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Inflammatory cytokine signatures and factors associated with cardiogenic shock in acute coronary syndrome: Insights from an observational study

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Abstract

Background: Cardiogenic shock (CS) complicating acute coronary syndrome (ACS) remains a leading cause of in-hospital cardiovascular mortality. Systemic inflammatory cytokines may contribute to CS pathophysiology but remain incompletely characterized. We aimed to delineate profiles of ACS patients with and without CS and evaluate their utility for CS identification.

Methods: In this single-centre observational study with a comparator sampling design, 150 ACS patients (August 2024-December 2025) were enrolled as ACS-CS (n = 60) and ACS-noCS (n = 90). A 13-analyte cytokine panel, selected a priori from an independent bioinformatics analysis of six GEO datasets, was quantified in serum by Luminex multiplex immunoassay within 24 hours of admission and before definitive therapy. Analyses comprised group comparison with Benjamini–Hochberg false discovery rate (FDR) correction, receiver operating characteristic (ROC) analysis, random-forest classification and multivariable logistic regression with Firth-penalised sensitivity analysis.

Results: ACS-CS patients were more frequently female (46.7% vs 22.2%; p = 0.002) and had higher diabetes prevalence (68.3% vs 37.8%; p < 0.001). Median SBP was lower (85 vs 127 mmHg; p < 0.001), LVEF reduced (27.5% vs 44.5%), BNP elevated (1009 vs 237.5 pg/mL; p < 0.001) and in-hospital mortality higher (35.0% vs 6.7%; p < 0.001). Eleven cytokines met both pre-specified criteria

(FDR < 0.05 and $\log_2FC > 0.5$). IL-6 was the strongest individual discriminator ($\log_2FC$ 2.62; AUC 0.870). A random-forest model incorporating the 13-cytokine panel achieved an internally cross-validated AUC of 0.958 (95% CI 0.92-0.98). IL-6, IL-10 and TNF- α remained independently associated with CS after adjustment for age and sex.

Conclusion: CS complicating ACS is accompanied by broad, coordinated systemic immune activation alongside hemodynamic failure. Multi-cytokine modelling showed high discrimination within this cohort, but all performance estimates are internal and potentially optimistic. These findings are hypothesis-generating and support prospective external validation of inflammatory profiling for risk stratification and as a rationale for immunomodulatory strategies.

Abbreviations: ACS (acute coronary syndrome), ALC (absolute lymphocyte count), ALP (alkaline phosphatase), ALT (alanine aminotransferase), ANC (absolute neutrophil count), aPTT (activated partial thromboplastin time), AST (aspartate aminotransferase), AUC (area under the receiver operating characteristic curve), BNP (B-type natriuretic peptide), bpm (beats per minute), CI (confidence interval), CK-MB (creatin kinase-MB), CRP (C-reactive protein), CS (cardiogenic shock), DBP (diastolic blood pressure), EPV (events per variable), FDR (false discovery rate), GEO (Gene Expression Omnibus), GM-CSF (granulocyte-macrophage colony-stimulating factor), GO (Gene Ontology), HbA1c (glycated haemoglobin), IABP (intra-aortic balloon pump), IEC (Institutional Ethics Committee), IFN- γ (interferon-gamma), IL (interleukin), INR (international normalised ratio), IQR (interquartile range), JAK/STAT3 (Janus kinase/signal transducer and activator of transcription 3), KEGG (Kyoto Encyclopedia of Genes and Genomes), LDH (lactate dehydrogenase), $\log_2FC$ ($\log_2$ fold-change), LVEF (left ventricular ejection fraction), MAPK (mitogen-activated protein kinase), MCP-1 (monocyte chemoattractant protein-1), M-CSF (macrophage colony-stimulating factor), NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), NLR (neutrophil-to-lymphocyte ratio), NLRP3 (NOD-like receptor protein 3 inflammasome), NS (not significant), NSTEMI (non-ST-elevation myocardial infarction), OR (odds ratio), PBMC (peripheral blood mononuclear cells), PCA (principal component analysis), PPI (protein-protein interaction), PT (prothrombin time), PTH (parathyroid hormone), PTI (prothrombin time index), RNA-seq (RNA sequencing), ROC (receiver operating characteristic), SBP (systolic blood pressure), scRNA-seq (single-cell RNA sequencing), SD (standard deviation), SIRS (systemic inflammatory response syndrome), STEMI (ST-elevation myocardial infarction), STRING (Search Tool for the Retrieval of Interacting Genes/Proteins), TLC (total leucocyte count), TNF- α (tumour necrosis factor-alpha), UA (unstable angina).

