

Supplementary Appendix

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Table S1. Cardiovascular, inflammatory, and renal biomarkers measured on admission in the CardShock and FROG ICU cohorts.

Biomarkers	Description
Cardio-vascular biomarkers	
High- <i>sensitivity</i> Troponin I and T	-Marker of cardiomyocyte injury.
N-terminal pro-B-type natriuretic peptide (NT-proBNP)	-Marker of cardiomyocyte stress.
Bio-adrenomedullin (bio-ADM)	-Vasodilatation, induction of angiogenesis. Marker of endothelial dysfunction.
Soluble form of suppression of tumorigenicity 2 (ST2)	-Involved in myocardial remodelling and Fibrosis. Marker of cardiomyocyte stress
Dipeptidyl peptidase 3 (DPP3)	-A metallopeptidase (mainly intracellular) involved in the metabolism of cardiovascular and inflammatory mediators with a direct negative inotropic action. Modulates the renin-angiotensin-aldosterone system. Prognostic marker in acute phase of shock.
Biomarkers of infection and/or inflammation	
Interleukin-6	-Pleiotropic cytokine with both pro- and anti-inflammatory activity. Marker of inflammation.
Procalcitonin (PCT)	-Precursor of calcitonin. Marker of infection, mostly bacterial.

Renal biomarker	
Cystatin C	-Ubiquitously expressed inhibitor of lysosomal and cysteine proteinases, reabsorbed by proximal tubular cells.
Plasmatic Neutrophil	Marker of decrease glomerular filtration rate.
gelatinase associated lipocain (NGAL)	- Involved in innate immunity. Marker of renal tubular injury

Table adapted from Soussi et al. Clinical phenotypes of cardiogenic shock survivors: insights into late host responses and long-term outcomes. ESC Heart Fail. 2023 Dec 4.

Table S2. Selected biological variables included in the LCA model in the CardShock and FROG-ICU cohorts.

CardShock derivation cohort (n=205)		FROG-ICU validation cohort (n=228)		
Variables at inclusion (n=8)	N (%) of Missing values	Variables at inclusion (n=8)	N (%) of Missing values	Directionality of abnormal values
ALT	39 (19%)	ALT	62 (27%)	Maximum
Bio-ADM	35 (17%)	Bio-ADM	0 (0%)	Maximum
Creatinine	0 (0%)	Creatinine	0 (0%)	Maximum
CRP	37 (18%)	CRP	0 (0%)	Maximum
<i>Hs-cTnT</i>	37 (18%)	<i>Hs-cTnI</i>	66 (29%)	Maximum
Lactate	0 (0%)	Lactate	0 (0%)	Maximum
NT-proBNP	37 (18%)	NT-proBNP	2 (1%)	Maximum
Platelets	0 (0%)	Platelets	11 (5%)	Minimum

Variables are cited in alphabetical order. For each variable, the closest to inclusion value within the first 24 hours after inclusion was extracted.

Abbreviations: LCA, latent class analysis; ICU, Intensive care unit; ALT, Alanine transaminase; Bio-ADM, Bio-adrenomedullin; CRP, C-reactive protein; *Hs-cTnI*, *high-sensitive cardiac troponin I*; *Hs-cTnT*, *high-sensitive cardiac troponin T*; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table S3. Description of the selection process of the class-defining variables in the CardShock and FROG-ICU cohorts.

Steps (chronological order)	Description
I	Readily available laboratory data and host response biomarkers which were collected/available in both CardShock and FROG-ICU cohorts were identified by SS.
II	Different laboratory data and host response biomarkers were preselected based on the prior published literature, their association with organ injury and outcome in CS with a consensus of two reviewers SS and CDS (biomarker experts) (Tables S2 and S3).
III	SS excluded the variables with more than 30% missing values in at least one of the cohorts.
IV	The final selection of the eight class-defining biomarker variables was made by consensus among three critical care cardiology experts BL, VPH and AM (conference call discussion).
V	SS assessed the correlation of the eight class-defining variables for an <i>a priori</i> value of the Spearman's rank correlation coefficients $ r \leq 0.5$ (Figure S2).

Table S4. Missing data across randomized controlled trials for class-defining variables

Variables at inclusion	OptimaCC trial (N= 57)	DOREMI trial (N= 192)	CULPRIT-SHOCK trial (N= 434)
ALT	6 (11%)	11 (6%)	0 (0%)
Bio-ADM	0 (0%)	71 (37%)	Not available
Creatinine	5 (9%)	0 (0%)	0 (0%)
CRP	Not available	71 (37%)	0 (0%)
<i>Hs-cTnT</i>	1 (2%)	73 (38%)	0 (0%)
Lactate	1 (2%)	1 (0.5%)	12 (3%)
NT-proBNP	1 (2%)	71 (37%)	0 (0%)
Platelets	3 (5%)	1 (0.5%)	Not available

Missing data are presented as numbers (%).

Variables are cited in alphabetical order. For each variable, the closest to inclusion value within the first 24 hours after inclusion was extracted.

Abbreviations: LCA, latent class analysis; ICU, Intensive care unit; ALT, Alanine transaminase; Bio-ADM, Bio-adrenomedullin; CRP, C-reactive protein; *Hs-cTnT*, *high-sensitive cardiac troponin T*; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table S5. Populations' characteristics in the five studied cohorts and trials.

	CardShock cohort (n=205)	FROG-ICU cohort (n=228)	OptimaCC trial (n=57)	DOREMI trial (n=192)	CULPRIT-SHOCK trial (n=434)
Demographics					
Age, years †	66 (60-75)	61 (51-72)	67 (55-78)	71 (63-80)	69 (60-77)
Sex, male, n (%)	151 (74%)	153 (67%)	38 (67%)	122 (63%)	330 (76%)
BMI, Kg/m ² †	26 (24-29)	26 (23-29)	25 (22-27)	26 (23-30)	27 (25-29)
Severity of illness					
Charlson age-comorbidity index †	4 (2-5)	3 (1-5)	2 (3-5)	--	2 (1-3)
SAPS II †	--	61 (49-72)	56 (44-70)	--	51 (31-69)
SOFA †	--	8 (5-10)	9 (8-12)	--	--
SCAI shock stage, n (%) †					
B	0 (0%)	0 (0%)	0 (0%)	11 (6%)	--
C	50 (24%)	153 (67%)	20 (35%)	155 (81%)	--
D	99 (48%)	38 (17%)	26 (46%)	22 (11%)	--
E	56 (27%)	37 (16%)	11 (19%)	4 (2%)	--
LVEF, % †	30 (20-45)	30 (20-45)	32 (25-40)	25 (20-40)	32 (25-40)
Admission diagnoses ‡					
ACS	165 (80%)	91 (40%)	55 (96%)	65 (34%)	434 (100%)
Prior cardiac arrest	57 (28%)	124 (54%)	29 (51%)	0 (0%)	236 (54%)
ICU stay and organ support					

Duration of ICU stay, days	5 (2-10)	8 (5-13)	8 (6-19)	5 (3-9)	5 (2-11)
Mechanical ventilation, n (%) †	113/204 (55%) *	202 (89%)	56 (98%)	57 (30%)	354 (81%)
Vasopressors/inotropes use, n (%) †	194/203 (96%) *	199 (87%)	57 (100%)	192 (100%)	385 (89%)
RRT, n (%) ‡	34/204 (17%) *	47 (21%)	9 (16%)	37 (19%)	65 (15%)
IABP, n (%) ‡	120/204 (59%) *	16 (7%)	28 (49%)	10 (5%)	31 (7%)
LVAD/VA-ECMO, n (%) ‡	4/203 (2%) *	27 (12%)	4 (7%)	7 (4%)	79 (18%)
Outcomes					
28-day mortality, n (%)	65 (32%)	59 (26%)	21 (37%)	70 (36%)	198 (46%)
One-year mortality, n (%)	82 (40%)	83 (36%)	--	--	--

Continuous variables are expressed as medians (IQR) and categorical variables as numbers (%).

* Categorical variables reported as numbers and proportions of available data.

† At inclusion.

‡ During ICU stay.

‡ Not mutually exclusive

Abbreviations: ICU, intensive care unit; BMI, body mass index; SAPS II, Simplified Acute Physiologic Score; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SCAI, Society for cardiovascular angiography and interventions; LVEF, Left ventricular ejection fraction; ACS, acute coronary syndrome; 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.

Table S6. Comparison of LCA models with different numbers of classes in the CardShock cohort (n= 205)

Class number	BIC	Class size					
		1	2	3	4	5	6
1	4112	205	-	-	-	-	-
2	3950	123	82	-	-	-	-
3	3916	113	58	34	-	-	-
4*	3908	73	56	49	27	-	-
5	3948	50	47	41	39	28	-
6	3985	50	46	36	30	29	14

Bayesian information criterion (BIC) is a metric for model selection. Lower values suggest model parsimony (i.e., simple models with high predictive power). BIC was the lowest in the four-class model.

*Selected four-class LCA model. The mean (standard deviation) posterior class-membership probabilities (i.e., the probability to belong to the assigned class) in the CardShock cohort was 0.87 (0.18) suggesting that the four classes are well-separated.

Abbreviations: LCA, Latent class analysis; BIC, Bayesian information criteria, IQR, Interquartile range.

Table S7. Comparison of LCA models with different numbers of classes in the FROG-ICU cohort (n= 228)

Class number	BIC	Class size					
		1	2	3	4	5	6
1	4769	228	-	-	-	-	-
2	4560	121	84	-	-	-	-
3	4548	89	78	61	-	-	-
4*	4538	75	72	46	35	-	-
5	4605	62	53	43	36	34	-
6	4642	64	51	44	41	15	13

Bayesian information criterion (BIC) is a metric for model selection. Lower values suggest model parsimony (i.e., simple models with high predictive power). BIC was the lowest in the four-class model.

*Selected four-class LCA model. The mean (standard deviation) posterior class-membership probabilities (i.e., the probability to belong to the assigned class) in the FROG-ICU cohort was 0.90 (0.14) suggesting that the four classes are well-separated.

Abbreviations: LCA, Latent class analysis; BIC, Bayesian information criteria, IQR, Interquartile range.

