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Soluble Triggering Receptor Expressed on Myeloid cells-1 is a marker of organ injuries in cardiogenic shock. Results from the CardShock Study

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Abstract.

Aims. Optimal outcome after cardiogenic shock (CS) depends on a coordinated healing response in which both debris removal and repair of the tissue extracellular matrix play a crucial role. Excessive inflammation can perpetuate a vicious circle, positioning leucocytes as central protagonists and potential therapeutic targets. High levels of circulating Triggering Receptor Expressed on Myeloid cells-1 (TREM-1), were associated with death in acute myocardial infarction confirming excessive inflammation as determinant of bad outcome. The present study aims to describe the association of soluble TREM-1 with 90-day mortality and with various organ injuries in patients with CS.

Methods and results. This is a post-hoc study of CardShock, a prospective, multicenter study assessing the clinical presentation and management in patients with CS. At the time of this study, 87 patients had available plasma samples at either baseline, and/or 48 hours and/or 96-120 hours for soluble TREM-1 (sTREM-1) measurements. Plasma concentration of sTREM-1 was higher in 90-day non-survivors than survivors at baseline (median: 1392 IQR: (724 - 2128) vs. 621 (525 - 1233) pg/mL, $p = 0.008$), 48 hours ($p=0.019$) and 96-120 hours ($p=0.029$). The highest tertile of sTREM-1 at baseline (threshold: 1347 pg/mL) was associated with 90-day mortality with an unadjusted HR: 3.08 CI95% (1.48 - 6.42). sTREM-1 at baseline was not associated to hemodynamic parameters (heart rate, blood pressure, use of vasopressors or inotropes) but rather with markers of organ injuries: renal (estimated glomerular filtration rate, $p=0.0002$), endothelial (bio-adrenomedullin, $p=0.018$), myocardial (Suppression of Tumourigenicity 2, $p=0.002$) or hepatic (bilirubin, $p=0.008$).

Conclusion. In CS patients TREM-1 pathway is highly activated and gives an early prediction of injuries of vital organ and outcome.

Keywords: Biomarkers, sTREM, Cardiogenic Shock, Outcome

INTRODUCTION

Cardiogenic shock (CS) reflects a state in which primary impairment of myocardial function results in end-organ hypoperfusion, and thus hypoxia (1-3). CS may complicate a heterogeneous group of diseases, ranging from acute coronary syndrome to acute decompensation of chronic congestive heart failure. A common feature is the rapid development of a profound inflammatory state originating from both the disease itself and its management aiming to restore the cardiac output. The systemic inflammation is responsible for pathologic vasodilation that further aggravate organ dysfunction (2,4-6). There is therefore an urgent unmet need for a way to break this vicious circle.

Among the mediators considered as perpetrators of inflammation in severe conditions seen in intensive care Units, the Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) seems to play a central role. TREM-1 is an immune receptor, mainly expressed on neutrophils and monocytes/macrophages (7). The engagement of TREM-1 through the binding of its, still unknown, ligand amplifies the inflammatory response mediated by Toll-like receptor activation (8). The deleterious role of TREM-1 has been shown during experimental septic shock (9,10), but also in animal models of myocardial infarction (11,12). Moreover, the inhibition of the TREM-1 pathway was able to restore the inflammatory balance, to reduce myocardial dysfunction, and finally to improve survival (11,12).

A soluble form of TREM-1 is present in the plasma and is a marker of the TREM-1 pathway activity (13). In a large nationwide cohort, we recently observed that plasma concentration of sTREM-1 was an independent predictor of the two-year risk of death in patients suffering from acute myocardial infarction (11). We make the hypothesis that sTREM-1 is highly active in cardiogenic shock and may be associated with organ injuries. Accordingly, we aim to

evaluate the TREM-1 pathway activation and its relationship with injuries of the main organs and outcome in a European cohort of CS patients.

METHODS

The Cardshock study: brief description

The Cardshock study (NCT: NCT01374867) is a prospective cohort of 219 patients with CS from nine hospitals in eight European countries performed within the Global REsearch on Acute Conditions Team (GREAT) network. The main goal was to describe the clinical presentation and management in patients with CS. The period of inclusion extended from October 2010 to 31 December 2012. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki. The results of the original study have been published (14). Briefly, consecutive adult patients were enrolled within six hours following the diagnosis of CS. Of note, in addition to the underlying cardiac cause, the following criteria were required: (1) systolic blood pressure <90 mmHg (in the absence of hypovolemia or after adequate fluid challenge) for 30 minutes or adjunction of a vasopressor to maintain adequate perfusion pressure, and (2) symptoms and/or signs of hypoperfusion (altered mental status, cold periphery, oliguria, lactatemia > 2 mmol/L). The main exclusion criteria were CS following cardiac or non-cardiac surgery and ongoing hemodynamically significant arrhythmia as the cause of CS.

Endpoints

For this post-hoc study, the primary endpoint was to assess the association between sTREM-1 and 90-day mortality. Secondary endpoints included the relationship between sTREM-1 and markers of organ failure.