1. Introduction

Acute coronary syndrome (ACS) encompasses a clinically urgent spectrum of ischaemic heart disease encompassing unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) underpinned by atherosclerotic plaque disruption, coronary thrombosis and varying degrees of myocardial ischaemia and necrosis [1,2]. Despite transformative advances in reperfusion strategies, antithrombotic pharmacotherapy and critical care management over the past three decades, ACS continues to impose a profound burden of premature cardiovascular morbidity and mortality globally [3].

Cardiogenic shock (CS) represents the most catastrophic complication of ACS occurring in approximately 5–10% of hospitalized patients and carrying in-hospital mortality exceeding 50% even in the contemporary revascularisation era [4,5]. Defined by sustained systolic BP < 90 mmHg with clinical evidence of systemic hypoperfusion attributable to reduced cardiac output [5], CS most commonly arises from extensive LV dysfunction following large anterior STEMI. The SHOCK trial established early revascularisation as cornerstone management [6] yet outcomes remain unacceptably poor demanding investigation of additional determinants and therapeutic targets.

The haemodynamic basis of CS is well characterized and represented as a vicious cycle of reduced cardiac output, compensatory neurohormonal activation, peripheral vasoconstriction and progressive myocardial ischaemia [7]. However, accumulating evidence reveals a parallel immunological crisis in CS including a systemic inflammatory response syndrome (SIRS)-like state characterized by cytokine surge, immune cell activation, endothelial dysfunction and vasoplegia that amplifies myocardial injury, drives multi-organ failure and independently worsens outcomes [8,9]. This dual haemodynamic-immunological crisis paradigm has critical therapeutic implications, opening avenues for targeted anti-inflammatory interventions.

The inflammatory response in ACS is orchestrated by cytokines released from activated macrophages, neutrophils, platelets, endothelial cells and necrotic cardiomyocytes [10]. Pro-inflammatory mediators including IL-6, TNF- α , IL-1 β , IL-8 and MCP-1 have been individually implicated in plaque destabilization, infarct expansion, ventricular remodelling and amplification of systemic inflammation in CS [11,12]. The anti-inflammatory cytokine IL-10 may paradoxically serve as a marker of immune counter-regulation in severe shock [13]. However, the comprehensive multi-analyte cytokine landscape in ACS-CS versus haemodynamically stable ACS has not been adequately explored using systematic multiplex profiling with integrated bioinformatics-guided panel selection.

Conventional biomarkers like troponin, CK-MB, BNP and lactate reflect established myocardial injury and haemodynamic decompensation but provide limited insight into the immunological dimension of CS, potentially missing the earliest phases of inflammatory escalation preceding irreversible haemodynamic collapse [14]. Cytokine profiling at hospital admission could identify a high-risk inflammatory phenotype before overt shock enabling proactive escalation of monitoring, haemodynamic support and potentially stratified immunomodulatory therapy.

This study was designed to (i) systematically characterize and compare the clinical, haemodynamic, biochemical, coagulation, haematological and metabolic profiles of ACS patients with and without CS; (ii) quantify a bioinformatics-guided panel of 13 serum cytokines at baseline using Luminex multiplex immunoassay; (iii) characterize inter-cytokine correlation networks and protein-protein (PPI) network architecture; and (iv) evaluate, in an exploratory fashion, the individual and combined

discriminatory performance of cytokines and conventional biomarkers for the identification of CS using ROC analysis, random-forest classification and multivariable logistic regression.