Table S8. Clinical and biological characteristics by subphenotype in the CardShock derivation cohort (n= 205)

	Subphenotype 1 (Adaptive) (n=49)	Subphenotype 2 (Non-Inflammatory) (n=56)	Subphenotype 3 (Cardiopathic) (n=73)	Subphenotype 4 (Inflammatory) (n=27)	p
Inflammation †					
White blood cell count, ×10 ⁹ /L	12.2 (8.7-15.8)	14.2 (10.4-17.0)	14.3 (12.4-18.4)	13.5 (8.7-18.7)	0.016
C-reactive protein, mg/L	11 (5-39)	3 (1-5)	40 (18-76)	85 (54-154)	<0.0001
Cardiovascular or hemodynamic †					
Heart rate, beats/min	88 (69-106)	80 (54-104)	102 (75-113)	95 (77-120)	0.034
Systolic blood pressure, mm Hg	80 (70-85)	74 (65-85)	80 (75-85)	80 (68-88)	0.097
Lactate, mmol/L	1.7 (1.2-2.8)	2.7 (1.5-6.6)	3.0 (2.0-5.2)	5.2 (2.6-8.7)	<0.0001
Cardiac index, L/min/m ²	1.8 (1.5-2.5)	1.9 (1.8-2.6)	2.4 (1.3-3.0)	1.8 (1.5-2.4)	0.80
LVEF, % †	27 (20-47)	35 (26-45)	30 (20-42)	34 (20-44)	0.17
RV dysfunction, n (%) † † (n=195)	10 (23%)	23 (43%)	24 (34%)	11 (42%)	0.17
Hs-cTnT, ng/L	169 (64-746)	2862 (941-6940)	5110 (2599-16144)	449 (111-2427)	<0.0001
NT-proBNP, pg/mL	2172 (1314-6110)	242 (139-668)	6432 (2629-11867)	29192 (9360-32983)	<0.0001
Bio-ADM, pg/ml	41 (32-52)	34 (20-54)	66 (49-80)	155 (113-209)	<0.0001
Pulmonary †					
PaO ₂ /FiO ₂ ratio	176 (103-282)	145 (92-257)	150 (106-229)	205 (97-308)	0.32
Renal †					
Blood urea nitrogen, mmol/L	7.5 (4.9-11.4)	6.9 (5.6-9.0)	10.3 (7.0-13.2)	24.5 (14.5-32.4)	<0.0001

Creatinine, $\mu\text{mol/L}$	86 (56-105)	85 (68-106)	111 (94-138)	225 (163-355)	<0.0001
Hepatic †					
Alanine transaminase, U/L	15 (9-24)	63 (36-88)	54 (33-121)	83 (12-870)	<0.0001
Hematologic †					
Hemoglobin, g/dL	13.0 (11.4-14.4)	13.7 (11.7-14.6)	12.8 (11.2-14.4)	11.5 (9.2-13.4)	0.0080
Platelets, $\times 10^9/\text{L}$	217 (173-314)	199 (153-267)	231 (186-269)	170 (84-237)	0.0040
Neurologic †					
Altered mental status, n (%) † (n=202)	27 (56%)	40 (73%)	50 (68%)	17 (65%)	0.34
Metabolic †					
Sodium, mmol/L	137 (134-141)	138 (135-140)	137 (134-139)	135 (131-139)	0.19
Bicarbonate, mmol/L	24 (22-26)	24 (22-25)	23 (20-25)	23 (20-26)	0.46
Glucose, mmol/L	9.0 (7.3-11.8)	10.7 (8.1-16.5)	12.4 (8.3-16.0)	9.0 (6.2-17.0)	0.016
Albumin, g/L	31 (26-33)	31 (27-36)	29 (25-33)	27 (22-33)	0.018

For each variable, the closest to inclusion value within the first 24 hours after inclusion was extracted.

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 X^2 test or Fisher-Freeman-Halton test for categorical variables as appropriate.

† At inclusion.

‡ During ICU stay.

‡ Not mutually exclusive

|| RV dysfunction was defined as an RV enlargement associated or not with a systolic dysfunction as assessed by echocardiography on admission.

Abbreviations: LVEF, Left ventricular ejection fraction; RV, right ventricle; *Hs-cTnT*, *high-sensitive cardiac troponin T*; Bio-ADM, Bio-adrenomedullin; NT-proBNP, N-terminal pro B-type natriuretic peptide; PaO₂/FiO₂ ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; IQR, interquartile range.

Table S9. Clinical and biological characteristics by subphenotype in the FROG-ICU validation cohort (n= 228)

	Subphenotype 1 (Adaptive) (n=72)	Subphenotype 2 (Non-Inflammatory) (n=35)	Subphenotype 3 (Cardiopathic) (n=75)	Subphenotype 4 (Inflammatory) (n=46)	p
Inflammation †					
White blood cell count, ×10 ⁹ /L	9.5 (7.5-11.8)	10.1 (6.7-14.7)	11.2 (9.3-16.5)	10.8 (7.9-14.8)	0.012
C-reactive protein, mg/L	93 (54-151)	59 (34-135)	144 (118-185)	123 (70-219)	<0.0001
Cardiovascular or hemodynamic †					
Heart rate, beats/min	88 (70-98)	92 (80-111)	90 (78-109)	90 (77-105)	0.11
Systolic blood pressure, mm Hg	120 (106-137)	126 (102-144)	115 (104-132)	120 (105-132)	0.56
Lactate, mmol/L	0.9 (0.7-1.1)	1.4 (1.1-2.1)	1.5 (1.1-2.2)	1.2 (0.8-1.8)	0.0010
Cardiac index, L/min/m ²	3.4 (2.6-4.4)	3.4 (2.8-4.6)	2.6 (2.6-2.9)	3.6 (2.1-4.1)	0.21
LVEF, % †	45 (30-55)	30 (20-45)	20 (31-48)	20 (30-35)	0.031
RV dysfunction, n (%) † (n=124)	1 (4%)	5 (18%)	3 (10%)	5 (14%)	0.35
Hs-cTnI, µg/L	42 (16-197)	17 (10-105)	255 (118-588)	108 (58-191)	<0.0001
NT-proBNP, pg/mL	656 (293-1370)	1664 (831-3629)	3437 (1708-5942)	13699 (7166-28560)	<0.0001
Bio-ADM, pg/ml	28 (22-36)	63 (35-76)	64 (45-105)	179 (104-320)	<0.0001
Pulmonary †					
PaO ₂ /FiO ₂ ratio	272 (237-356)	299 (140-370)	230 (164-310)	183 (139-228)	0.0010
Renal †					

Blood urea nitrogen, mmol/L	5.4 (3.2-7.1)	9.9 (6.2-13.1)	8.3 (5.7-11.3)	18.0 (11.1-22.5)	<0.0001
Creatinine, $\mu\text{mol/L}$	67 (49-78)	87 (61-122)	90 (66-139)	232 (172-305)	<0.0001
Hepatic †					
Alanine transaminase, U/L	58 (32-113)	49 (21-1047)	58 (37-102)	75 (21-231)	0.89
Bilirubin, $\mu\text{mol/L}$	9 (7-12)	14 (7-24)	11 (9-18)	20 (12-55)	<0.0001
Hematologic †					
Hemoglobin, g/dL	11.3 (10.1-12.5)	10.7 (9.2-13.0)	10.6 (9.8-11.4)	9.1 (8.5-9.9)	<0.0001
Platelets, $\times 10^9/\text{L}$	169 (132-213)	172 (91-306)	164 (109-237)	131 (69-237)	0.48
Neurologic †					
Altered mental status, n (%) † (n=158)	54 (90%)	13 (68%)	49 (89%)	18 (75%)	0.051
Metabolic †					
Sodium, mmol/L	140 (138-142)	140 (136-143)	141 (138-144)	139 (134-143)	0.20
Bicarbonate, mmol/L	23 (21-26)	24 (21-26)	23 (21-26)	24 (22-26)	0.82
Glucose, mmol/L	6.9 (5.3-8.0)	7.2 (5.5-9.4)	7.0 (6.2-8.4)	7.3 (5.6-9.2)	0.27
Total protein, g/L	56 (52-59)	57 (53-62)	53 (49-58)	53 (46-58)	0.0070

For each variable, the closest to inclusion value within the first 24 hours after inclusion was extracted.

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 X^2 test or Fisher-Freeman-Halton test for categorical variables as appropriate.

† At inclusion.

‡ During ICU stay.

‡ Not mutually exclusive

‡ RV dysfunction was defined as an RV enlargement associated or not with a systolic dysfunction as assessed by echocardiography on admission.

Abbreviations: LVEF, Left ventricular ejection fraction; RV, right ventricle; *Hs-cTnI*, *high-sensitive cardiac troponin I*; Bio-ADM, Bio-adrenomedullin; NT-proBNP, N-terminal pro B-type natriuretic peptide; PaO₂/FiO₂ ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; IQR, interquartile range.

Table S10. Cox proportional hazards models to adjust for confounding (Charlson age-comorbidity index, ischemic origin, prior cardiac arrest, creatinine, lactate and Bio-ADM on admission) for 28-day mortality in the CardShock and the FROG-ICU cohorts.

	CardShock cohort (n = 205)		FROG-ICU cohort (n = 228)	
Variable	Adjusted HR (CI 95%)	P value	Adjusted HR (CI 95%)	P value
Model with subphenotypes	Harrell's C-index= 0.79 (95% CI: 0.75, 0.87) Optimism=0.03		Harrell's C-index = 0.74 (95% CI: 0.70, 0.83) Optimism = 0.03	
Subphenotypes (Adaptive as reference)				
Non-Inflammatory	1.63 (0.39 – 6.73)	0.49	1.48 (0.48 – 4.61)	0.49
Cardiopathic	2.15 (0.73 – 6.27)	0.16	1.62 (0.63 – 4.16)	0.31
Inflammatory	2.50 (1.04 – 5.67)	0.042	2.10 (1.10 – 8.03)	0.038
Natural log lactate (mmol/l)	1.98 (1.30 – 3.02)	<0.0001	1.91 (1.15 – 3.16)	0.011
Natural log creatinine (µmol/L)	1.31 (0.52 – 3.27)	0.55	0.73 (0.39 - 1.35)	0.32
Natural log Bio-ADM (pg/ml)	1.15 (0.85 - 4.67)	0.11	1.47 (0.98 – 2.21)	0.058
Charlson age-comorbidity index	1.18 (1.04 - 1.33)	0.008	1.11 (0.99 - 1.25)	0.051
Ischemic CS	1.72 (0.62 – 4.76)	0.29	1.03 (0.58 – 1.83)	0.90
Prior CA	1.32 (0.69 - 2.54)	0.39	1.86 (1.01 - 3.46)	0.048
Model without subphenotypes	Harrell's C-index= 0.76 (95% CI: 0.70, 0.86) Optimism= 0.04		Harrell's C-index = 0.71 (95% CI: 0.64, 0.82) Optimism = 0.04	
Natural log lactate (mmol/l)	2.12 (1.39 – 3.22)	<0.0001	1.99 (1.27 – 3.10)	0.0020
Natural log creatinine (µmol/L)	1.26 (0.62 - 2.55)	0.51	0.83 (0.48 - 1.44)	0.51

Natural log Bio-ADM (pg/ml)	1.20 (0.91 - 3.57)	0.083	1.66 (1.19 – 2.30)	0.0024
Charlson age-comorbidity index	1.16 (1.03 - 1.31)	0.015	1.12 (1.05 - 1.25)	0.040
Ischemic CS	2.21 (0.85 – 5.75)	0.11	1.03 (0.59 – 1.82)	0.89
Prior CA	1.36 (0.73 - 2.53)	0.32	1.84 (1.01 – 3.35)	0.046

Inference was combined from the sets of 20 imputed samples using Rubin's rules.

After adjustment for Charlson Age-Comorbidity Index, ischemic CS, prior CA, creatinine, lactate and Bio-ADM on admission, membership in the inflammatory subphenotype was independently associated with 28-day mortality in the CardShock (derivation) and FROG-ICU (validation) cohorts. Prior to entry into Cox models, raw creatinine, lactate and Bio-ADM values were natural log transformed. The model calibration was good according to the Grønnesby–Borgan test in the derivation and validation cohorts (p values of 0.45 and 0.54 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, creatinine, lactate and Bio-ADM with an increase in Harrell's C-index by 3% ($p = 0.038$) and 3% ($p = 0.028$) respectively in the CardShock and the FROG-ICU cohorts.

Abbreviations: HR, Hazard ratio; CI 95%, 95% Confidence interval, ICU, intensive care unit; Bio-ADM, Bio-adrenomedullin; CS, cardiogenic shock CA, cardiac arrest.