Data collection

Demographic data, previous medical history, clinical, biochemical, and hemodynamic parameters on baseline and 48 hours were collected. Serial blood samples were initially collected in 178 patients at baseline, 12, 24, 48, 72 hours, and between 96 and 120 hours;

plasma was frozen and stored at -80°C . Arterial blood gas and lactate were analyzed locally while creatinine, C-reactive protein (CRP), alanine transferase (ALT), bilirubin, high-sensitivity troponin T (hsTnT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were analyzed at baseline (Roche Diagnostics, Basel, Switzerland) at a central laboratory (ISLAB, Kuopio, Finland). Estimated glomerular filtration rates (eGFR, calculated from creatinine values using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation), bio-adrenomodulin (bio-ADM, Sphingotec GmbH, Hennigsdorf, Germany), procalcitonin (PCT, Sphingotec GmbH, Hennigsdorf, Germany) suppression of tumourigenicity 2 (ST2, measured at INSERM UMR-S 942, Paris, France) were measured at baseline and 48 hours from these samples. From available samples, sTREM-1 was measured in triplicate using ELISA (RnD Systems, MN, USA) at baseline, 48 hours and 96-120 hours post-baseline in Inotrem laboratory, Nancy, France. CS management was also recorded in detail (use and duration): vasopressors/inotropic drugs, mechanical assistance, ventilatory support. The endpoint of interest was 90-day all-cause mortality which was assessed through direct contact with the patient (or next of kin) or through hospital records and population registries. Patients with no 90-day vital status ($n=2$) or no follow-up data ($n=1$) were not included.

Statistical analyses

Analytical data are presented as the median with 25th and 75th percentiles (median (interquartile range)) for continuous variables, whereas categorical variables as numbers and percentages. Comparisons of baseline characteristics according to groups were conducted by using Wilcoxon or Kruskal–Wallis tests for continuous variables and the Fisher exact test or χ^2 test for categorical variables. Log-rank test or Cox proportional-hazards regression were used to analyze the association of sTREM-1 by tertile with 90-day mortality in univariable analyses. Low sTREM-1 included the first two tertiles and high sTREM-1 included

the third tertile of sTREM-1 concentration at baseline. For illustration, a survival curve was drawn according to the third tertile value (high sTREM-1) by using the Kaplan–Meier method. Considering that only 60 samples were available at baseline with 29 events, multiple Cox regression models with a combination of four variables maximum were generated to assess the impact of high sTREM-1 threshold on 90-day mortality. Variables included in these multiple models were those with no collinearity for continuous variables and those with a p-value < 0.1 in univariate Cox model analyses. Thus, each model included unique successive associations of the significant variables in univariate Cox models: sTREM-1 threshold at baseline + variable_n + variable_{n+1} + variable_{n+2}. To assess the impact of missing samples, a comparison of baseline characteristics was performed to patients with available samples at baseline. A two-sided p-value ≤ 0.05 was regarded as statistically significant. Statistical analyses were performed using R, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population characteristics

From the 219 CS patients enrolled in the CardShock study, 87 patients were finally included in this ancillary study, and among them, 60, 56 and 45 patients had available samples at baseline, 48 hours and 96-120 hours respectively (**Figure S1**).

Characteristics of the included population (n=87) at baseline are presented in **Table S1**. Briefly, this population was mainly composed of males 65 (75 %), aged (median) 68 (interquartile 25%-75%) (58 - 78) years old with ischemic heart disease as first medical history in 31 (36 %) patients. The primary recorded cause of CS was acute coronary syndrome in 70 (80 %). Severity criteria at baseline were a low systolic blood pressure at 76 (70 - 84) mmHg, with reduced LV ejection fraction at 30 (20 – 45) %, and major signs of congestion (NT-proBNP: 3193 (631 - 9715) ng/L). Organ dysfunction at baseline was characterized by increased lactate at 2.9 (2.0 - 6.0) mmol/L. Sixty-one percent and 72% were treated with norepinephrine and dobutamine respectively. Invasive ventilation was required in 67 % for a median duration of 7 (4 - 11) days. Ninety-day mortality of the 87 CS patients included was 46%. Differences in baseline characteristics between the population with available samples and those without are presented in **Table S1**.

Time course and association with 90-day mortality of sTREM-1 values in CS patients

Figure 1 shows that sTREM-1 values were higher in 90-day non-survivors than in survivors at baseline (1392 (724 - 2128) vs. 621 (525 - 1233) pg/mL, p=0.008), 48 hours (p=0.019) and 96-120 hours (p =0.029). **Figure S2** shows that there is an association between 90-day mortality and only the highest tertile of sTREM-1 at baseline (sTREM-1 > 1347 pg/mL defining high sTREM-1, Hazard ratio (HR): 3.58, Confidence Interval 95% (1.38 - 9.27)). Univariate cox regression analysis found an association between high sTREM-1 and 90-day mortality (HR:

3.08 (1.48 - 6.42)) (**Table S2**). Six hundred eighty Cox multivariate models were generated to test the latter association. A high sTREM-1 threshold was associated with an increased risk of death (HR>1) at 90 days in all generated models. Significance ($p \leq 0.05$) and trend ($p < 0.1$) were reached in 49% and 70% of the generated models respectively.

