troponin T*; Hs-cTnI, *high-sensitive cardiac troponin I*; ST2, soluble form of suppression of tumorigenicity 2; Bio-ADM, Bio-adrenomedullin; DPP3, Dipeptidyl peptidase 3; NGAL, neutrophil gelatinase-associated lipocalin; SP, subphenotype.

aetiology of CS (ischemic vs. non-ischemic) (Supplementary Figs. S3–S6).

Association between LCA-derived subphenotypes and outcomes

Patients in the inflammatory subphenotype had the highest 28-day mortality in the CardShock and the FROG-ICU cohorts (Tables 2 and 3 and Fig. 3A). In a

Cox proportional hazards model adjusted for traditional risk factors (i.e., Charlson age-comorbidity index, SCAI shock stage, ischemic origin of CS and prior cardiac arrest), membership in the cardiopathic and inflammatory subphenotypes were independently associated with 28-day mortality (the adaptive subphenotype as reference) in the CardShock and the FROG-ICU cohorts. In a second Cox regression model adjusted for

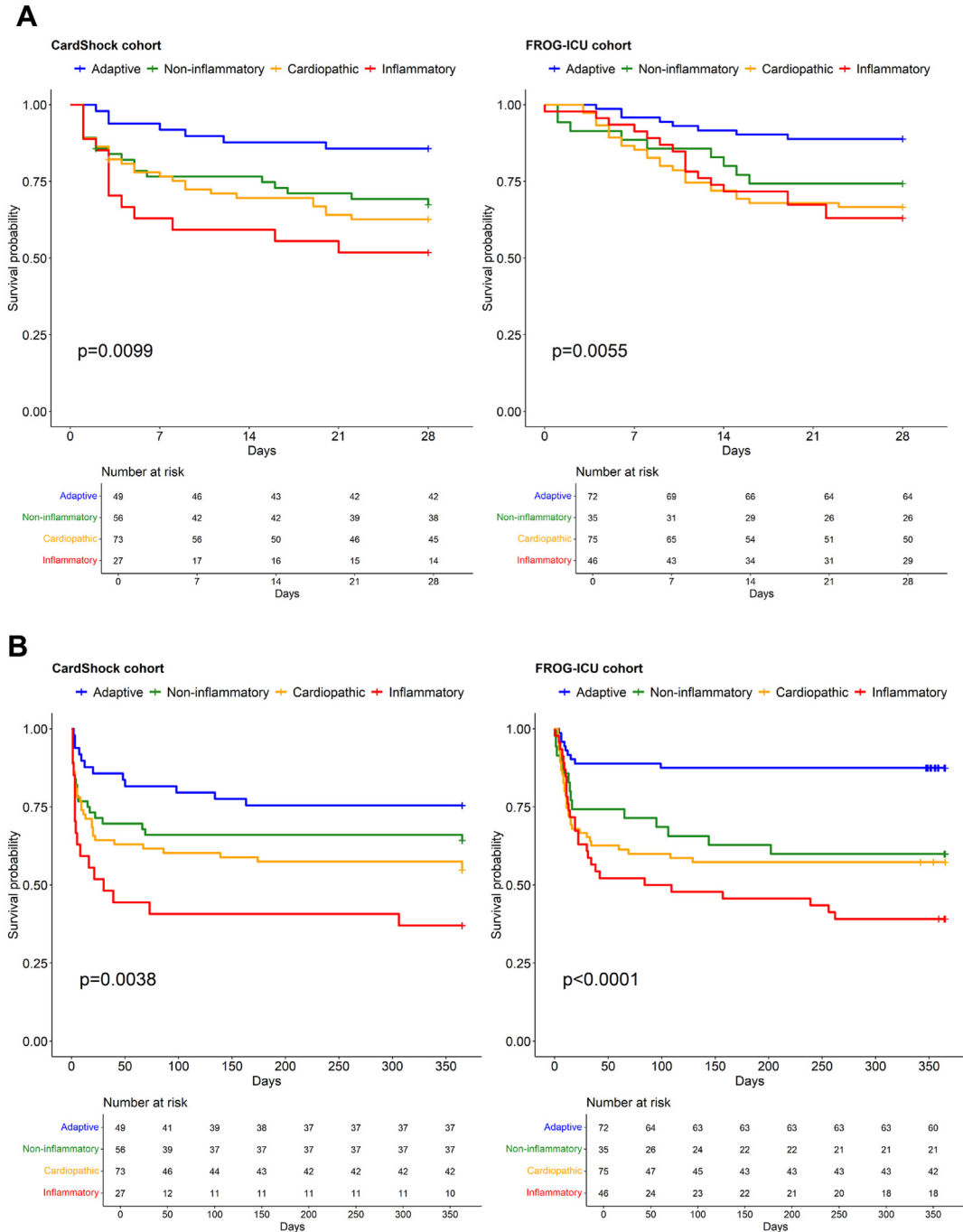


Fig. 3: (A) 28-day survival curves according to subphenotype membership in the CardShock cohort and the FROG-ICU cohort. **(B)** One-year survival curves according to subphenotype membership in the CardShock and FROG-ICU cohorts. The log-rank tests between the survival curves of the different subphenotypes showed a $p < 0.05$ in the two cohorts.

Charlson age-comorbidity index, ischemic origin of CS, prior cardiac arrest, creatinine, lactate and bioadrenomedullin on admission, membership in the inflammatory subphenotype was independently associated with 28-day mortality in the CardShock and the FROG-

ICU cohorts. When added to these traditional risk factors in the two Cox regression models, subphenotype membership significantly improved the model discrimination (C-statistic) (Table 4 and Supplementary Table S10). In the second Cox model, the

subphenotypes improved the C-index showing that they added value to models beyond that what could be obtained from a simple linear combination of the variables themselves (Supplementary Table S10).