Table S11. Characteristics by subphenotype in the OptimaCC trial (n= 57)

	Subphenotype 1 (Adaptive) (n=17)	Subphenotype 2 (Non-Inflammatory) (n=16)	Subphenotype 3 (Cardiopathic) (n=19)	Subphenotype 4 (Inflammatory) (n=5)	p
Demographics					
Age, years †	67 (55-74)	59 (51-65)	79 (71-82)	65 (65-72)	0.0027
Sex, male, n (%)	11 (65%)	13 (81%)	10 (53%)	4 (80%)	0.30
BMI, Kg/m ² †	25 (23-28)	23 (20-26)	26 (22-27)	25 (21-26)	0.39
Past medical history †					
Previous MI or unstable angina, n (%)	1 (6%)	1 (6%)	2 (10%)	0 (0%)	0.85
Previous stroke or transient ischemic attack, n (%)	0 (0%)	1 (6%)	3 (16%)	0 (0%)	0.27
Chronic kidney disease, n (%)	1 (6%)	0 (0%)	2 (10%)	0 (0%)	0.53
Diabetes mellitus, n (%)	2 (12%)	0 (0%)	4 (21%)	0 (0%)	0.19
Severity of illness					
Charlson age-comorbidity index †	3 (1-4)	2 (1-3)	4 (3-6)	3 (2-3)	0.0020
SAPS II †	44 (39-59)	54 (44-66)	62 (52-78)	59 (51-84)	0.015
SOFA score †	8 (6-10)	9 (9-11)	10 (9-12)	11 (10-15)	0.15
SCAI shock stage, n (%) †					0.021

C	11 (65%)	13 (81%)	9 (47%)	2 (40%)	
D	0 (0%)	3 (19%)	7 (37%)	1 (20%)	
E	6 (35%)	0 (0%)	3 (16%)	2 (40%)	
ICU stay and organ support					
Duration of ICU stay, days	7 (6-11)	7 (6-11)	14 (6-23)	20 (11-28)	0.30
Mechanical ventilation, n (%) †	17 (100%)	16 (100%)	17 (89%)	4 (80%)	0.16
Epinephrine use, n (%) † (n=56)	7 (44%)	3 (20%)	5 (33%)	2 (40%)	0.56
RRT, n (%) ‡	0 (0%)	2 (12%)	2 (10%)	0 (0%)	0.43
IABP, n (%) ‡	6 (35%)	5 (31%)	15 (79%)	2 (40%)	0.016
VA-ECMO, n (%) ‡	1 (6%)	0 (0%)	1 (5%)	2 (40%)	0.022
Inflammation †					
White blood cell count, ×10 ⁹ /L	14.00 (12.50-19.00)	20.35 (15.43-23.45)	18.30 (12.77-22.67)	13.30 (11.54-14.10)	0.10
Cardiovascular or hemodynamic †					
Heart rate, beats/min	91 (74-102)	100 (84-106)	96 (83-123)	93 (57-116)	0.52
Systolic blood pressure, mm Hg	96 (93-117)	100 (93-117)	109 (99-114)	110 (97-128)	0.75
Lactate, mmol/L	2.0 (1.5-2.6)	4.4 (3.9-6.3)	5.1 (3.6-8.7)	5.4 (5.0-5.9)	0.00037
Cardiac index, L/min/m ²	2.0 (1.8- 2.7)	2.0 (1.3-2.4)	1.8 (1.6-2.3)	2.1 (1.9-2.6)	0.50
LVEF, %	39 (25-50)	35 (27-38)	31 (21-34)	30 (26-33)	0.37
RV dysfunction, n (%) ‡ (n=50)	14 (87.5%)	13 (92.9%)	10 (66.7%)	5 (100.0%)	0.15
Hs-cTnT, pg/ml	1.7 (0.9-3.7)	8.6 (3.7-18.5)	19.6 (9.3-37.8)	32.9 (1.8-33.7)	<0.0001

NT-proBNP, pg/mL	2596 (1018-5671)	435 (282-701)	7090 (4107-13458)	20766 (7543-21321)	<0.0001
Bio-ADM, pg/ml	60 (22-85)	29 (21-36)	61 (50-95)	141 (107-149)	0.0017
Pulmonary †					
PaO ₂ /FiO ₂ ratio	284 (163-392)	236 (210-300)	214 (152-284)	192 (136-265)	0.35
Renal †					
Blood urea nitrogen, g/L	0.46 (0.36-0.59)	0.52 (0.41-0.56)	0.55 (0.42-0.69)	0.99 (0.90-1.30)	0.013
Creatinine, μmol/L	73 (62-106)	115 (86-134)	130 (110-144)	229 (196-284)	0.0027
Hepatic †					
Alanine transaminase, U/L	65 (49-136)	175 (149-235)	110 (76-195)	2337 (1062-4051)	0.0068
Bilirubin, mg/L	5 (4-7)	5 (3-6)	7 (5-11)	11 (8-14)	0.044
Hematologic †					
Hemoglobin, g/dL	12.5 (11.1-13.4)	13.3 (12.4-14.2)	12.8 (11.7-13.8)	14.5 (12.6-14.7)	0.16
Platelets, ×10 ⁹ /L	261 (184-310)	229 (178-264)	236 (154-280)	154 (119-194)	0.36
Neurologic †					
Altered mental status, n (%)	7 (41%)	8 (50%)	11 (58%)	3 (60%)	0.76
Metabolic †					
Sodium, mmol/L	138 (134-140)	138 (137-140)	137 (132-138)	137 (136-141)	0.29
Bicarbonate, mmol/L	22 (18- 24)	16 (13-18)	17 (15-19)	16 (16-16)	0.034
Glucose, g/L	1.82 (1.30-2.18)	1.79 (1.34-2.39)	2.01 (1.46-2.95)	1.70 (1.28-2.11)	0.65
Outcomes					
Refractory shock, n (%) ‡	0 (0%)	2 (12%)	7 (37%)	3 (60%)	0.0055

Death 28 days, n (%)	4 (23%)	5 (31%)	10 (53%)	2 (40%)	0.31
Composite outcome of in-ICU mortality, receipt of VA-ECMO/LVAD or RRT initiation, n (%) *	4 (23%)	5 (31%)	12 (63%)	3 (60%)	0.028

For each variable, the closest to inclusion value within the first 24 hours after inclusion was extracted.

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 X² test or Fisher-Freeman-Halton test for categorical variables as appropriate.

† At inclusion.

‡ During ICU stay.

‡ Not mutually exclusive

|| RV dysfunction was defined as an RV enlargement associated or not with a systolic dysfunction as assessed by echocardiography on admission.

Abbreviations: ICU, intensive care unit; BMI, body mass index; MI, myocardial infarction; SAPS II, Simplified Acute Physiologic Score; SOFA score, Sequential Organ Failure Assessment score; SCAI, Society for cardiovascular angiography and interventions; ACS, acute coronary syndrome; OHCA, out-of-hospital cardiac arrest; LVEF, Left ventricular ejection fraction; RV, right ventricle; RRT, renal replacement therapy; IABP, Intra-aortic balloon pump; LVAD, Left ventricular assist device; VA-ECMO, Veno-arterial Extracorporeal membrane oxygenation; Hs-cTnT, *high-sensitive cardiac troponin T*; Bio-ADM, Bio-adrenomedullin; NT-proBNP, N-terminal pro B-type natriuretic peptide; PaO₂/FiO₂ ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; IQR, interquartile range.

Table S12. Characteristics by subphenotype in the DOREMI trial (n= 192).

	Subphenotype 1 (Adaptive) (n=57)	Subphenotype 2 (Non-Inflammatory) (n=41)	Subphenotype 3 (Cardiopathic) (n=66)	Subphenotype 4 (Inflammatory) (n=28)	p
Demographics					
Age, years †	71 (62-82)	66 (60-78)	75 (65-80)	72 (66-85)	0.12
Sex, male, n (%)	33 (58%)	27 (66%)	48 (73%)	14 (50%)	0.14
BMI, Kg/m ² †	26 (23-29)	25 (22-31)	26 (23-30)	26 (24-31)	0.90
Past medical history †					
Previous myocardial infarction, n (%)	24 (42%)	12 (29%)	21 (32%)	11 (39%)	0.50
Previous percutaneous coronary intervention, n (%)	18 (32%)	9 (22%)	17 (26%)	5 (18%)	0.52
Previous coronary-artery bypass grafting, n (%)	11 (19%)	7 (17%)	13 (20%)	8 (29%)	0.68
Previous stroke or transient ischemic attack, n (%)	7 (12%)	6 (15%)	7 (11%)	8 (29%)	0.14
Chronic kidney disease, n (%)	25 (46%)	7 (20%)	29 (51%)	17 (65%)	0.0029
Chronic obstructive pulmonary disease, n (%)	8 (14%)	1 (2%)	13 (20%)	3 (11%)	0.077

Severity of illness					
SCAI shock stage, n (%) †					0.72
B	6 (10%)	2 (5%)	1 (1%)	2 (7%)	
C	43 (76%)	33 (81%)	56 (85%)	23 (82%)	
D	6 (11%)	5 (12%)	8 (12%)	3 (11%)	
E	2 (3%)	1 (2%)	1 (1%)	0 (0%)	
Admission diagnoses ‡					
ACS	8 (14%)	19 (46%)	36 (54%)	2 (7%)	<0.0001
ICU stay and treatments/organ support					
Duration of ICU stay, days	14 (8-28)	9 (5-25)	14 (5-23)	13 (2-30)	0.53
Mechanical ventilation, n (%) †	14 (25%)	11 (27%)	29 (44%)	3 (11%)	0.0070
Vasopressors use, n (%) † (n=191)	22 (39%)	18 (44%)	39 (60%)	13 (46%)	0.11
Milrinone use, n (%) †	26 (46%)	23 (56%)	34 (51%)	13 (46%)	0.74
RRT, n (%) ‡	11 (19%)	4 (10%)	16 (24%)	6 (21%)	0.32
IABP, n (%) ‡	2 (3%)	2 (5%)	6 (9%)	0 (0%)	0.27
LVAD/VA-ECMO, n (%) ‡	7 (12%)	8 (19%)	9 (14%)	1 (4%)	0.29
Inflammation †					
White blood cell count, ×10 ⁹ /L	10.2 (8.0-13.7)	12.5 (10.1-15.0)	13.9 (11.4-20.0)	11.6 (9.6-15.2)	<0.0001

C-reactive protein, mg/L	22 (13-34)	8 (4-12)	73 (37-137)	45 (28-105)	<0.0001
Cardiovascular or hemodynamic †					
Heart rate, beats/min	90 (72-105)	92 (78-105)	94 (77-111)	84 (70-95)	0.19
Systolic blood pressure, mm Hg	110 (96-118)	100 (90-112)	109 (99-120)	104 (88-119)	0.077
Lactate, mmol/L	2.3 (1.3-3.0)	2.7 (1.9-4.3)	3.6 (2.3-5.4)	3.9 (3.0-7.1)	<0.0001
Cardiac index, L/min/m ²	1.6 (1.3-1.7)	1.5 (1.2-1.9)	1.6 (1.5-1.8)	1.7 (1.5-1.9)	0.81
LVEF, %	23 (20-30)	22 (18-50)	26 (22-40)	25 (19-40)	0.31
RV dysfunction, n (%)	2 (3%)	5 (12%)	6 (9%)	3 (11%)	0.42
Hs-cTnT, ng/L	48 (38-85)	1010 (131-3850)	3264 (425-8122)	87 (48-132)	<0.0001
NT-proBNP, pg/mL	10584 (5976-21983)	2569 (1412-6229)	22671 (13760-33617)	32581 (17695-68799)	<0.0001
Bio-ADM, pg/ml	81 (45-131)	31 (23-78)	88 (52-140)	232 (167-358)	<0.0001
Pulmonary †					
PaO ₂ /FiO ₂ ratio	373 (244-482)	276 (204-399)	237 (166-376)	404 (233-421)	0.076
Renal †					
Blood urea nitrogen, mmol/L	14 (10-20)	9 (6-16)	14 (11-20)	27 (15-31)	<0.0001
Creatinine, μmol/L	141 (111-159)	119 (75-143)	158 (129-228)	249 (216-339)	<0.0001
Hepatic †					
Alanine transaminase, U/L	34 (25-58)	124 (45-471)	117 (47-383)	122 (41-1245)	<0.0001
Bilirubin, μmol/L	16 (10-26)	13 (9-30)	14 (10-26)	22 (14-41)	0.19

Hematologic †					
Hemoglobin, g/dL	11.3 (9.4-13.4)	12.9 (11.6-14.3)	11.6 (9.9-12.9)	10.6 (9.9-12.8)	0.012
Platelets, ×10 ⁹ /L	243 (183-308)	212 (157-284)	269 (219-315)	181 (142-225)	0.00014
Metabolic †					
Sodium, mmol/L	136 (132-138)	137 (134-139)	135 (132-138)	134 (132-137)	0.18
Bicarbonate, mmol/L	24 (22-28)	21 (19-26)	20 (17-22)	18 (15-22)	<0.001
Albumin, g/L	29 (26-33)	30 (26-33)	29 (26-32)	33 (27-35)	0.42
Outcomes					
28-days mortality, n (%)	16 (28%)	15 (37%)	26 (39%)	13 (46%)	0.36
Composite outcome of in-ICU mortality, receipt of ECMO/LVAD/Impella device or RRT initiation, n (%)	23 (40%)	16 (39%)	35 (53%)	16 (57%)	0.24

For each variable, the closest to inclusion value within the first 24 hours after inclusion was extracted.