Association of sTREM-1 at baseline and clinical patterns

Characteristics of the population at baseline according to the highest tertile of sTREM-1 are presented in **Table 1**. Briefly, patients in the high sTREM-1 group as compared to patients in the low sTREM-1 group had no difference for demographic data, medical history (except for chronic kidney disease more frequent in the high sTREM-1 group, $p=0.083$), or cause of CS. Similarly, there were no differences at baseline for hemodynamic variables, namely heart rate, systolic blood pressure, and catecholamines use between high and low sTREM-1 patients (**Figure 3**). Conversely, high sTREM-1 concentrations were associated with features of organ failure. Thus, compared to low sTREM-1, high sTREM-1 was associated injuries in various organs: renal (eGFR: 33 (17 - 48) vs. 65 (35 - 87) mL/min/1.73 m², $p=0.0002$), endothelial (bio-ADM: 90 (46 - 151) vs. 41 (31 - 73) pg/mL, $p=0.018$), cardiac (ST2: 542 (274 - 899) vs. 180 (125 - 290) ng/mL, $p=0.002$), and hepatic (bilirubin: 14 (10 - 28) vs. 9 (5 - 12) $\mu\text{mol/L}$, $p=0.008$) dysfunctions (**Figure 4**). Other inflammatory biomarkers such as CRP, PCT were also increased in high sTREM-1 compared to low sTREM-1 patients ($p=0.019$ and 0.0002 respectively, **Table 1**). Of note, in a subgroup of patients with no prior kidney disease, eGFR was also reduced in the high sTREM-1 group, (41 (25 - 52) vs. 71 (46 - 92) mL/min/1.73 m², $p= 0.0013$). At 48 hours, these biomarkers of organ injuries showed improvement (**Figure S3**).

DISCUSSION

In this European multicenter cohort of CS patients, we found the TREM-1 pathway highly activated. More specifically, high sTREM-1 concentrations were associated with various organ injuries (heart, liver, kidney, endothelium) which translated to poor 90-day outcome.

TREM-1 has been widely studied in the context of septic shock, where the concentrations of its soluble form (sTREM-1) has been shown to predict the outcome (15). The median sTREM-1 plasma concentration in septic shock setting was around 500 pg/mL. Here, we observed very high sTREM-1 concentrations (median 838 pg/mL) reflecting an intense activation of the TREM-1 pathway. Moreover, we observed strikingly greater circulating sTREM-1 on admission among non-survivors of CS. Although this association could seem trivial, simply reflecting the severity of shock, sTREM-1 was not related to the traditional parameters of hemodynamic compromise (heart rate, arterial pressure, use of vasopressors or inotropes). Instead, sTREM-1 associated with markers of organ injuries: kidney (glomerular filtration rate), liver (bilirubin), endothelium (adrenomedullin), and heart (Suppression of tumorigenicity 2). Findings of the present study support a role for TREM-1 in perpetuating the vicious cycle triggered by the initial myocardial dysfunction toward other vital organs. Our study suggest that TREM-1, by perpetuating hyperinflammation and cell injury in the vital organs might be a direct link between heart inflammation and injuries of the main organs, independently from hemodynamic status. Altogether our data support the notion that overactivation of the inflammatory response, not targeted by the current treatments might explain the consistently high global mortality in CS (45-50%) despite the improvement of care, including early reperfusion and mechanical circulatory support devices (6).

TREM-1 is a part of the TREM family that comprises 5 other members (TREM-2, TREML 1-4) clustered on human chromosome 6. TREM-1 associates with the adaptor protein DNAX activating 12 (DAP12) for signaling (16). Its engagement triggers a signaling pathway involving that finally results in the production of metalloproteases, pro-inflammatory cytokines and chemokines, including monocyte chemoattractant proteins 1 and 3 (MCP-1, MCP-3), macrophage inflammatory protein 1 α (MIP1- α), interleukin 1 β (IL-1 β), IL-6, IL-8, TNF α , along with rapid neutrophil degranulation and oxidative burst, with a parallel downregulation of anti-inflammatory IL-10 (18).

Among the TREM family, TREM-1 has been identified on both human and murine neutrophils, mature monocytes and macrophages. Its expression by these effector cells is dramatically increased in skin, biological fluids and tissues infected by bacteria and fungi (18). The activation of TREM-1 by its, yet unknown, ligand in the presence of Toll-like receptor (TLR) ligands amplifies the production of proinflammatory cytokines. Besides, activation of these TLRs upregulates TREM-1 expression (8). Thus, TREM-1 and TLRs cooperate in mounting an inflammatory response. During CS, the priming of the immune response (TLR activation) is not achieved by bacterial products, but through the release by necrotic cells and damaged extra-cellular matrix of endogenous damage-associated molecular patterns (DAMPs or Alarmins).