There was also a significant difference in one-year mortality between the four subphenotypes in the CardShock and FROG-ICU cohorts with overall a higher long-term all-cause mortality in the cardiopathic and inflammatory subphenotypes (Tables 2 and 3 and Fig. 3B).

Subphenotype membership prediction in the clinical trials

A simplified classifier (i.e., distances to the different subphenotype centroids) was developed in the CardShock cohort to allow subphenotype assignment in independent RCTs.

Differences in standardized class-defining variables between subphenotypes using the simplified classifier are presented in Supplementary Fig. S7 (CardShock and FROG-ICU cohorts) and Fig. 4 (OptimaCC, DOREMI and CULPRIT-SHOCK trials). In the three selected RCTs, at least six of the eight biomarker class-defining variables used in the CardShock and FROG-ICU cohorts were available (Fig. 4 and Supplementary Table S4). Unadjusted ORs for the association of the

four subphenotypes with 28-day mortality in the three trials and the two prospective observational cohorts (CardShock and FROG-ICU) are presented individually and after merging the five studies (N = 1116) (Fig. 5).

Overall, the four subphenotypes identified by the simplified classifier in the three studied RCTs (OptimaCC, DOREMI and CULPRIT-SHOCK), had similar baseline and biological characteristics, and risks of death (i.e., a higher mortality in the cardiopathic and inflammatory subphenotypes) compared with the corresponding LCA-derived subphenotypes in the CardShock and FROG-ICU cohorts (Supplementary Tables S11–S13).

Exploratory analysis of heterogeneity of treatment effect across subphenotypes

The associations between the different interventions and clinical outcomes (28 day-mortality and a composite outcome of in-ICU mortality, receipt of VA-ECMO/LVAD/Impella device or RRT initiation) by subphenotypes were assessed and tests for interaction between the treatment and the subphenotypes were performed in the different RCTs.