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 X² test or Fisher-Freeman-Halton test for categorical variables as appropriate.

† At inclusion.

‡ During ICU stay.

‡ Not mutually exclusive

|| MACE was defined in the original study as a resuscitated cardiac arrest or a requirement of a cardiac transplant or mechanical circulatory support or a nonfatal myocardial infarction or a transient ischemic attack or stroke.

Abbreviations: ICU, intensive care unit; BMI, body mass index; SCAI, Society for cardiovascular angiography and interventions; ACS, acute coronary syndrome; LVEF, Left ventricular ejection fraction; RV, right ventricle; RRT, renal replacement therapy; IABP, Intra-aortic balloon pump; LVAD, Left ventricular assist device; ECMO, Extracorporeal membrane oxygenation; *Hs-cTnI*, *high-sensitive cardiac troponin I*; Bio-ADM, Bio-adrenomedullin; NT-proBNP, N-terminal pro B-type natriuretic peptide; PaO₂/FiO₂ ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; MACE, major adverse cardiovascular events; IQR, interquartile range.

Table S13. Characteristics by subphenotype in the CULPRIT-SHOCK trial (n= 434).

	Subphenotype 1 (Adaptive) (n=115)	Subphenotype 2 (Non-Inflammatory) (n=136)	Subphenotype 3 (Cardiopathic) (n=138)	Subphenotype 4 (Inflammatory) (n=45)	p
Demographics					
Age, years †	69 (61-77)	63 (55-74)	71 (63-79)	73 (67-78)	<0.0001
Sex, male, n (%)	78 (68%)	118 (87%)	107 (77%)	27 (60%)	<0.0001
BMI, Kg/m ² †	27 (24-30)	27 (25-29)	28 (25-31)	28 (25-30)	0.44
Past medical history †					
Previous myocardial infarction, n (%), n=431	22 (19%)	15 (11%)	22 (16%)	8 (18%)	0.34
Previous PCI, n (%), n=431	26 (23%)	24 (18%)	25 (18%)	10 (23%)	0.71
Previous CABG, n (%), n=431	5 (4%)	4 (3%)	10 (7%)	4 (9%)	0.27
Previous stroke or transient ischemic attack, n (%), n=431	8 (7%)	3 (2%)	11 (8%)	4 (9%)	0.15
Chronic kidney disease, n (%), n=430	6 (5%)	3 (2%)	10 (7%)	11 (25%)	<0.0001
Chronic heart failure, n (%), n=431	8 (7%)	4 (3%)	12 (9%)	7 (16%)	0.029
Peripheral arterial disease, n (%), n=431	19 (16%)	2 (1%)	20 (14%)	4 (9%)	<0.0001
Diabetes mellitus, n (%) n=430	38 (33%)	25 (19%)	55 (40%)	27 (61%)	<0.0001
Severity of illness					

SAPS II †	43 (24-62)	52 (30-74)	51 (35-68)	65 (44-81)	0.0023
ACS, n (%)	115 (100%)	136 (100%)	138 (100%)	45 (100%)	0.99
Cardiac arrest, n (%), n=433	61 (53%)	96 (71%)	58 (42%)	21 (47%)	<0.0001
ICU stay and treatment/organ support					
Duration of ICU stay, days	5 (2-11)	6 (2-10)	5 (2-11)	3 (1-11)	0.26
Immediate multivessel PCI, n (%) †	55 (48%)	66 (48%)	67 (49%)	21 (47%)	0.99
Mechanical ventilation, n (%) †, n=433	85 (74%)	115 (85%)	113 (82%)	41 (91%)	0.034
Vasopressors/inotropes use, n (%) †, n=433	94 (82%)	121 (90%)	126 (91%)	44 (98%)	0.015
RRT, n (%) †	11 (10%)	12 (9%)	25 (18%)	17 (38%)	0.0010
IABP, n (%) †	6 (5%)	9 (7%)	14 (10%)	2 (4%)	0.58
LVAD/VA-ECMO, n (%) †	21 (24%)	24 (18%)	32 (23%)	13 (29%)	0.70
Inflammation †					
White blood cell count, ×10 ⁹ /L	11.8 (9.6-15.3)	14.4 (10.3-19.0)	16.7 (12.9-22.2)	16.8 (13.2-20.8)	<0.0001
C-reactive protein, mg/L	5 (3-11)	2 (1-3)	18 (6-57)	33 (11-112)	<0.0001
Cardiovascular or hemodynamic †					
Heart rate, beats/min	85 (67-104)	86 (73-100)	96 (75-115)	90 (60-110)	0.012
Systolic blood pressure, mm Hg	110 (84-128)	103 (90-125)	100 (88-125)	98 (80-123)	0.16
Lactate, mmol/L	2.0 (1.2-3.4)	4.5 (2.4-7.8)	3.9 (2.1-7.8)	7.5 (4.6-13.1)	<0.0001
LVEF, % †	45 (33-55)	45 (38-50)	33 (25-45)	25 (20-35)	<0.0001
Hs-cTnT, ng/L	182 (61-388)	450 (235-1104)	2173 (1116-4582)	1068 (354-3312)	<0.0001

NT-proBNP, pg/mL	1523 (330-3533)	234 (100-523)	4007 (1700-9238)	12832 (4045-22245)	<0.0001
Renal †					
Creatinine, µmol/L	94 (74-118)	100 (87-122)	122 (101-151)	194 (162-245)	<0.0001
Hepatic †					
Alanine transaminase, U/L	100 (86-122)	97 (81-114)	129 (70-259)	358 (162-859)	<0.0001
Hematologic †					
Hemoglobin, g/dL	13.5 (12.7-14.5)	14.1 (12.7-15.4)	13.2 (11.7-14.6)	11.9 (10.4-13.2)	<0.0001
Neurologic †					
Altered mental status, n (%) †, n=432	80 (70%)	105 (78%)	88 (64%)	34 (76%)	0.084
Metabolic †					
Sodium, mmol/L	136 (130-140)	137 (133-139)	136 (132-141)	139 (134-143)	0.033
Glucose, mmol/L	8.8 (7.1-13.8)	12.6 (8.7-16.4)	12.4 (9.9-17.6)	12.8 (9.6-16.3)	0.00020
Outcomes					
28-day mortality, n (%)	34 (30%)	45 (33%)	79 (57%)	40 (89%)	<0.0001
Composite outcome of in-ICU mortality, receipt of VA-ECMO/LVAD/Impella device or RRT initiation, n (%)	40 (35%)	48 (35%)	81 (59%)	38 (84%)	<0.0001

For each variable, the closest to inclusion value within the first 24 hours after inclusion was extracted.

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 X² test or Fisher-Freeman-Halton test for categorical variables as appropriate.

† At inclusion.

‡ During ICU stay.

Abbreviations: ICU, intensive care unit; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary-artery bypass grafting; COPD, Chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiologic Score; ACS, acute coronary syndrome; LVEF, Left ventricular ejection fraction; RRT, renal replacement therapy; IABP, Intra-aortic balloon pump; LVAD, Left ventricular assist device; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation; *Hs*-cTnT, *high-sensitive cardiac troponin T*; NT-proBNP, N-terminal pro B-type natriuretic peptide; IQR, interquartile range.

Table S14. Characteristics by the exposure to epinephrine for at least 24h after inclusion in the CardShock cohort

	No epinephrine use (n=169)	Epinephrine use (n=29)	p
Demographics			
Age, years †	66 (59-74)	67 (61-74)	0.79
Sex, male, n (%)	127 (75%)	19 (65%)	0.27
BMI, Kg/m ²	26 (23-28)	27 (25-31)	0.014
Past medical history †			
Previous myocardial infarction, n (%)	40 (24%)	6 (21%)	0.72
Previous PCI, n (%)	25 (15%)	2 (7%)	0.25
Previous CABG, n (%)	11 (6%)	3 (10%)	0.45
Previous stroke or transient ischemic attack, n (%)	17 (10%)	4 (14%)	0.54
Chronic kidney disease, n (%)	14 (8%)	5 (17%)	0.13
Chronic heart failure, n (%)	28 (17%)	4 (14%)	0.70
Peripheral arterial disease, n (%)	18 (11%)	3 (10%)	0.96
COPD, n (%)	19 (11%)	3 (10%)	0.88
Diabetes mellitus, n (%)	49 (29%)	8 (28%)	0.87
Severity of illness			
Charlson age-comorbidity index †	4 (2-5)	3 (2-5)	0.93
APACHE II †	16 (11-24)	24 (22-29)	<0.0001

SCAI shock stage, n (%) †			0.036
C	45 (27%)	3 (10%)	
D	83 (49%)	13 (45%)	
E	41 (24%)	13 (45%)	
Admission diagnoses ‡			
ACS	133 (79%)	25 (86%)	0.35
Cardiac arrest	43 (25%)	12 (41%)	0.077
ICU stay and organ support			
Duration of ICU stay, days	5 (3-10)	4 (1-15)	0.56
Mechanical ventilation, n (%) † (n=197)	84 (50%)	24 (83%)	<0.0001
RRT, n (%) ‡ (n=197)	19 (11%)	12 (41%)	<0.0001
IABP, n (%) ‡ (n=197)	102 (60%)	16 (57%)	0.74
LVAD/ECMO, n (%) ‡ (n=196)	2 (1%)	2 (7%)	0.045
LCA-derived subphenotypes			
			0.057
Adaptive, n (%)	46 (27%)	2 (7%)	
Non-inflammatory, n (%)	45 (27%)	10 (34%)	
Cardiopathic, n (%)	58 (34%)	10 (34%)	
Inflammatory, n (%)	20 (12%)	7 (24%)	
Outcomes			
28-day mortality, n (%)	42 (25%)	19 (65%)	<0.0001

The information of the use of epinephrine for at least 24h after inclusion was available for 198 patients.

For each variable, the closest to inclusion value within the first 24 hours after inclusion was extracted.

Continuous variables are expressed as medians (IQR) and categorical variables as numbers (%).

Comparisons were performed using Mann–Whitney U test for continuous variables and X^2 test or Fisher's exact test for categorical variables as appropriate.

† At inclusion.

‡ During ICU stay.

‡ Not mutually exclusive

Abbreviations: 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; ICU, intensive care unit; RRT, renal replacement therapy; IABP, Intra-aortic balloon pump; LVAD, Left ventricular assist device; ECMO, Extracorporeal membrane oxygenation; IQR, interquartile range.

Figure S1. Current FROG-ICU analysis study flow chart (validation cohort). CS, cardiogenic shock; CA, cardiac arrest; PE, pulmonary embolism.