The deleterious role of TREM-1 in amplifying the inflammatory response has been observed in numerous animal models of infections (pneumonia, peritonitis), but also chronic inflammatory disorders such as inflammatory bowel diseases or atherosclerosis (9, 10, 19, 20). We have also observed in a cohort of 1015 myocardial infarction patients that sTREM-1 plasma concentration independently predicted 2-year outcome (11). Our group has showed that genetic invalidation of the TREM-1 gene or pharmacologic modulation by the use of a

synthetic inhibitory peptide (Nangibotide) protected animals (mice, rats, and pigs) from hyperresponsiveness, myocardial failure, organ dysfunction, and death, following myocardial infarction (11, 12). Nangibotide, a first-in-class TREM-1 inhibitor has already demonstrated preliminary safety and efficacy results in a phase 2a trial in septic shock patients and a phase 2b trial (ASTONISH) is underway in this indication (21). Our current findings support that this molecule is worth being investigated in CS patients as well.

We acknowledge several limitations in this study. First, this is a post-hoc analysis of a multicenter European cohort study carried out at the beginning of 2010. Since then, global management of cardiogenic shock improved from early revascularization process of STEMI-related CS to extended use of mechanical assistance devices in case of refractory CS. However, this does not jeopardize the association between sTREM-1 concentration at baseline and our main outcomes. Second, due to the small sample size, we were unable to perform a fully adjusted survival analysis to confirm that sTREM-1 is independently associated with 90-day mortality. To address this limitation, we generated multivariate Cox models with all possible unique combinations of four variables, all associated with 90-day mortality in univariate analysis. Accordingly, results of the present study will require confirmation in further multi-national studies for each stratum of the ABCDE new definition of CS to ensure that sTREM-1 consistently predicts organ dysfunctions and poor outcome (1).

In conclusion, the present study suggests that, sTREM-1, an inflammatory biomarker, when elevated in plasma may predict injuries in vital organs in CS patients and a poor 90-day outcome.

Legends

Figure 1: Comparison of the time-course of sTREM-1, from baseline to 96-120 hours, between 90-day survivors and non survivors.