2. Materials and methods

2.1 Study design and setting

This was a hospital-based observational study conducted at a tertiary care hospital in North India. Patients presenting with acute coronary syndrome (ACS) and fulfilling the predefined eligibility criteria were recruited during the study period. Patients presenting with cardiogenic shock were recruited into the ACS-CS group and patients with ACS without cardiogenic shock were recruited as the comparison group. Clinical assessments, laboratory investigation and cytokine sampling were performed within 24 hours of hospital admission, representing baseline acute-phase measurements. The proportion of patients with CS in the present study reflects the composition of the recruited study cohort by design and was not intended to estimate the population prevalence or incidence of CS among patients with ACS. Given the observational and exploratory nature of the study, no formal power-based sample size calculation was performed; the sample size is consistent with that of similar observational studies in this domain [15].

2.2 Study population

A total of 150 patients with ACS were enrolled between August 2024 and December 2025. Eligible participants were aged 18–85 years with ACS confirmed in accordance with the Fourth Universal Definition of Myocardial Infarction and current ACC/AHA and ESC guidelines [1,16,17]. Written informed consent was obtained from all participants or their legally authorized representatives. Patients presenting with cardiogenic shock were assigned to the ACS-CS group ($n = 60$) and patients with ACS without cardiogenic shock to the comparison group (ACS-noCS, $n = 90$). Cardiogenic shock was defined as sustained systolic blood pressure (SBP) < 90 mmHg or the need for vasopressor and/or inotropic support to maintain SBP ≥ 90 mmHg (SHOCK trial definition [6]) accompanied by clinical signs of hypoperfusion such as cool extremities, oliguria and reduced cardiac output [5]. Seventeen of the 60 ACS-CS patients (28.3%) had an SBP ≥ 90 mmHg recorded at sampling (90 mmHg in 15; 94 and 98 mmHg in one patient each) while receiving vasoactive support. Cardiogenic shock constituted 40.0% of the present recruited cohort but this proportion reflects the two-group sampling design and should not be interpreted as the prevalence or incidence of CS in the general ACS population.

Exclusion criteria included (i) acute kidney injury at presentation, (ii) neurological impairment that could confound clinical assessment, (iii) clinically overt infection or sepsis at admission (defined by fever, clear infectious focus or positive microbiological cultures), and (iv) refusal to provide informed consent. Criterion (iii) was applied specifically to minimize confounding of the cytokine signal by concurrent infection, so that the observed inflammatory profile could be attributed to the sterile systemic inflammatory response of CS rather than to sepsis.

2.3 Ethical approval

All procedures contributing to this work were approved by the Institutional Ethics Committee (IEC-INT/2023/PhD-899) and comply with the ethical standards on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2013. Informed consent was obtained from all participants or their legally authorized representatives before enrollment.

2.4 Clinical data collection

Standardized data were collected at admission including demographics (age, sex), presenting symptoms (chest pain, syncope, shortness of breath, palpitations), vital signs (SBP, DBP, pulse rate, respiratory rate), shock index (pulse rate/SBP; threshold >1.0 indicating haemodynamic compromise), comorbidities (diabetes mellitus, hypertension, smoking, alcohol use), left ventricular ejection fraction (LVEF) by biplane Simpson's method on echocardiography within 24 hours, and in-hospital mortality.

2.5 Laboratory investigations

Approximately 8 mL of venous blood was collected at admission, prior to initiation of definitive therapy, mechanical circulatory support or renal replacement therapy and before escalation of definitive haemodynamic management. Samples for routine haematological investigations were collected in EDTA vials while samples for cytokine quantification were collected in serum separator tubes. All cytokine measurements reported in this study were therefore performed on serum.