In the CULPRIT-SHOCK (PCI of the culprit lesion only vs. immediate multivessel PCI) and the DOREMI (milrinone vs. dobutamine) RCTs no significant

Variable	CardShock cohort (n = 205)		FROG-ICU cohort (n = 228)	
	Adjusted HR (CI 95%)	p value	Adjusted HR (CI 95%)	p value
Model with subphenotypes	Harrell's C-index = 0.70 (95% CI: 0.64, 0.76) Optimism = 0.04		Harrell's C-index = 0.68 (95% CI: 0.61, 0.75) Optimism = 0.04	
Subphenotypes (Adaptive as reference)				
Non-Inflammatory	1.96 (0.77–5.00)	0.16	2.64 (0.95–7.30)	0.062
Cardiopathic	2.65 (1.09–6.40)	0.031	2.99 (1.31–6.80)	0.0093
Inflammatory	2.80 (1.07–7.30)	0.036	3.32 (1.29–8.60)	0.013
Charlson age-comorbidity index	1.18 (1.06–1.30)	0.0026	1.10 (0.99–1.20)	0.075
Ischemic CS	1.43 (0.63–3.20)	0.40	1.07 (0.60–1.90)	0.83
Prior CA	0.48 (0.10–2.30)	0.35	1.75 (0.95–3.20)	0.073
SCAI shock stage (C as reference)				
D	1.91 (0.86–4.20)	0.11	1.09 (0.55–2.20)	0.81
E	5.33 (1.02–27.90)	0.048	1.35 (0.67–2.70)	0.40
Model without subphenotypes	Harrell's C-index = 0.67 (95% CI: 0.61, 0.73); Optimism = 0.03		Harrell's C-index = 0.64 (95% CI: 0.57, 0.71) Optimism = 0.04	
Charlson age-comorbidity index	1.19 (1.08–1.30)	0.00054	1.15 (1.04–1.30)	0.0064
Ischemic CS	1.79 (0.84–3.80)	0.13	1.12 (0.64–1.90)	0.70
Prior CA	0.57 (0.13–2.50)	0.45	1.53 (0.86–2.70)	0.15
SCAI shock stage (C as reference)				
D	2.08 (0.96–4.50)	0.065	1.35 (0.69–2.70)	0.37
E	4.90 (1.01–23.80)	0.048	1.69 (0.88–3.30)	0.11

After adjustment for Charlson Age-Comorbidity Index, ischemic CS, prior CA and SCAI shock stages, membership in the cardiopathic and inflammatory subphenotypes were independently associated with 28-day mortality in the CardShock (derivation) and FROG-ICU (validation) cohorts. The model calibration was good according to the Grønnesby-Borgan test in the derivation and validation cohorts (p values of 0.79 and 0.18 respectively). A significant improvement in Cox regression model discrimination was found when adding subphenotype membership on top of Charlson Age-Comorbidity Index, ischemic CS, prior CA and SCAI shock stages with an increase in Harrell's C-index by 4% (p = 0.033) and 6% (p = 0.0068) respectively in the CardShock and the FROG-ICU cohorts. Abbreviations: HR, Hazard ratio; CI 95%, 95% Confidence interval, ICU, intensive care unit; CS, cardiogenic shock CA, cardiac arrest; SCAI, Society for cardiovascular angiography and interventions.

Table 4: Cox proportional hazards models to adjust for confounding (Charlson age-comorbidity index, SCAI shock stages, ischemic origin, prior cardiac arrest) for 28-day mortality in the CardShock and the FROG-ICU cohorts.