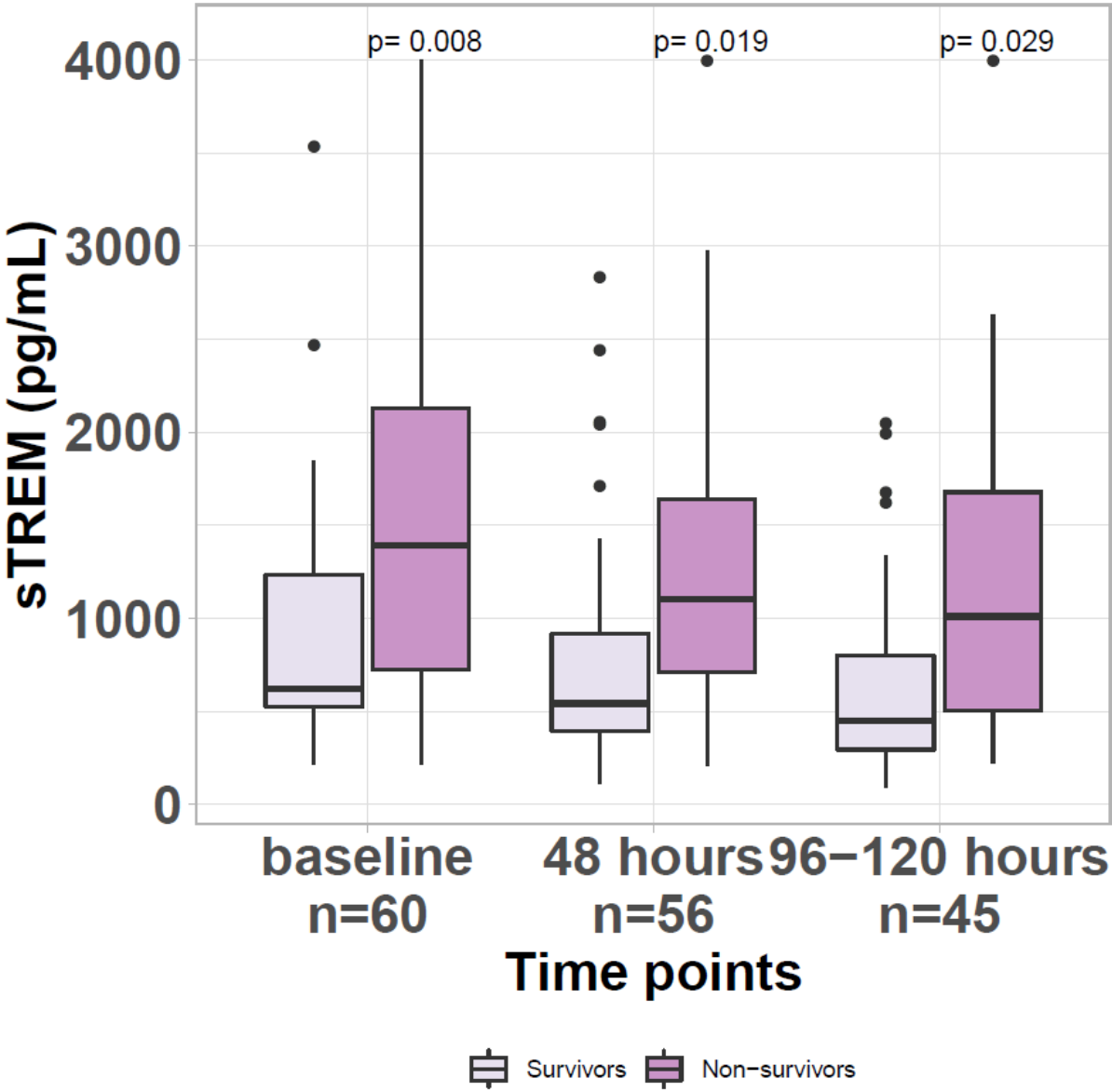


Figure 2: Kaplan–Meier analysis at 90-day all-cause mortality in cardiogenic shock patients with, at baseline, high sTREM-1 >1347 ng/mL vs. low sTREM values ≤1347 ng/mL. HR, hazard ratio.