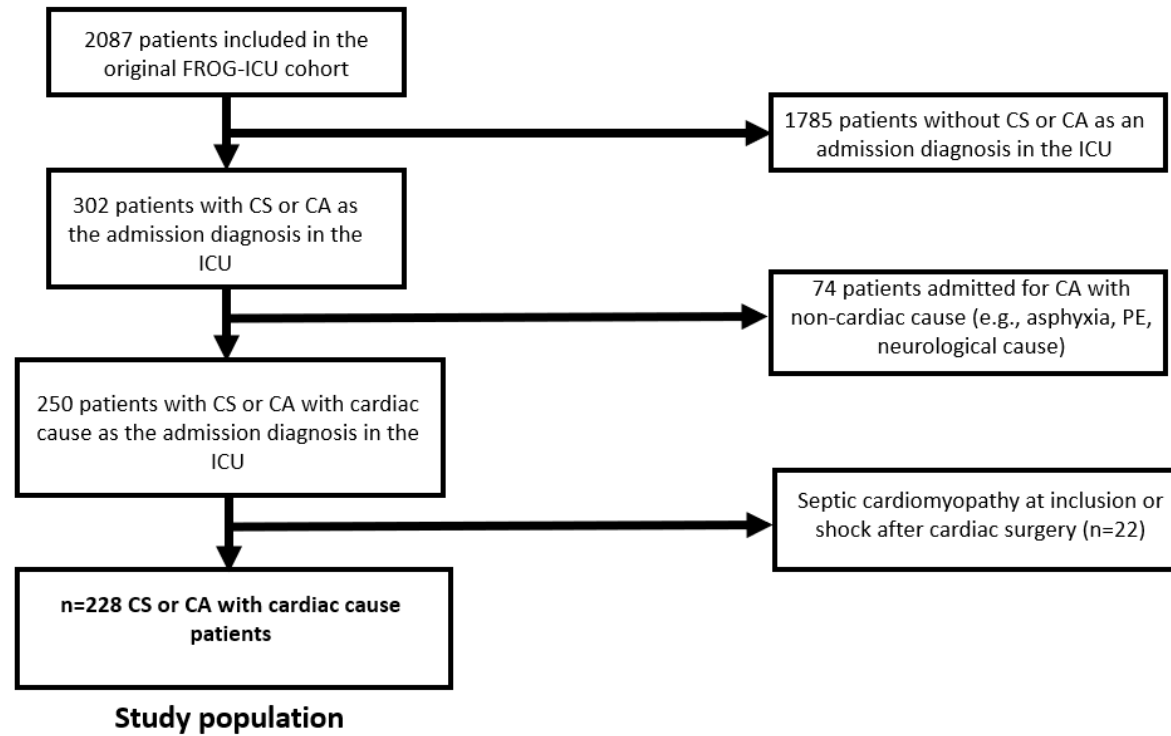


Figure S2. Heatmap of correlation between selected variables for phenotyping in the CardShock (A) and FROG-ICU cohorts (B).

Heatmap shows greater color (blue or pink) when the Spearman's rank correlation coefficient is greater in positive or negative direction.

Abbreviations: ALT, Alanine transaminase; Bio-ADM, Bio-adrenomedullin; CRP, C-reactive protein; *Hs-cTnI*, *high-sensitive cardiac troponin I*; *Hs-cTnT*, *high-sensitive cardiac troponin T*; NT-proBNP, N-terminal pro B-type natriuretic peptide.

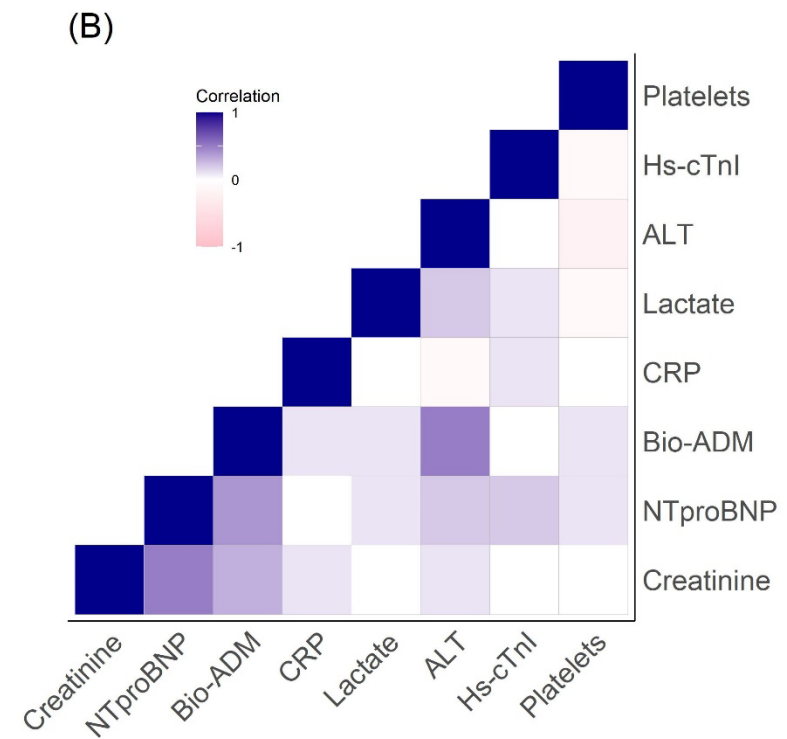
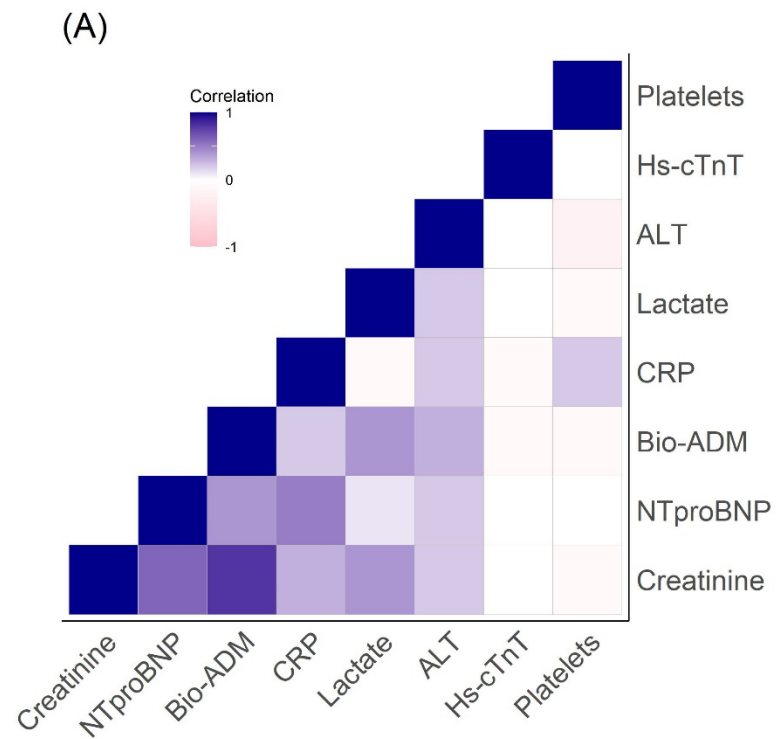
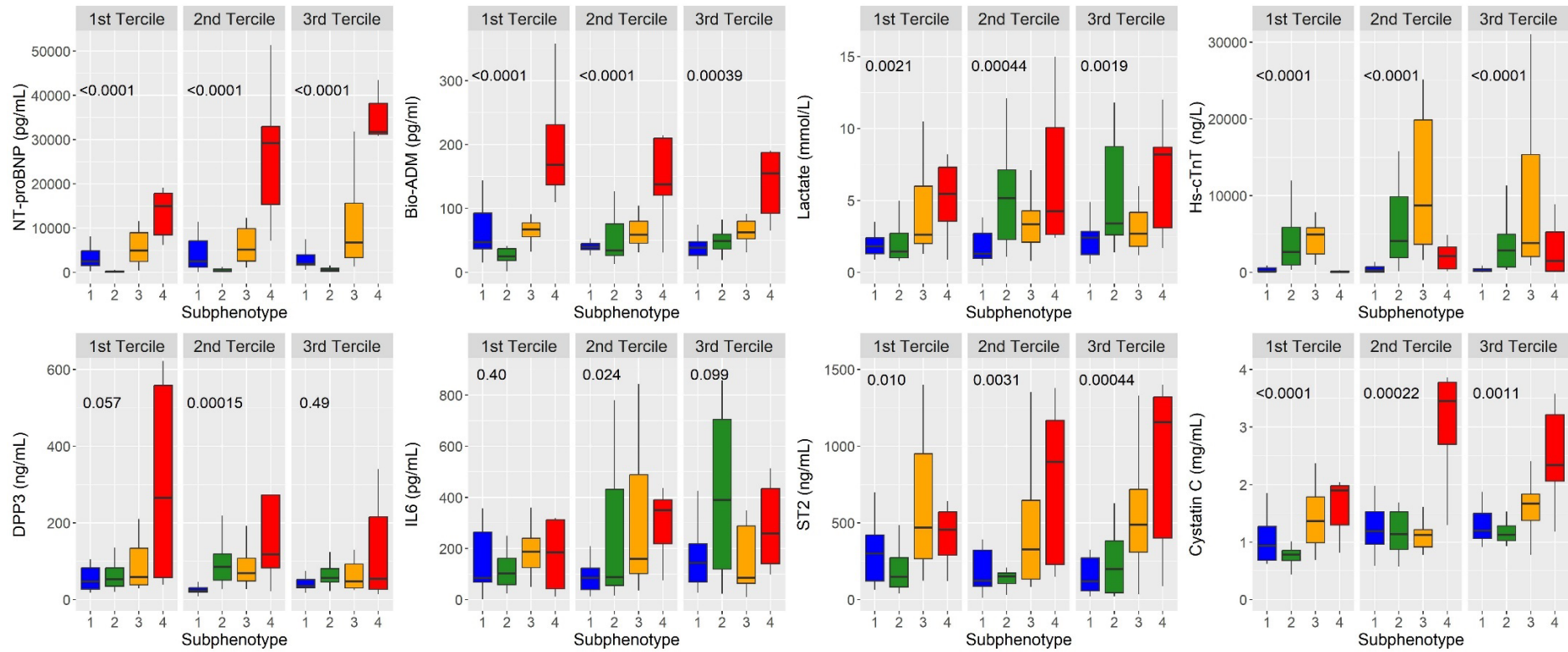
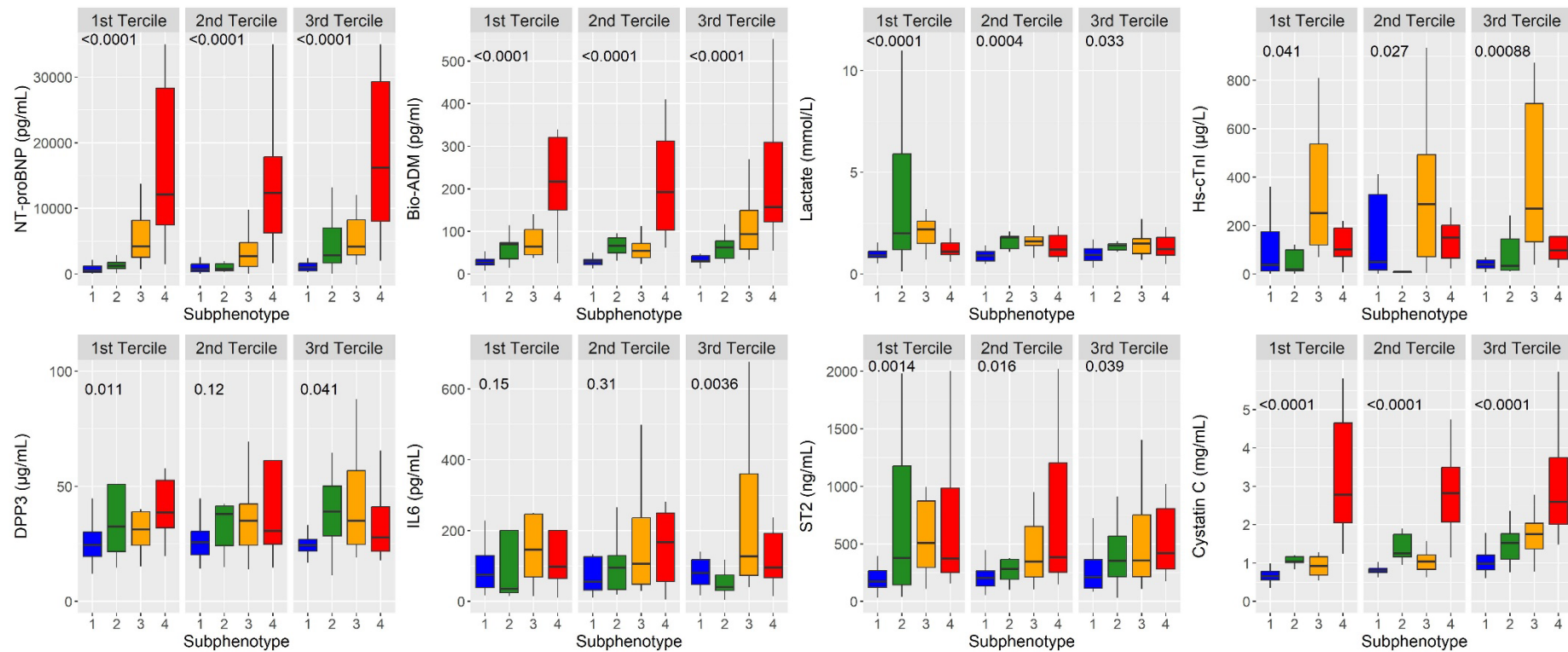


Figure S3. Comparison of host response biomarkers levels across subphenotypes (adaptive (1), non-inflammatory (2), cardiopathic (3) and inflammatory (4)) tertiles of age in the derivation (CardShock) (A) and validation (FROG-ICU) (B) cohorts.