The following laboratory parameters were analyzed: complete blood count with differential leucocyte count; cardiac biomarkers including high-sensitivity troponin I, CK-MB, myoglobin, B-type natriuretic peptide (BNP), D-dimer (measured by fluorescence immunoassay) and lactate dehydrogenase (LDH); renal function tests (urea, creatinine); liver function tests (ALT, AST, ALP, total and direct bilirubin, total protein and albumin); serum electrolytes (sodium, potassium, chloride, calcium, magnesium); inflammatory markers (C-reactive protein, procalcitonin, serum ferritin); metabolic and endocrine parameters (HbA1c, uric acid, serum iron, parathyroid hormone (PTH), vitamin D3, vitamin B12); coagulation profile (prothrombin time (PT), prothrombin time index (PTI), international normalized ratio (INR), activated partial thromboplastin time (aPTT)); and the lipid profile.

2.6 Cytokine panel selection: Bioinformatics-guided approach

Cytokine panel selection was guided by integrated computational analysis of six GEO datasets from geographically diverse ACS cohorts (Egypt, USA, South Korea, Japan, China; GSE202937, GSE236610, GSE60993, GSE184073, GSE179645, GSE252710) encompassing whole blood, serum, coronary plaque and PBMC samples analyzed by RNA-seq, microarray and scRNA-seq platforms. Differential expression analysis used DESeq2 (RNA-seq) and Limma (microarray) in R/Bioconductor ($|\log_2FC| > 1$, $p < 0.05$, FDR-adjusted $p < 0.05$). Functional enrichment (GO, KEGG, Reactome) and STRING-based PPI network analysis (hub cytokines by degree centrality) were performed. Thirteen analytes satisfying one or more of four pre-specified criteria - differential expression, network centrality, literature validation in ACS and Luminex assay availability - were selected including GM-CSF, IFN- γ , IL-1 β , IL-4, IL-6, IL-8, IL-9, IL-10, IL-12p70, IL-18, MCP-1, M-CSF and TNF- α . The panel was fixed before any analysis of the present cohort; no data-driven selection of panel analytes was performed on the

150-patient dataset. Dataset characteristics, the differentially expressed genes driving inclusion and the rationale for each analyte are given in Supplementary Table 2.

2.7 Serum cytokine quantification: Luminex multiplex immunoassay

Serum was obtained by centrifugation of serum separator tubes at 2000–2500 × g for 15 minutes at 4 °C and stored at –80 °C until analysis. A multiplex bead-based immunoassay (Luminex platform) was used for simultaneous quantification of the 13 analytes. The assay used distinct fluorescent bead sets coated with analyte-specific capture antibodies. Following incubation with biotinylated detection antibodies (16 – 18 hours at 2 – 8°C), streptavidin–phycoerythrin was added and fluorescence signals were acquired using a Luminex MAGPIX reader. Analyte concentrations were interpolated from analyte-specific standard curves. Samples were assayed in duplicate and mean values were used for analysis. The laboratory personnel were blinded to the clinical group allocation.

2.8 Statistical Analysis

Analyses were performed in R version 4.3.1 (packages: pROC, randomForest, caret, logistf, ResourceSelection, dplyr) with supporting computation in Python 3.12 (NumPy, SciPy, Pandas, Statsmodels). A fixed random seed (42) was used for all cross-validation and resampling procedures. The complete annotated analysis script is provided as Supplementary File (Analysis Code).

Distributional characteristics of continuous variables were examined using the Shapiro–Wilk test and guided descriptive presentation. Continuous variables are reported as median [interquartile range (IQR)], or as mean ± SD where the distribution was approximately symmetrical; irrespective of the descriptive format, all between-group comparisons of continuous variables were performed using the Mann–Whitney U (Wilcoxon rank-sum) test, so that a single test is applied consistently across Table 1. Categorical variables are reported as n (%) and compared using the Pearson chi-square test without continuity correction. Two-sided p-values below 0.001 are reported as < 0.001.