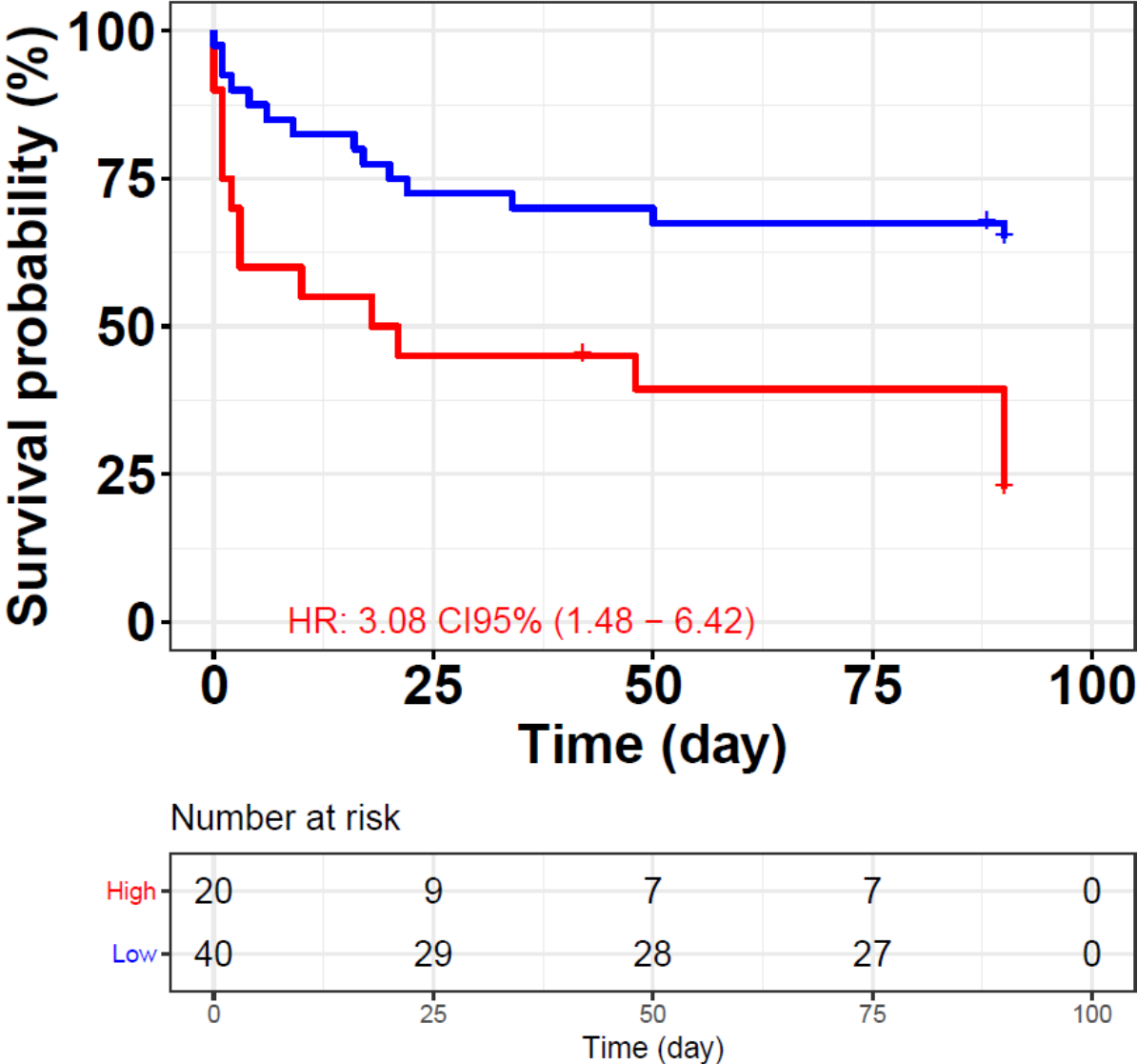


Figure 3: Comparison of haemodynamic variables between cardiogenic shock patients with high and low sTREM-1 values at baseline and catecholamine use during ICU stay.