(A)



(B)

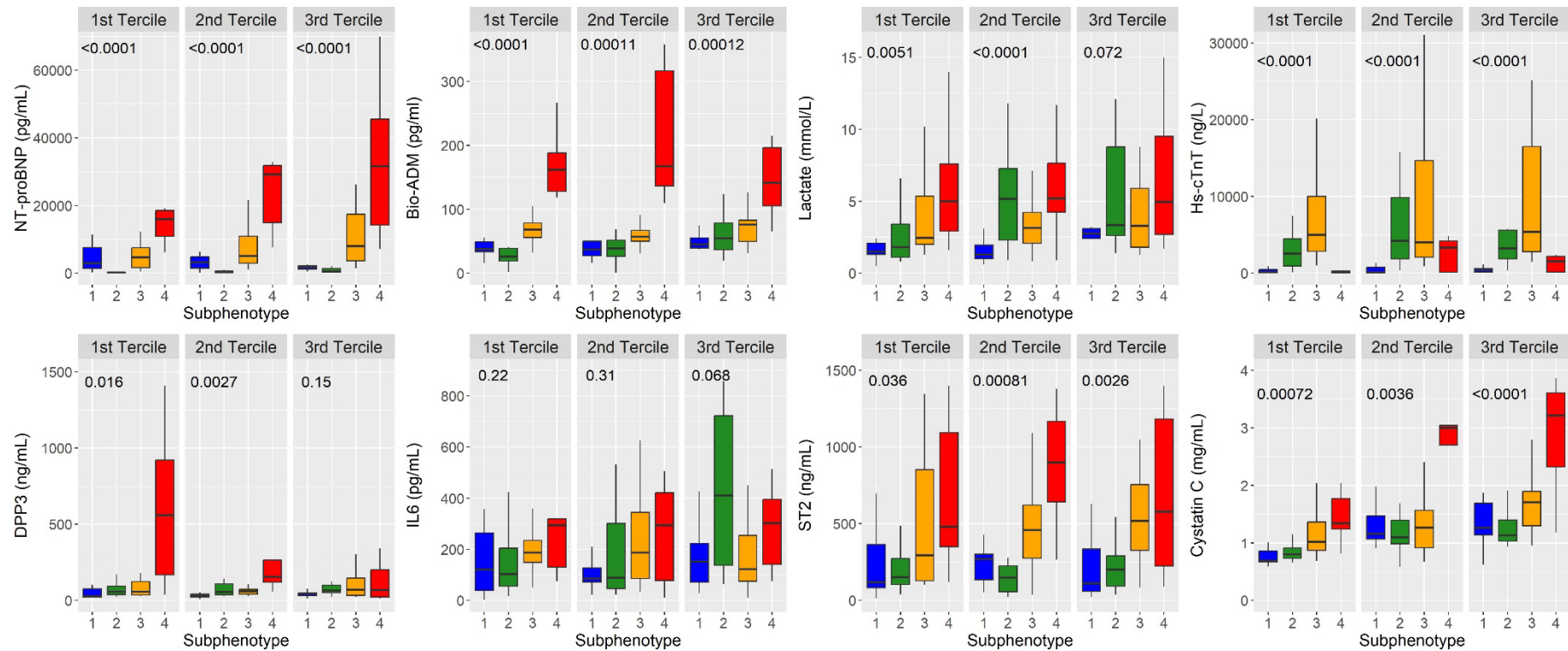


Comparison for each biomarker within subgroups was performed using the Kruskal-Wallis test. Data are shown as median (IQR).

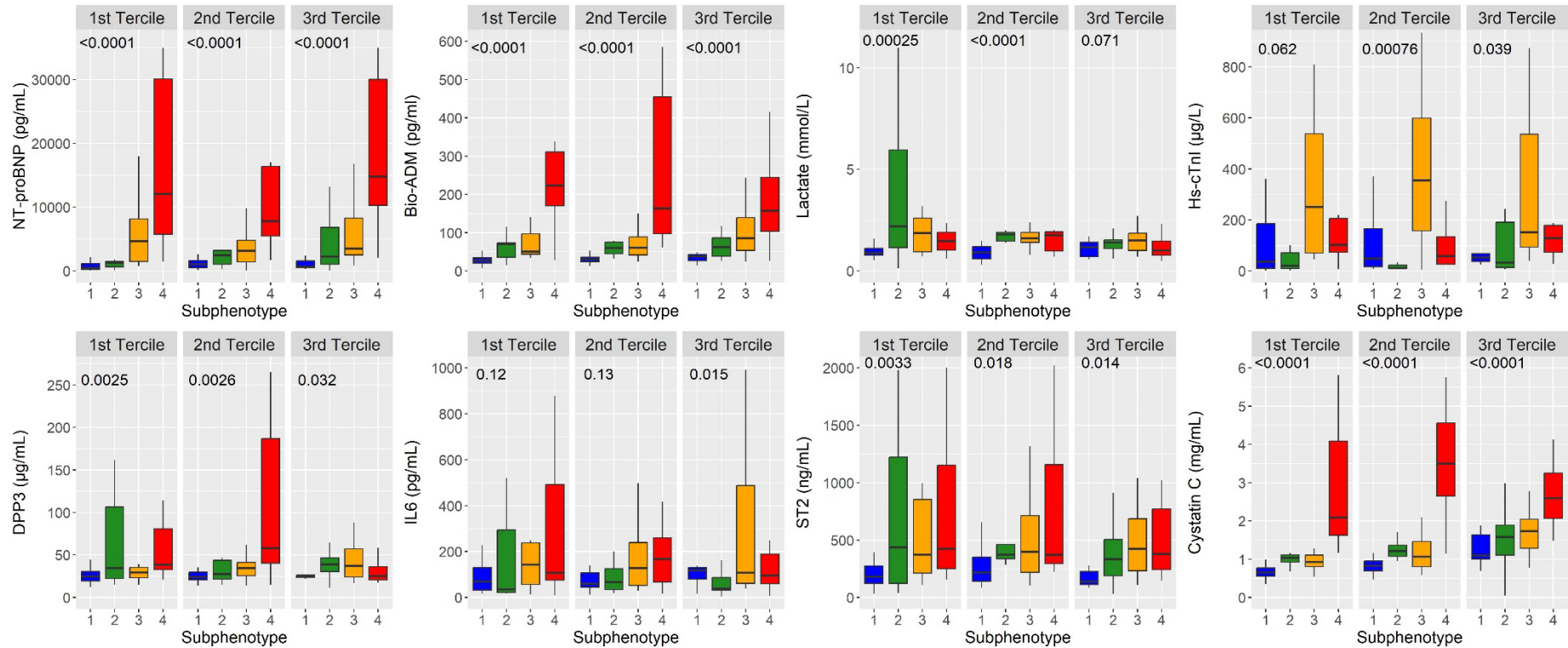
Abbreviations: NT-proBNP, N-terminal pro B-type natriuretic peptide; DPP3, Dipeptidyl peptidase 3; Bio-ADM, Bio-adrenomedullin; IL6, Interleukin-6; ST2, soluble form of suppression of tumorigenicity 2; Hs-cTnT, *high-sensitive cardiac troponin T*; Hs-cTnI, *high-sensitive cardiac troponin I*; NS, not significant.

Figure S4. Comparison of host response biomarkers levels across subphenotypes (adaptive (1), non-inflammatory (2), cardiopathic (3) and inflammatory (4)) tertiles of Charlson age-comorbidity index in the derivation (CardShock) (A) and validation (FROG-ICU) (B) cohorts.

(A)



(B)

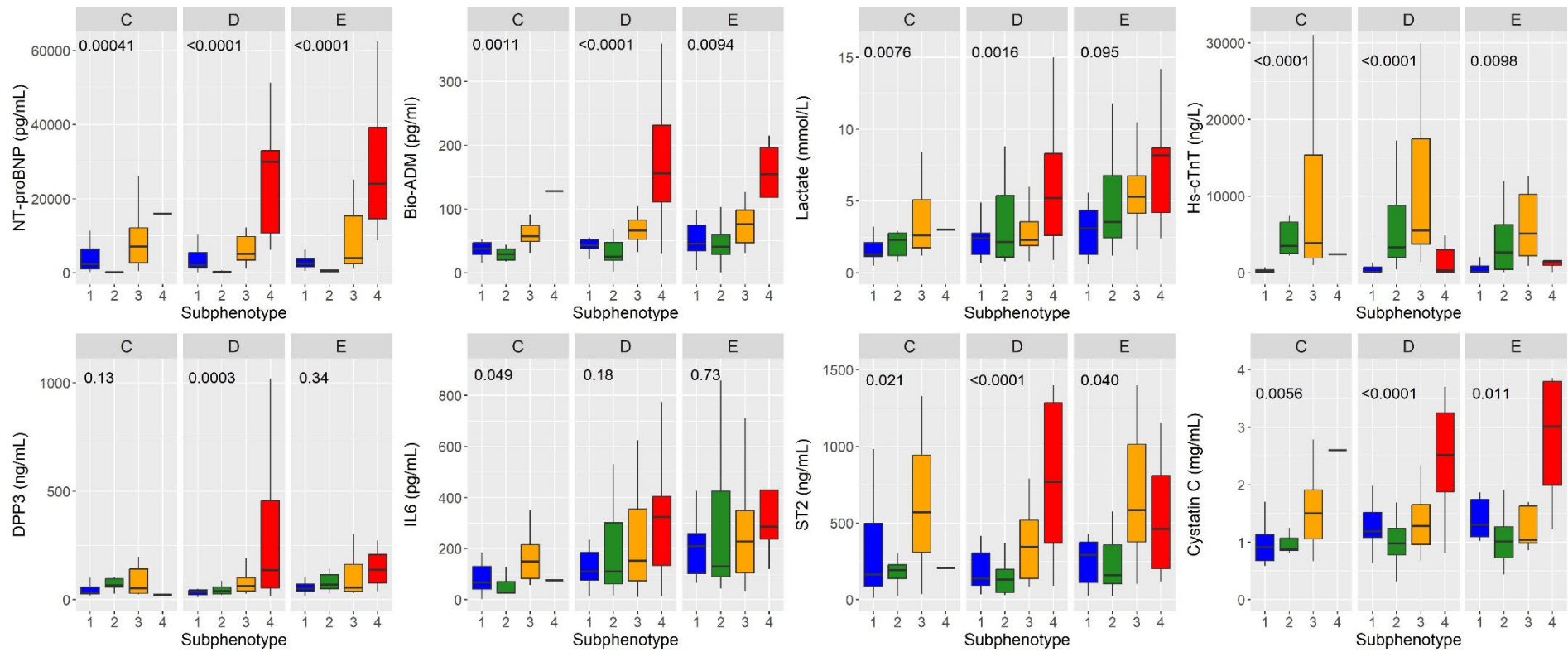


Comparison for each biomarker within subgroups was performed using the Kruskal-Wallis test. Data are shown as median (IQR).