Cytokine concentrations were log₂-transformed before analysis. Fold-change was calculated as the difference in median log₂ concentration between groups, which is algebraically equivalent to the log₂ ratio of the group medians. Between-group comparisons across the 13 analytes used the Wilcoxon rank-sum test with Benjamini–Hochberg FDR correction. An analyte was considered significantly differentially expressed only if it met both pre-specified criteria: FDR < 0.05 and log₂FC > 0.5. Inter-cytokine relationships were characterised by Pearson correlation on log₂-transformed values.

Discriminatory ability was assessed by ROC analysis with AUC, 95% CI and optimal cut-off by the Youden index. Random-forest classification (500 trees, 5-fold cross-validation) used all 13 pre-specified panel analytes with no feature selection; variable importance was quantified by mean decrease in accuracy, and a bootstrap 95% CI (2000 resamples) was computed for the cross-validated AUC.

Multivariable logistic regression was used to identify factors independently associated with CS. The adjustment set comprised age, sex and the five cytokines with the highest individual AUCs; no

stepwise or automated selection was applied. The events-per-variable (EPV) ratio was reported and the data were formally inspected for complete and quasi-separation. Because the EPV ratio was borderline and the log₂-transformed cytokines were moderately correlated, Firth penalised logistic regression was fitted as a pre-planned sensitivity analysis. Model performance was summarised by the apparent AUC with 95% CI and by the 5-fold cross-validated AUC; calibration was assessed by the Hosmer–Lemeshow goodness-of-fit test ($g = 10$) and by the calibration slope and intercept estimated from cross-validated predicted probabilities.

For in-hospital mortality, two multivariable logistic models were compared: a clinical-parameters model (ALT, ALP, LVEF, BNP, CK-MB, CRP) and a combined model additionally including IL-8, IL-10, MCP-1, IL-12p70 and IL-4. Both models were evaluated using cross-validated predicted probabilities generated from identical folds. Discrimination was compared using the Hanley-McNeil method for correlated ROC curves, with the difference in AUC reported with a 95% CI and p-value. All tests were two-sided and $p < 0.05$ was considered statistically significant.

3. Results

3.1 Demographic profile

In accordance with the sampling design, the cohort comprised 60 patients with ACS-CS and 90 patients with ACS-noCS. Mean age was comparable between the two groups (59.95 ± 11.69 years vs 59.17 ± 10.72 years; $p = 0.679$). Sex distribution differed significantly, with female patients over-represented in the ACS-CS group (46.7% vs 22.2%; $p = 0.002$). All assessed presenting symptoms were more frequent in ACS-CS: chest pain (90% vs 48.9%), syncope (88.3% vs 22.2%), shortness of breath (85% vs 45.6%), and palpitations (63.3% vs 36.7%), all $p \leq 0.001$ (Table 1).

3.2 Comorbidities, risk factors and In-hospital mortality

Diabetes mellitus was significantly more common in patients with ACS-CS compared to ACS-noCS (68.3% vs 37.8%; $p < 0.001$). Smoking was significantly less frequent in the ACS-CS group (25% vs 44.4%; $p = 0.016$) while hypertension (63.3% vs 55.6%; $p = 0.343$) and alcohol use (18.3% vs 23.3%; $p = 0.464$) did not differ significantly. In-hospital mortality was markedly higher in the ACS-CS group (35% [21/60]) compared with the ACS-noCS group (6.7% [6/90]; $p < 0.001$) (Table 1).

3.3 Haemodynamic parameters

Patients with ACS-CS presented with a markedly compromised haemodynamic profile: lower systolic (85 [80–90] vs 127 [112–140] mmHg) and diastolic blood pressure (60 [56–62] vs 80 [70–90] mmHg), higher pulse rate (104 [98–112.5] vs 84.5 [78–93.75] bpm), elevated shock index (1.23 [1.15–1.36] vs 0.66 [0.57–0.81]) and increased respiratory rate (22 [20–22] vs 20 [18–20]/min), all $p < 0.001$ (Table 1).