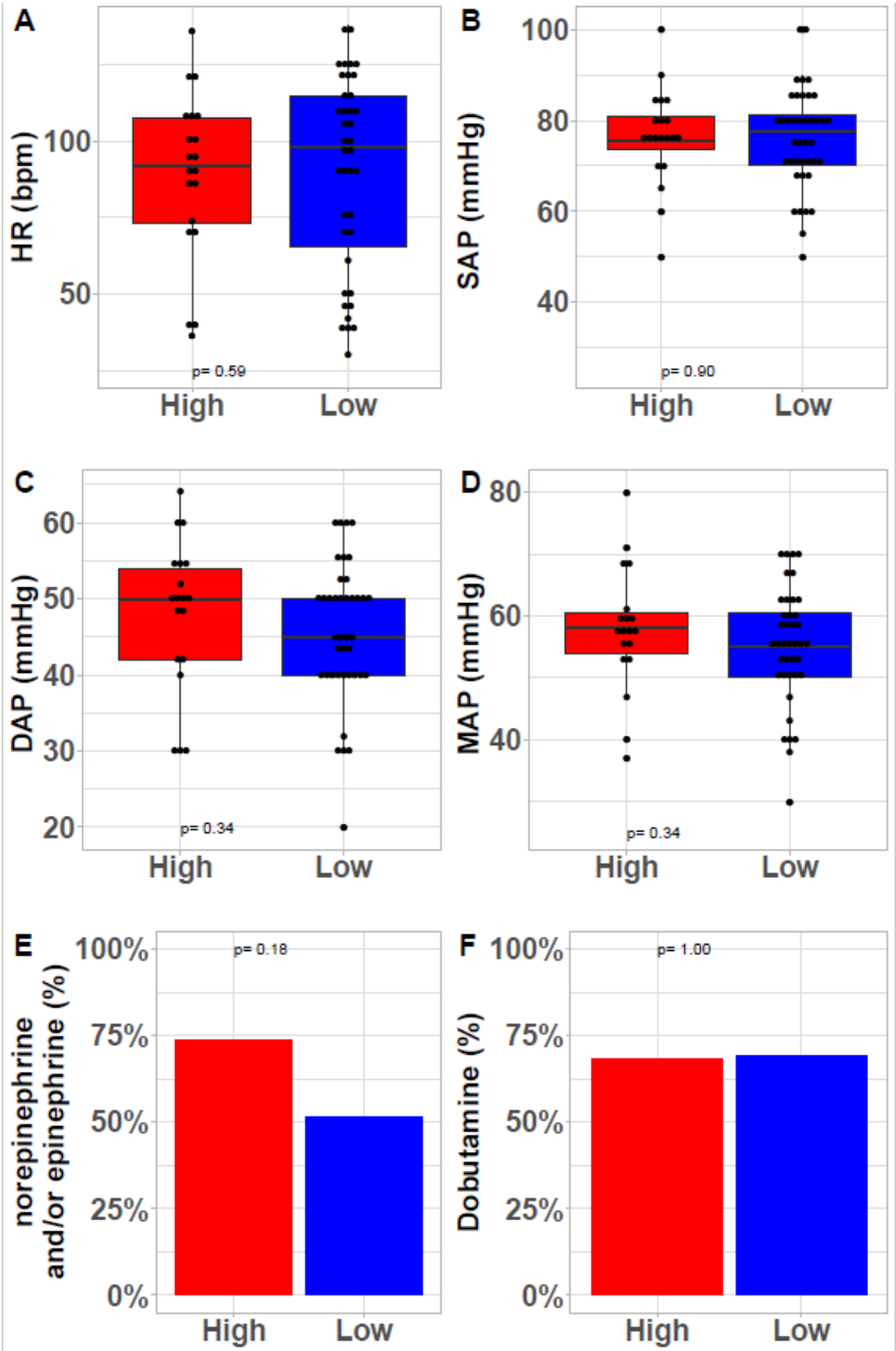
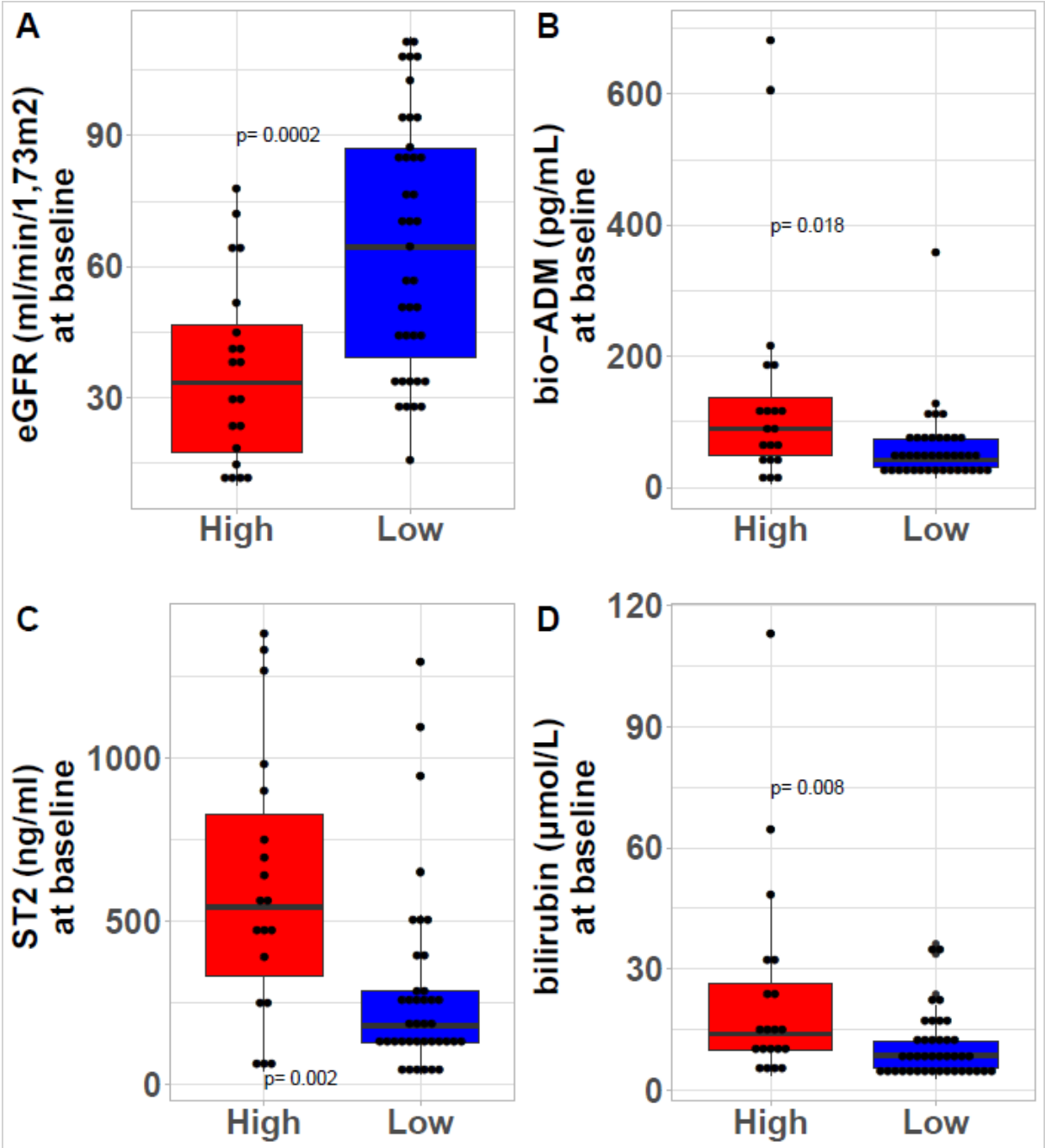