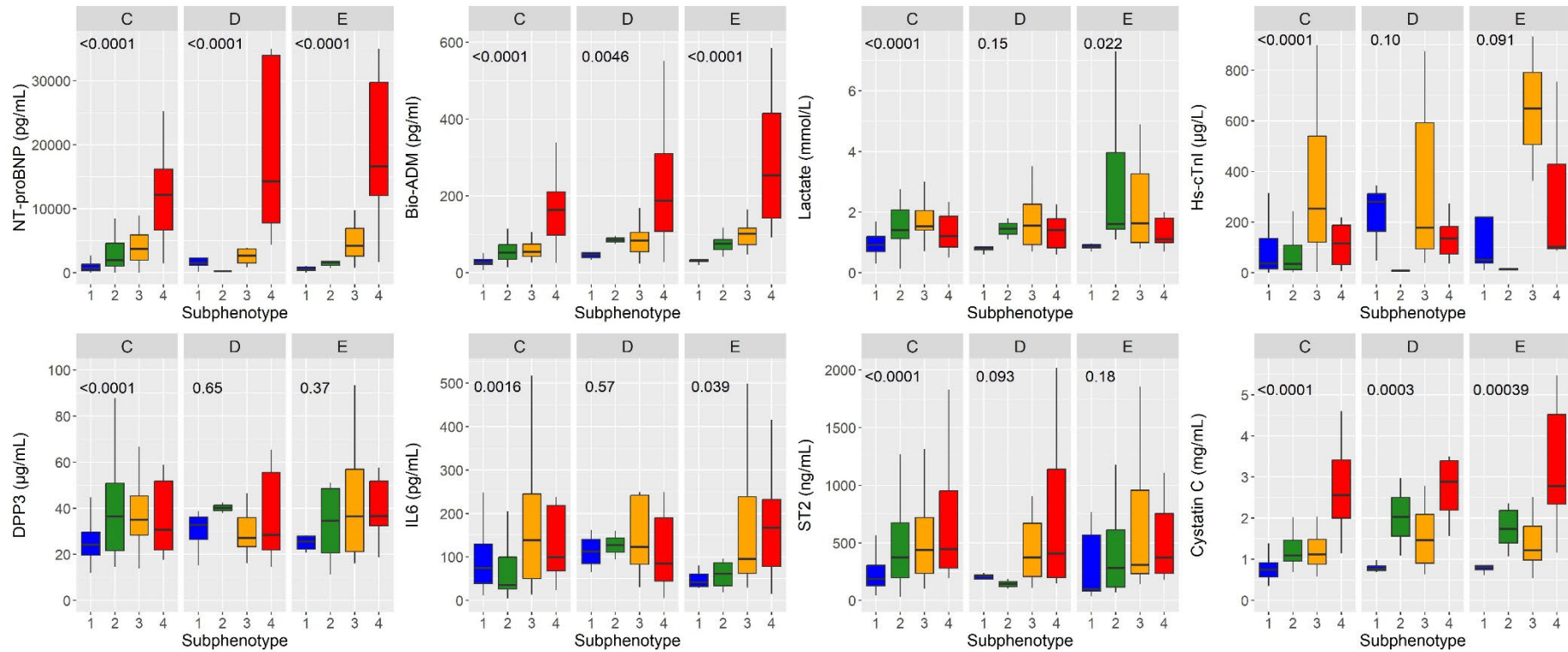
Abbreviations: NT-proBNP, N-terminal pro B-type natriuretic peptide; DPP3, Dipeptidyl peptidase 3; Bio-ADM, Bio-adrenomedullin; IL6, Interleukin-6; ST2, soluble form of suppression of tumorigenicity 2; Hs-cTnT, *high-sensitive cardiac troponin T*; Hs-cTnI, *high-sensitive cardiac troponin I*; NS, not significant.

Figure S5. Comparison of host response biomarkers levels across subphenotypes ((adaptive (1), non-inflammatory (2), cardiopathic (3) and inflammatory (4)) based on SCAI shock stage (C, D and E) in the derivation (CardShock) (A) and validation (FROG-ICU) (B) cohorts.

(A)



(B)

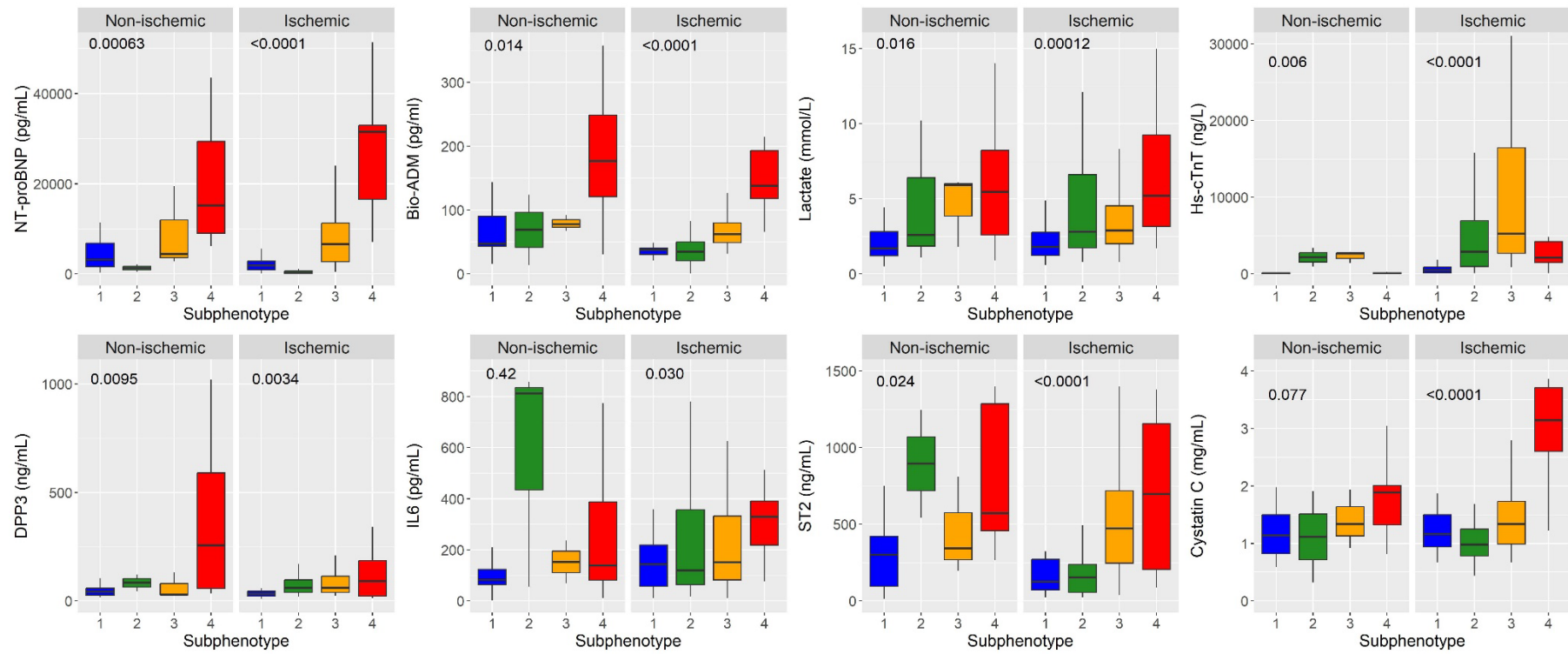


Comparison for each biomarker within subgroups was performed using the Kruskal-Wallis test. Data are shown as median (IQR).

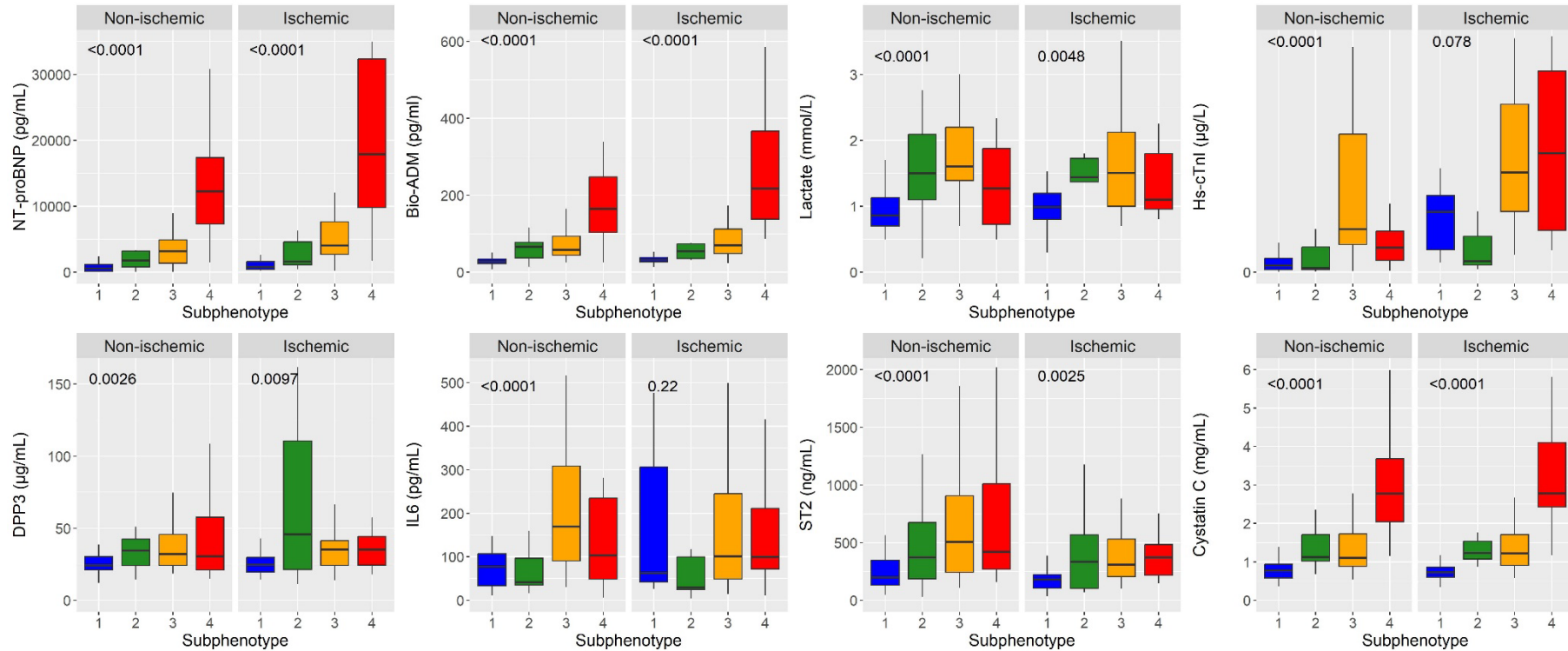
Abbreviations: NT-proBNP, N-terminal pro B-type natriuretic peptide; DPP3, Dipeptidyl peptidase 3; Bio-ADM, Bio-adrenomedullin; IL6, Interleukin-6; ST2, soluble form of suppression of tumorigenicity 2; Hs-cTnT, *high-sensitive cardiac troponin T*; Hs-cTnI, *high-sensitive cardiac troponin I*; NS, not significant.