3.4 Cardiac biomarkers and left ventricular function

Consistent with severe myocardial injury, LVEF was profoundly reduced (27.5% [23–32] vs 44.5% [37–52]) and was accompanied by significantly elevated Troponin I (8.96 [1.33–18.49] vs 1.02 [0.04–7.67] ng/mL), CK-MB (54.55 [46.88–61] vs 6.25 [2.10–23.13] U/L), BNP (1009 [348.75–1680.5] vs 237.5 [65.28–481.5] pg/mL), D-dimer (1050 [487.75–2195.75] vs 432.5 [163.25–878.75] ng/mL) and LDH (964 [810.25–1282.25] vs 190.21 [145.45–278.02] U/L), all $p < 0.001$. Myoglobin did not differ significantly ($p = 0.364$) (Table 1).

3.5 Hepatic, renal, electrolyte and systemic inflammatory markers

Liver enzymes were markedly elevated (ALT: 418 [345.75–509.5] vs 45 [29.58–63.5] U/L; AST: 434.5 [347.25–542.25] vs 61 [45.3–121.75] U/L; ALP: 414.5 [299.5–540.5] vs 91.5 [76.5–106.5] U/L; all $p < 0.001$) with reduced albumin (3.19 [2.91–3.53] vs 3.6 [3.2–3.91] g/dL; $p < 0.001$) and total protein (6.16 [5.56–6.85] vs 6.70 [6.10–7.19] g/dL; $p = 0.002$). Urea (65.8 [39.38–95.5] vs 36.5 [28.78–47.53] mg/dL; $p < 0.001$) and creatinine (1.05 [0.92–1.18] vs 0.98 [0.86–1.10] mg/dL; $p = 0.008$) were higher. Inflammatory markers, including CRP (153.86 [132.10–195.75] vs 9.36 [3.13–23.38] mg/L; $p < 0.001$), procalcitonin (0.76 [0.67–0.84] vs 0.50 [0.40–0.83] ng/mL; $p < 0.001$) and ferritin (488.5 [225.4–1159] vs 271 [206.6–311.9] ng/mL; $p < 0.001$), were markedly raised. Electrolyte derangements included hyponatraemia (135.5 vs 139 mEq/L; $p < 0.001$), hypochloraemia (99.15 vs 103 mEq/L; $p < 0.001$), hypocalcaemia (8.80 vs 9.07 mg/dL; $p = 0.047$) and mild hyperkalaemia (4.52 vs 4.20 mEq/L; $p = 0.022$) (Table 1).

3.6 Haematological profile and coagulation

A pro-inflammatory haematological shift characterized ACS-CS with elevated neutrophils (79.30% [71.50–85.75] vs 71.15% [66.62–76.53]; $p < 0.001$) and markedly reduced lymphocytes (10.55% [6.60–18.10] vs 19.40% [12.68–22.98]; $p < 0.001$) with a corresponding reduction in absolute lymphocyte count (1.00 [0.67–1.69] vs 1.82 [1.33–2.13] $\times 10^9$ /L; $p < 0.001$), yielding a heightened neutrophil-to-lymphocyte ratio. Eosinophils (0.65% [0.20–1.50] vs 1.10% [0.70–1.80]; $p = 0.015$) and basophils (0.30% [0.18–0.50] vs 0.40% [0.30–0.50]; $p = 0.013$) were also lower whereas total leucocyte count ($p = 0.079$), absolute neutrophil count ($p = 0.867$), monocytes ($p = 0.556$) and platelets ($p = 0.548$) did not differ significantly. Haemoglobin was lower (11.85 [10.17–13.33] vs 12.75 [11.40–13.67] g/dL; $p = 0.008$). Coagulation was significantly deranged, with prolonged PT (13.75 [11.88–18.62] vs 11.55 [10.90–12.97] s; $p < 0.001$), higher INR (1.18 [1–1.55] vs 1 [0.93–1.10]; $p < 0.001$), lower PTI (87.5 [68.12–100] vs 99.5 [90.25–100]%; $p < 0.001$) and prolonged aPTT (29.86 [28–35.95] vs 28.60 [26.55–31.60] s; $p = 0.016$) (Table 1).