Figure 4: Comparison of organ dysfunction variables between cardiogenic shock patients with high and low sTREM-1 values at baseline.



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Declaration of Conflicting Interests

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Data availability

Data are available from the corresponding author on reasonable request.

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Table 1: Characteristics at baseline between high (>1347 ng/mL) and low sTREM (\leq 1347 ng/mL) (n = n available).

variable	n	Global	n high sTREM-1	high sTREM -1	n low sTREM-1	low sTREM-1	p-value
Age (years)	60	68 (59 - 79)	20	67 (61 - 79)	40	70 (57 - 78)	0.91
Male gender (%)	60	42 (70 %)	20	16 (80 %)	40	26 (65 %)	0.23
BMI (kg/m ²)	59	27.3 (24.7 - 28.7)	19	27.5 (25.7 - 28.7)	40	26.1 (23.4 - 29.2)	0.34
Medical history							
Ischemic heart disease	60	23 (38 %)	20	10 (50 %)	40	13 (32 %)	0.19
Chronic heart failure	60	14 (23 %)	20	7 (35 %)	40	7 (18 %)	0.20
Atrial Fibrillation	60	11 (18 %)	20	4 (20 %)	40	7 (18 %)	1.00
Chronic respiratory disease	60	6 (10 %)	20	3 (15 %)	40	3 (8 %)	0.39
Chronic kidney disease	60	12 (20 %)	20	7 (35 %)	40	5 (12 %)	0.083
Stroke	60	4 (7 %)	20	0 (0 %)	40	4 (10 %)	0.29
Underlying Causes							
Resuscitation prior to baseline	60	18 (30 %)	20	8 (40 %)	40	10 (25 %)	0.23
Acute coronary syndrome	60	47 (78 %)	20	14 (70 %)	40	33 (82 %)	0.33
Decompensated chronic heart failure	60	8 (13 %)	20	4 (20 %)	40	4 (10 %)	0.42
Others*	60	8 (13 %)	20	5 (25 %)	40	3 (8 %)	0.10
Clinical parameters at baseline							
Systolic blood pressure at baseline (mmHg)	60	76 (70 - 82)	20	76 (72 - 82)	40	78 (70 - 82)	0.90
Diastolic blood pressure at baseline (mmHg)	59	50 (40 - 52)	19	50 (42 - 54)	40	45 (40 - 50)	0.34
Mean blood pressure at baseline (mmHg)	59	56 (51 - 61)	19	58 (53 - 61)	40	55 (50 - 61)	0.34
Heart rate at baseline(bpm)	59	96 (70 - 110)	20	92 (72 - 108)	39	98 (61 - 115)	0.59
LV ejection fraction at baseline (%)	57	30 (20 - 45)	20	20 (18 - 35)	37	35 (25 - 45)	0.016
Biology at baseline							
lactate at baseline (mmol/L)	58	2.8 (2.0 - 6.8)	20	6.0 (2.8 - 10.9)	38	2.5 (1.8 - 3.6)	0.001
pH at baseline	60	7.30 (7.20 - 7.40)	20	7.28 (7.12 - 7.38)	40	7.30 (7.25 - 7.40)	0.12
eGFR at baseline (mL/min/1.73m ²)	59	49 (30 - 78)	20	33 (17 - 48)	39	65 (35 - 87)	0.0002
Creatinine at baseline (μ mol/L)	59	116 (81 - 165)	20	156 (116 - 328)	39	96 (67 - 140)	0.0002
Bilirubin at baseline (μ mol/L)	60	10 (6 - 16)	20	14 (10 - 28)	40	9 (5 - 12)	0.008
ALT at baseline (UI/L)	60	42 (20 - 78)	20	47 (26 - 231)	40	38 (18 - 72)	0.12
NT-proBNP at baseline (ng/L)	59	3672 (570 - 11623)	20	8168 (3244 - 32231)	39	1447 (252 - 8976)	0.0008
hs-TNT at baseline(ng/L)	59	1593 (165 - 3677)	20	1587 (161 - 4131)	39	2324 (335 - 3677)	0.78
PaO ₂ /FiO ₂ at baseline (%)	54	180 (104 - 306)	18	181 (98 - 304)	36	180 (110 - 309)	0.64
PCT at baseline (ng/mL)	60	0.21 (0.08 - 0.72)	20	1.44 (0.27 - 4.83)	40	0.17 (0.07 - 0.37)	0.0002
CRP at baseline (mg/L)	59	19 (4 - 60)	20	42 (20 - 68)	39	7 (4 - 43)	0.019
bio-adrenomodulin (pg/mL)	60	53 (33 - 90)	20	90 (46 - 151)	40	41 (31 - 73)	0.018
ST2 (ng/mL)	58	266 (131 - 517)	19	542 (274 - 899)	39	180 (125 - 290)	0.002
Treatments							
Norepinephrine administered	58	34 (59 %)	19	14 (74 %)	39	20 (51 %)	0.10
Norepinephrine length (days)	54	1 (0 - 2)	16	2 (0 - 3)	38	0 (0 - 2)	0.22
Epinephrine administered	58	15 (26 %)	19	8 (42 %)	39	7 (18 %)	0.062

variable	n	Global	n high sTREM-1	high sTREM -1	n low sTREM-1	low sTREM-1	p-value
Epinephrine length (days)	58	0 (0 - 1)	19	0 (0 - 2)	39	0 (0 - 0)	0.054
Dobutamine administered	58	40 (69 %)	19	13 (68 %)	39	27 (69 %)	0.95
Dobutamine length (days)	44	1 (0 - 2)	13	2 (0 - 2)	31	1 (0 - 3)	0.96
Dopamine administered	58	13 (22 %)	19	5 (26 %)	39	8 (21 %)	0.74
Dopamine length (days)	53	0 (0 - 0)	16	0 (0 - 0)	37	0 (0 - 0)	0.73
Non-invasive ventilation	59	7 (12 %)	20	3 (15 %)	39	4 (10 %)	0.68
Non-invasive ventilation length (days)	6	1 (1 - 1)	2	1 (1 - 1)	4	1 (1 - 2)	0.72
Invasive ventilation	60	38 (63 %)	20	16 (80 %)	40	22 (55 %)	0.058
Invasive ventilation length (days)	37	5 (2 - 11)	16	4 (2 - 12)	21	6 (2 - 11)	0.68
Percutaneous coronary intervention	60	35 (58 %)	20	8 (40 %)	40	27 (68 %)	0.042
Intra-aortic balloon pump	60	35 (58 %)	20	13 (65 %)	40	22 (55 %)	0.46
Outcomes							
Hospital length of stay (days)	60	14 (5 - 28)	20	12 (2 - 24)	40	14 (8 - 32)	0.53
In-hospital non-survivors	60	24 (40 %)	20	13 (65 %)	40	11 (28 %)	0.005
90-day non-survivors	60	29 (48 %)	20	15 (75 %)	40	14 (35 %)	0.003

Others: Myocarditis n= 2 , Valvular disease n= 6