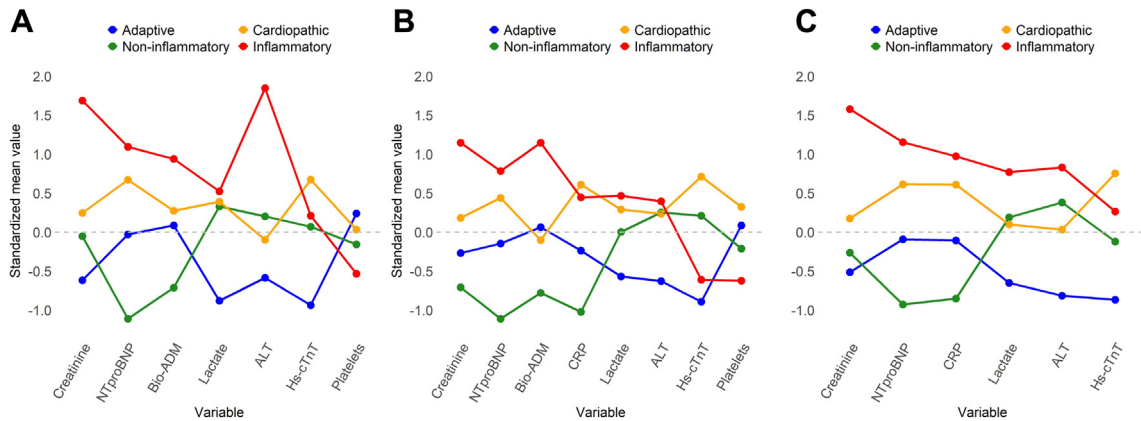


Fig. 4: Comparison of the available class-defining variables across the simplified classifier driven subphenotypes at inclusion in (A) the OptimaCC trial (N = 57), (B) the DOREMI trial (N = 192), and (C) the CULPRIT-SHOCK trial (N = 434). Description: continuous variables were plotted after natural log transformation. Every normalized variable was standardized such that all means are scaled to 0 and SDs to 1. Group means of standardized values are shown by subphenotypes. A value of +1 for the standardized variable (y-axis) indicates that the mean value for a given subphenotype was one SD higher than the mean value in a whole cohort. Sizes of the subphenotype classes determined by the parsimonious classifier (n): OptimaCC trial (A): adaptive subphenotype N = 11, non-inflammatory subphenotype N = 21, cardiopathic subphenotype N = 17, inflammatory subphenotype N = 8; DOREMI trial (B): adaptive subphenotype N = 24, non-inflammatory subphenotype N = 46, cardiopathic subphenotype N = 94, inflammatory subphenotype N = 28; CULPRIT-SHOCK (C): adaptive subphenotype N = 106, non-inflammatory subphenotype N = 141, cardiopathic subphenotype N = 101, inflammatory subphenotype N = 86. The median (IQR) frequencies of assignment of an individual to a given subphenotype across the 20 imputed datasets in the OptimaCC, DOREMI and CULPRIT-SHOCK trials were 0.80 (0.80–0.90), 0.75 (0.75–0.85) and 0.95 (0.90–0.95) respectively. Abbreviations: SD, standard deviations; NT-proBNP, N-terminal pro B-type natriuretic peptide; Bio-ADM, Bio-adrenomedullin; CRP, C-reactive protein; ALT, Alanine transaminase; Hs-cTnT, high-sensitive cardiac troponin T; Hs-cTnI, high-sensitive cardiac troponin I.

interaction between subphenotypes and treatment effect was observed (Supplementary Figs. S8 and S9).

We evaluated heterogeneity in the response to epinephrine by pooling data from the OptimaCC RCT comparing epinephrine vs. norepinephrine and the CardShock cohort. In the CardShock cohort, we considered that epinephrine was used when CS patients were treated with epinephrine alone or in association with other inotropes/vasopressors for at least 24 h after inclusion (Supplementary Table S14). The interaction analysis adjusted for the severity of shock (i.e., SCAI shock stages) was not significant ($p > 0.10$) (Supplementary Fig. S10).