3.7 Metabolic, endocrine and lipid parameters

HbA1c (7.50 [5.90–8.53] vs 6.10 [5.70–7.20]%; $p < 0.001$), uric acid (8.55 [6.20–11.88] vs 7.00 [6.22–7.86] mg/dL; $p = 0.003$) and serum iron (91.50 [60.30–118.00] vs 74.24 [60.83–85.75] μ g/dL; $p = 0.022$) were higher in ACS-CS, while PTH was lower (45.00 [28.80–52.42] vs 62.00 [46.50–69.55] pg/mL; $p < 0.001$). Total cholesterol (148.5 [119.75–184.50] vs 174.0 [157.25–189.75] mg/dL; $p < 0.001$), LDL (75.55 [60.90–100.84] vs 100.25 [82.81–116.50] mg/dL; $p < 0.001$), HDL cholesterol (38.05 [27.90–48.28] vs 41.35 [37.10–46.00] mg/dL; $p = 0.027$) and T3 (0.93 [0.68–1.30] vs 1.14 [0.92–1.27] ng/mL; $p = 0.012$) were lower in ACS-CS. Vitamin D3, vitamin B12, TSH, T4, triglycerides, VLDL and magnesium did not differ significantly (Table 1).

3.8 Cytokine profiling: differential expression ACS-CS vs ACS-noCS

After $\log_2$ transformation and FDR correction, 11 out of 13 analytes met both pre-specified criteria ($\text{FDR} < 0.05$ and $\log_2\text{FC} > 0.5$) and were significantly upregulated in ACS-CS. IL-12p70 showed borderline statistical significance ($\text{FDR} = 0.047$) but did not meet the fold-change threshold ($\log_2\text{FC} = 0.42$) and is therefore regarded as marginal rather than as a positive finding. IL-9 met neither criterion ($p = 0.245$; $\text{FDR} = 0.245$).

The largest effect sizes were observed for IL-6 ($\log_2\text{FC} = 2.62$; $\text{FDR} = 2.47 \times 10^{-13}$), IL-4 ($\log_2\text{FC} = 2.70$), IL-1 β ($\log_2\text{FC} = 2.23$) and GM-CSF ($\log_2\text{FC} = 2.08$). Substantial upregulation was also seen for IL-10 ($\log_2\text{FC} = 1.82$), M-CSF ($\log_2\text{FC} = 1.75$), TNF- α ($\log_2\text{FC} = 1.65$), IL-8 ($\log_2\text{FC} = 1.33$), IL-18 ($\log_2\text{FC} = 1.30$), IFN- γ ($\log_2\text{FC} = 1.19$) and MCP-1 ($\log_2\text{FC} = 0.77$) (Table 2, Figures 1 and 2, Supplementary Figure A, B).

3.9 Inter-cytokine correlation and Protein-Protein Interaction (PPI) network analysis

Pearson correlation analysis showed a well-defined inter-cytokine correlation pattern. Strong positive correlations were evident among IL-6, TNF- α and IL-1 β ($r = 0.50 - 0.63$) suggesting shared transcriptional regulation via NF- κ B/MAPK pathways. GM-CSF exhibited moderate positive correlations ($r = 0.33-0.53$) with several analytes in line with its role in myeloid cell amplification. In contrast, IL-9 and IL-10 demonstrated weak correlations with other cytokines ($r < 0.30$) indicating relatively independent regulatory behavior (Supplementary Figure C).