Figure S6. Comparison of host response biomarkers levels across subphenotypes (adaptive (1), non-inflammatory (2), cardiopathic (3) and inflammatory (4)) by cause of cardiogenic shock (ischemic versus non-ischemic).

(A)



(B)



Comparison for each biomarker within subgroups was performed using the Kruskal-Wallis test. Data are shown as median (IQR).

Abbreviations: NT-proBNP, N-terminal pro B-type natriuretic peptide; DPP3, Dipeptidyl peptidase 3; Bio-ADM, Bio-adrenomedullin; IL6, Interleukin-6; ST2, soluble form of suppression of tumorigenicity 2; *Hs-cTnT*, *high-sensitive cardiac troponin T*; *Hs-cTnI*, *high-sensitive cardiac troponin I*; NS, not significant.

Figure S7. Differences in standardized class-defining variables between subphenotypes (adaptive (1), non-inflammatory (2), cardiopathic (3) and inflammatory (4)) using LCA and the simplified classifier in the CardShock (A) and FROG-ICU (B) cohorts.

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.

In the CardShock cohort, to identify the LCA-derived inflammatory subphenotype 4 patients using the simplified classifier: sensitivity was 81% (95%CI (67-96)) and specificity was 97% (95%CI (95-100)). The sensitivity and specificity for identifying the LCA-derived cardiopathic subphenotype 3 were 87% (95%CI (80-95)) and 90% (95%CI (86-96)) respectively.

To externally validate the simplified classifier, we assessed its performance to discriminate LCA-derived subphenotype membership in the validation FROG-ICU cohort. The sensitivity and specificity for identifying the LCA-derived inflammatory subphenotype 4 were 67% (95%CI (54-81)) and 96% (95%CI (93-99)) respectively. To identify the LCA-derived cardiopathic subphenotype 3 patients: sensitivity was 79% (95%CI (69-88)) and specificity was 82% (95%CI (76-88)).

Abbreviations: SD, standard deviations; LCA, latent class analysis; SP, subphenotype; 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*.

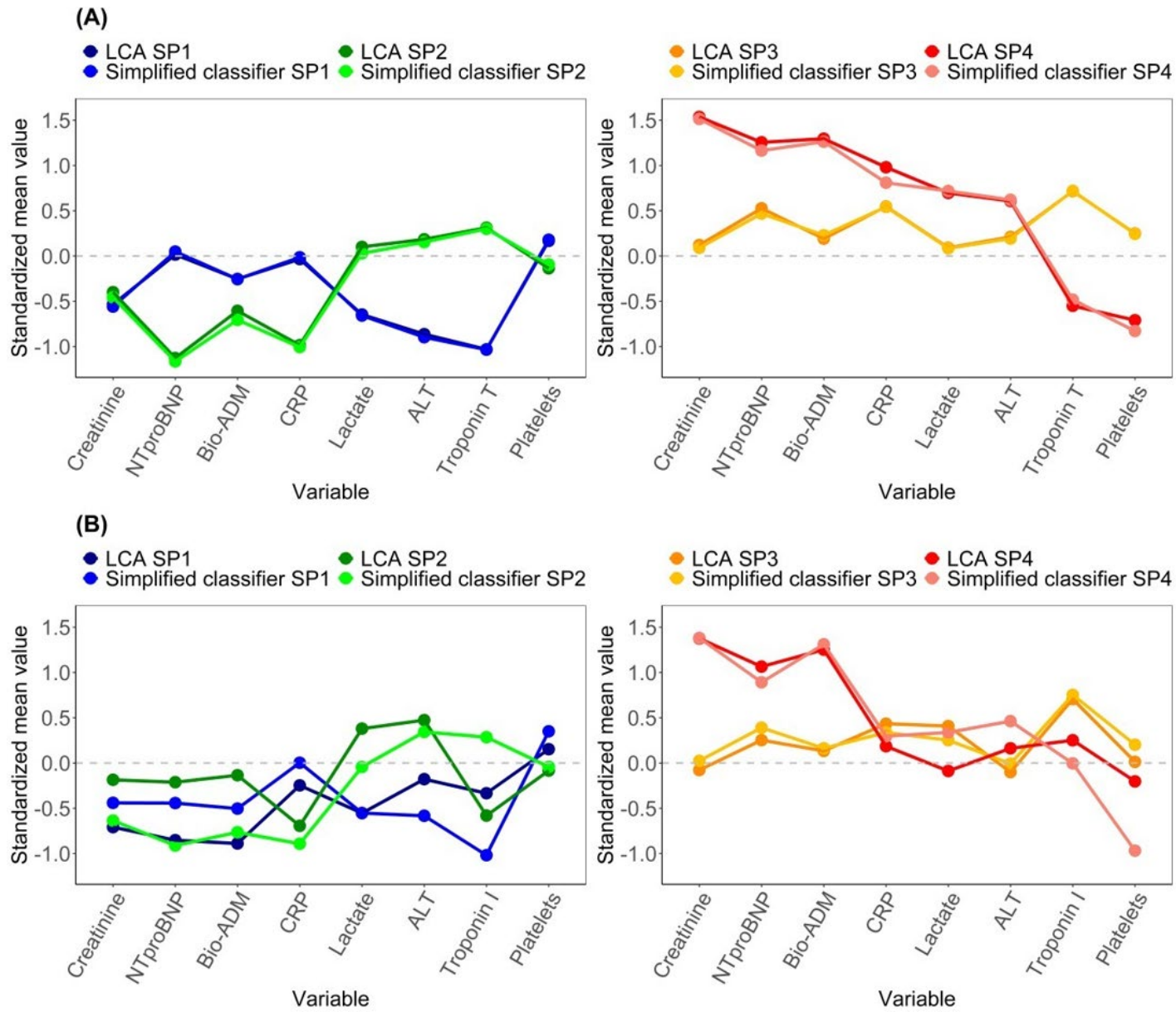
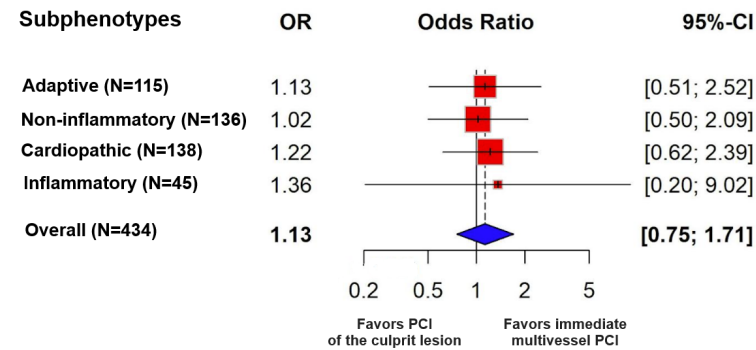


Figure S8. Association between an immediate multivessel revascularization strategy and clinical outcomes **(A)** 28-day mortality and **(B)** a composite outcome of in-ICU mortality, receipt of ECMO/LVAD/Impella device or renal replacement therapy initiation, by subphenotypes in the CULPRIT-SHOCK trial.

Square dots represent unadjusted odds ratios, and the black lines denote 95% confidence intervals. The interaction term (logistic regression model) showed a $p=0.98$ and $p=0.42$ for 28-day mortality and the composite outcome respectively.

Abbreviations: LVAD, Left ventricular assist device; ECMO, Extracorporeal membrane oxygenation; PCI, percutaneous coronary intervention.

(A)



(B)

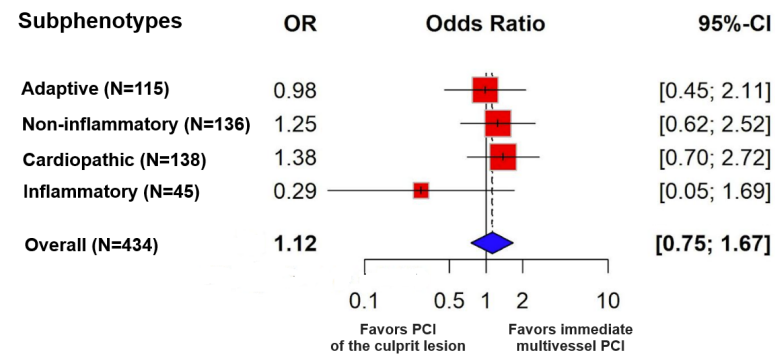
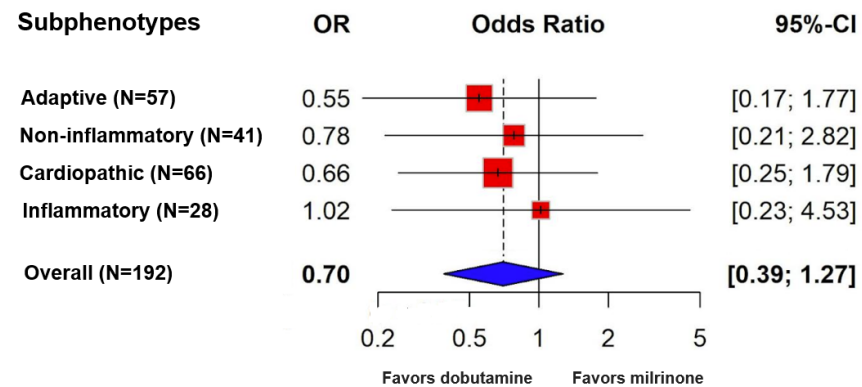


Figure S9. Association between milrinone use and clinical outcomes **(A)** 28-day mortality and **(B)** a composite outcome of in-ICU mortality, receipt of ECMO/LVAD/Impella device or renal replacement therapy initiation, by subphenotypes in the DOREMI trial.

Square dots represent unadjusted odds ratios, and the black lines denote 95% confidence intervals. The interaction term (logistic regression model) showed a $p=0.83$ and $p=0.54$ for 28-day mortality and the composite outcome respectively.

Abbreviations: LVAD, Left ventricular assist device; ECMO, Extracorporeal membrane oxygenation.

(A)



(B)

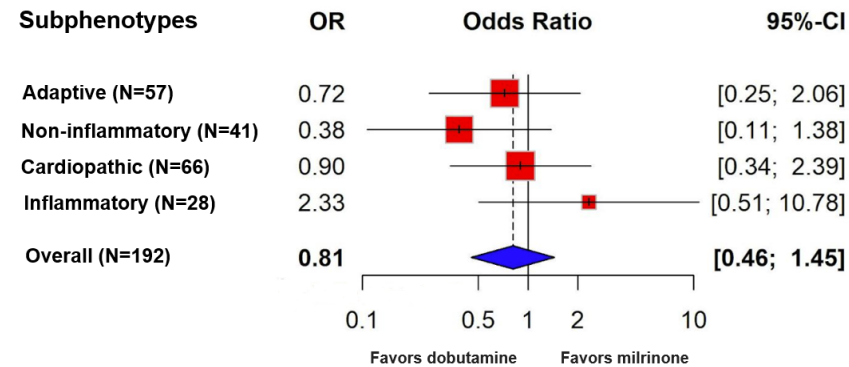


Figure S10. Association between epinephrine use and clinical outcomes, **(A)** 28-day mortality and **(B)** a composite outcome of in-ICU mortality, receipt of VA-ECMO/LVAD or renal replacement therapy initiation, by subphenotypes when pooling the OptimaCC and CardShock studies.

Square dots represent adjusted odds ratios to the SCAI shock stages, and the black lines denote 95% confidence intervals. Odds ratio <1 favors epinephrine use.

The interaction term (logistic regression model) showed a $p=0.25$ and $p=0.78$ for 28-day mortality and the composite outcome respectively.

Abbreviations: LVAD, Left ventricular assist device; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation; SCAI, Society for cardiovascular angiography and interventions.