Discussion

Four biological/molecular CS subphenotypes were identified on ICU admission using a model-based clustering approach in prospective observational cohorts. Based on their clinical/molecular profiles and outcomes, we labelled the identified subphenotypes as adaptive (i.e., adaptive host response with less severe shock, less organ dysfunction and lower mortality), non-inflammatory (i.e., less systemic inflammation), cardiopathic (i.e., more myocardial injury and fibrosis), and inflammatory (i.e., more severe shock, more organ/endothelial dysfunction, more systemic inflammation and higher mortality). When adjusting for traditional

risk factors including the severity of illness and shock severity, the cardiopathic and inflammatory subphenotypes were independently associated with increased early mortality. Further, a simplified classifier was developed for prospective use and allowed the identification of similar subphenotypes in clinical trials. These results highlight that biological/molecular heterogeneity exists within the CS clinical syndrome with different underlying mechanistic signatures and clinical outcomes.

Only a few studies have used a phenotyping/clustering approach to better understand heterogeneity in CS. Those studies have used admission baseline laboratory data to identify clinical phenotypes.^{24,37,38} Zweck et al. used a clustering approach to identify three clinical phenotypes.²⁴ However, the authors haven't used biological markers of cardiac injury or congestion (e.g., troponin, NTproBNP) in their clustering of CS patients. The same authors retrospectively assigned CS patients in external prospective cohorts to the nearest clinical phenotype with an association of the 'hemometabolic' phenotype with the highest risk of early mortality.³⁷ Jentzer et al. further replicated the three aforementioned clinical phenotypes in a large North American CS patients' cohort and reported differences in echocardiographic characteristics and one-year outcome across phenotypes.³⁸ The current study used a more comprehensive panel of organ injury and host response

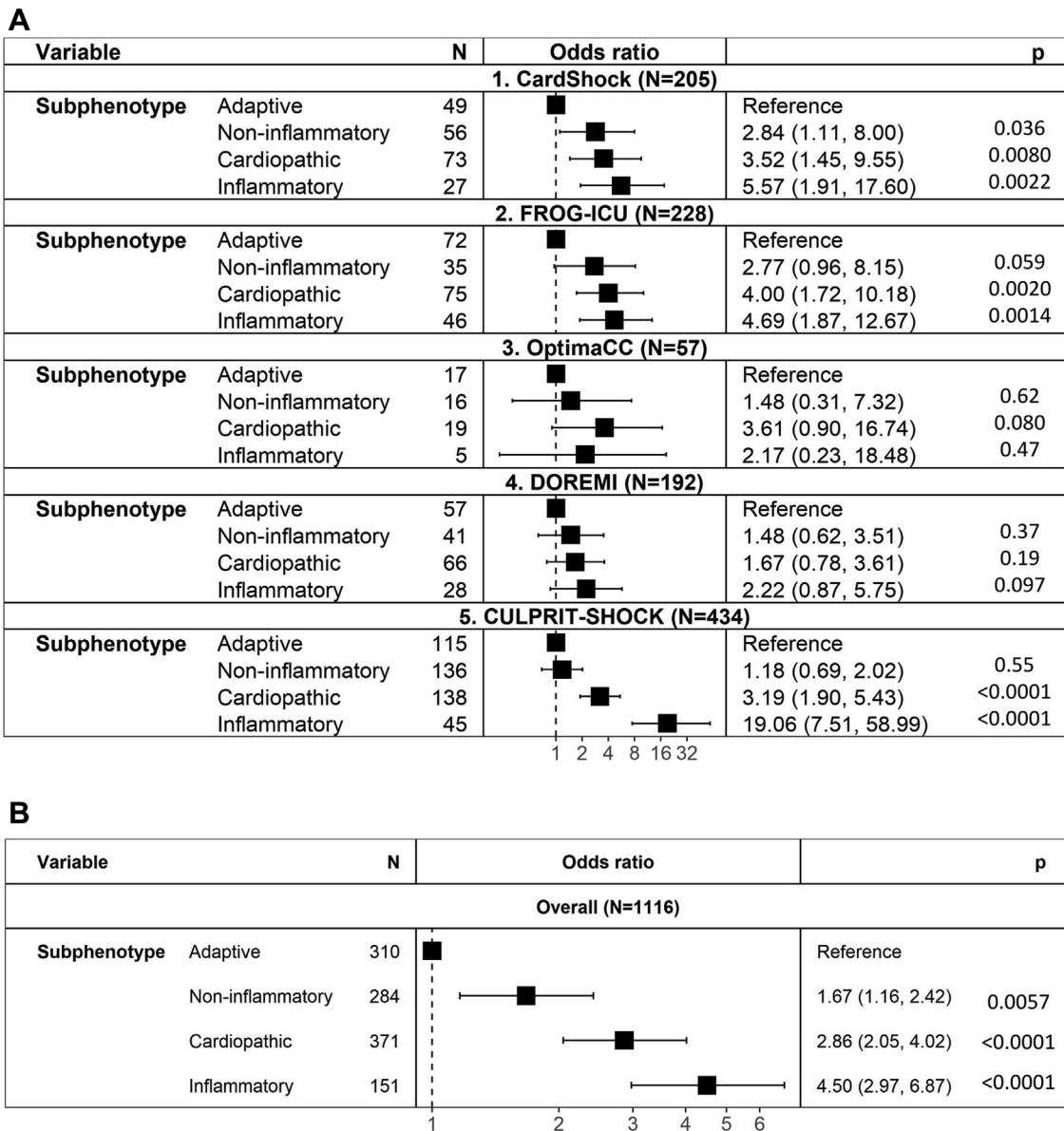


Fig. 5: Unadjusted odds ratios of the association of the four subphenotypes with death within 28 days after ICU admission across the five studies individually (A) and after merging them (B).

biomarkers that provide deeper insights into underlying pathways/mechanistic signatures. Hence, patients in the cardiopathic had the highest concentration of circulating marker of myocardial injury/fibrosis and patients in the inflammatory subphenotype presented with the highest concentrations of biomarkers of renal injury, alteration of the RAAS pathway, endothelial dysfunction, and inflammation (Fig. 2B). Most of the differences in host response biomarker concentrations persisted across subphenotypes in the CardShock and FROG-ICU cohorts after subgroup analysis stratified by

traditional patient groupings based on age terciles, Charlson age-comorbidity index terciles, severity of illness (SCAI shock stages) and the cause of CS (ischemic vs. non-ischemic).

CS patients manifesting the cardiopathic and inflammatory subphenotypes had a higher 28-day and one-year mortality. When added to traditional risk factors including the SCAI shock stages, lactate and creatinine on admission in the CardShock and FROG-ICU cohorts, subphenotype membership significantly improved Cox models' performance with a better

discrimination (significantly higher C-statistic) and a good calibration. In these models, the inflammatory subphenotype was independently associated with 28-day mortality.

In the current study, the LCA subphenotyping approach was simplified using centroid distances (i.e., nearest subphenotype) and showed retrospective applicability in RCTs cohorts. This simplified strategy is likewise amenable for prospective use at the bedside for patient selection and enrolment in future clinical trials.^{8,37}

The exploratory analysis of heterogeneity of treatment effect across subphenotypes in the three RCTs and the CardShock cohort showed no significant interaction for clinical outcomes. Identifying distinct biomarker-driven subphenotypes is promising, but it does not guarantee the distinction of specific pathways with causal links to treatment effects that might ultimately allow a personalization of intervention in CS patients. In this case, neutral RCT results may be explained by the absence of a significant treatment effect in all the molecular subphenotypes.

To further externally replicate these CS subphenotypes, a model-based clustering approach (i.e., LCA) could be applied to other independent cardiogenic shock studies. This phenotyping approach based on biomarker data also needs further evaluation in other completed neutral RCTs with different established (e.g., temporary mechanical circulatory support) or novel targeted interventions (e.g., inflammation/endothelium modulation, antibody treatment).^{39,40}

The findings of the current study suggest that overlapping systemic pathway activation in CS (e.g., myocardial injury/fibrosis, downregulation of the RAAS, endothelial dysfunction, and inflammation) may lead to different biological/molecular subphenotypes which are not necessarily associated with initial severity of shock (i.e., SCAI shock stages).^{4,41} Host response and organ injury biomarker data using unsupervised clustering approaches may allow capture of aspects of CS pathobiology that are not fully elucidated by readily available clinical/laboratory data. These analyses may not only allow pathway enrichment and prognostic enrichment, but also support future RCTs of personalized interventions in CS patients who are prospectively enrolled based on a biological/molecular pattern rather than the traditional inclusion of consecutive patients.² The implementation of a simplified classifier/clustering algorithm associated with the development of bedside point-of-care biomarker assays may allow real-time CS patient assignment in a specific subphenotype in future RCTs and early treatment allocation. This subphenotype-guided approach may be incorporated in future RCTs that test the modulation of actionable biological targets (e.g., anti-adrenomedullin and anti-DPP3 antibodies)^{42–44} and increase the likelihood of identifying a targeted treatment effect in the CS clinical syndrome.

The major strengths of this study are i) the use of *de novo* LCA separately in two prospective cohorts of CS patients with biomarker data to identify/characterize distinct subphenotypes associated with clinical outcomes even after adjusting for the severity of shock (SCAI shock stages) ii) the development of a simplified classifier that accurately identified CS subphenotypes to allow their prospective identification in future RCTs, and iii) their identification in three independent RCTs with a more homogenized/selected CS population and a better control of confounders than in non-randomized studies.

Nonetheless, this study has limitations. First, only common available biological/biomarker data in the CardShock and FROG-ICU cohorts were included in the LCA models. In the future, combining clinical features, hemodynamic/electrocardiogram waveforms data, echocardiographic/imaging data, microcirculation monitoring, and host response biomarkers (i.e., omics) may allow to 'improve' these CS subphenotypes. Nonetheless there are no guarantees that increasing data granularity/complexity will lead to better predictive enrichment. A feature that identifies a specific pathway process with causal links to treatment effects could be sufficient. Second, retrospective secondary analyses of RCTs were performed with no original stratification of randomization by subphenotypes. Third, there is a risk of overfitting when developing LCA models. To address overfitting, we used The Bayesian Information Criteria (BIC) statistic which is derived from maximum likelihood values of a fitted LCA model and introduces a penalty for models with more parameters to avoid overfitting. This approach was used in two independent cohorts (CardShock and FROG-ICU) to determine the optimal number of classes that fit the best the data. An optimal 4-class model was selected separately in both derivation and validation cohorts. Along this line, we believe that the risk of overfitting was minimized in the LCA models. Fourth, there is no consensus to determine *a priori* the required sample size for LCA models as it depends on the number of selected indicators, the quality of indicators to separate the classes, and the selected number of latent classes. In our study, the four classes/subphenotypes were well-separated in the CardShock and the FROG-ICU cohorts with mean (SD) posterior class-membership probabilities (i.e., the probability to belong to the assigned class) of 0.87 (0.18) and 0.90 (0.14) respectively (Supplementary Tables S6 and S7). This indicates that the clusters/subphenotypes are stable given the current sample size. In the three RCTs, we used a simplified classifier (centroid distances) to assign patients to the four subphenotypes individually. This approach is not dependent on the sample size of the RCTs. Fifth, the range of missingness (%) by class-defining variable was between 0% and 38% across the five studies (Supplementary Tables S2 and S4). Nonetheless, in the previous subphenotyping

research, missing data for class-defining variables of less than 40% was considered as acceptable.^{8,26} Sixth, to assign patients in the different subphenotypes in the three RCTs, a majority vote in multiple imputed datasets was used. This approach does not fully incorporate the uncertainty typically handled in multiple imputation methods using standard combining rules. Although the imputation process was repeated multiple times, the potential errors in patient allocation were not taken into account (i.e., similar to single imputation). Nonetheless, biases were minimized by using an appropriate method of imputation. The median (IQR) frequencies of assignment of an individual to a given subphenotype across the imputed datasets in the OptimaCC, DOREMI and CULPRIT-SHOCK trials were 0.80 (0.80–0.90), 0.75 (0.75–0.85) and 0.95 (0.90–0.95) respectively (Fig. 4). This suggests that our multiple imputation with majority vote approach to handle missing data is robust since subjects were assigned to the same subphenotype in a large majority of the imputed datasets. Finally, the analysis of heterogeneity of treatment effect is only exploratory and hypothesis-generating due to additional relevant limitations.

Despite these limitations, the authors were able to derive and externally replicate distinct clinically relevant biomarker-driven CS subphenotypes associated with different underlying pathobiology and early and late adverse clinical outcomes across varying study designs, inclusion criteria and locations with more than one thousand CS patients with biomarker data.

Analysis of prospective observational cohorts and RCTs of CS patients allowed the identification of four distinct subphenotypes based on biomarker data at inclusion. Overall, both early and late mortality were higher in the cardiopathic and inflammatory subphenotypes. When adjusted for standard clinical risk factors (e.g., SCAI shock stage), the cardiopathic and inflammatory subphenotypes remained independently associated with mortality and significantly improved risk stratification. No significant interaction was observed between treatment effect and subphenotypes.

Future CS adaptive trials using enrichment strategies (e.g., evaluation of biomarker and subphenotype-based interventions) should be designed in association with the development of bedside biomarker assays. This may allow a more effective identification of targeted therapeutic strategies (e.g., antibody treatments) based on the underlying biological/molecular signatures to improve clinical outcomes in CS patients (i.e., precision medicine).^{41,45}

Contributors

S.S., C.C.D.S., E.G., B.H., H.V.P., J.C.J., C.J., A.K., B.L., T.T., J.P., J.C.M., P.R.L., R.M., H.T., and A.M.: Study concept and design. S.S., M.A., E.G., R.M., T.T., A.K., M.S., F.A., K.D., Z.L., J.L., A.N., A.R., K.P.: Acquisition of data. S.S., M.A., K.D., Z.L. and C.J.: Analysis and interpretation of data. S.S., A.M.: Drafting of the manuscript. All declared authors: Critical revision of the manuscript for important intellectual content. S.S., E.G., C.J. and Z.L. had

access to and have verified the underlying data of this work. All declared authors read and approved the final version of the manuscript.

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CCCTBG trans-trial group study for InFACT—the International Forum for Acute Care Trialists: S.S., J.C.M. and C.C.D.S.

Data sharing statement

Requests for access to study data should be directed to the corresponding author for consideration. Deidentified participant data with a data dictionary can be provided pending appropriate institutional review board approvals.

Declaration of interests

None of the authors of this paper has a financial or personal relationship with other persons or organizations that could inappropriately influence or bias the content of the paper.

Dr. C.J. received honoraria for lectures/presentations from Bristol Myers Squibb (New York, US), Edwards Lifesciences (Irvine, California, US), Daichi Sankyo (Tokyo, Japan) and Boehringer-Ingelheim (Ingelheim, Germany). He received grants or had contracts with the German research foundation, the German ministry for economy and energy, the State of Nordrhein-Westfalia, the German space agency, the European Union and Edwards Lifescience (Irvine, California, US). He had leadership or fiduciary role in the German cardiac society, the German society for internal medicine, the German society for medical intensive care and the European society for intensive care medicine.

Dr. H.T. had leadership or fiduciary role in the German cardiac society.

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The remaining authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2024.103013>.

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