The STRING-based protein-protein interaction (PPI) network of the 13 panel proteins (confidence ≥ 0.70) comprised 14 nodes as IL-12p70 is represented by its two subunits, IL-12A and IL-12B. The remaining 12 proteins were densely interconnected while IL-12B was linked to IFN-gamma, TNF- α and IL-10 and IL12A to only IL12B (Supplementary Figure D). The PPI enrichment p-value ($< 1.0 \times 10^{-16}$) indicates a coordinated and biologically coherent inflammatory network. KEGG annotation of this protein network highlighted cytokine-cytokine receptor interaction, NF- κ B signaling, interleukin signaling and TNF signaling as the most significantly over-represented pathways; this network-level annotation is distinct from, and complementary to, the transcriptome-level enrichment performed on the six GEO datasets during panel selection (Supplementary Table 2) (Supplementary Figure D).

3.10 Individual cytokine ROC analysis for CS identification

IL-6 achieved the highest individual AUC (0.870; sensitivity 85.0%, specificity 78.9% at 68.22 pg/mL). IL-10 (AUC 0.847; sensitivity 86.7%) and M-CSF (AUC 0.847; sensitivity 88.3%) performed comparably, followed by TNF- α (AUC 0.841; sensitivity 90.0% at 116.78 pg/mL) and IL-1 β (AUC 0.822). The five leading analytes therefore fell within an AUC range of 0.822-0.870 (Figure 3, cut-offs in Supplementary Table 1, AUC for all 13 cytokines in Supplementary Table 3). All cut-offs are specific to serum measured by the assay described in Methods and are not transferable to plasma or other platforms without re-derivation.

3.11 Multi-cytokine random forest classification

A random forest model incorporating all 13 cytokines achieved a cross-validated accuracy of 86.7% and an internally cross-validated AUC of 0.958 (bootstrap 95% CI 0.92-0.98). The confusion matrix showed correct classification of 80/90 (88.9%) ACS-noCS cases and 50/60 (83.3%) ACS-CS cases. Variable importance ranked IL-6 highest (0.143), followed by TNF- α (0.108), IL-4 (0.108), M-CSF (0.107) and IL-10 (0.097) (Supplementary Figure E).

This estimate exceeds that of the best single analyte (IL-6, AUC 0.870), but both estimates derive from the same 150-patient cohort. Because the model was developed and evaluated on one dataset using internal cross-validation only, the reported performance is likely to be optimistic and should be regarded as exploratory; external validation is required before any clinical application can be considered.

3.12 Multivariable logistic regression: Independent predictors of CS

The multivariable model included age, sex and the five cytokines with the highest individual AUCs namely IL-6 (AUC 0.870), M-CSF (0.847), IL-10 (0.847), TNF- α (0.841) and IL-1 β (0.822); the next-ranked analyte, GM-CSF, had an AUC of 0.815. All cytokine concentrations were log₂-transformed prior to entry and no stepwise or automated selection was applied. Three cytokines remained independently associated with CS after adjustment. TNF- α showed the highest adjusted odds ratio (OR 2.63, 95% CI 1.33-5.20; $p = 0.005$) followed by IL-10 (OR 2.01, 95% CI 1.13-3.56; $p = 0.017$) and IL-6 (OR 1.81, 95% CI 1.18-2.77; $p = 0.006$). M-CSF and IL-1 β did not retain significance. Male sex was associated with lower odds of CS (OR 0.069, 95% CI 0.014-0.34; $p = 0.001$), and age was not significantly associated with CS.

The model contained 60 events and 7 predictors (events-per-variable = 8.6). Formal assessment showed no evidence of complete or quasi-separation. Because the events-per-variable ratio was below the conventional threshold of 10 and the log₂-transformed cytokines were moderately correlated, a Firth penalized sensitivity analysis was performed. The Firth model yielded qualitatively consistent results (IL-6 OR 1.72, 95% CI 1.12-2.65; IL-10 OR 1.89, 95% CI 1.08-3.31; TNF- α OR 2.41, 95% CI 1.24-4.68), with attenuation of the male-sex estimate (OR 0.096, 95% CI 0.024-0.383). The apparent AUC was 0.951 (bootstrap 95% CI 0.919-0.984) and the 5-fold cross-validated AUC was 0.932. The Hosmer-Lemeshow test gave no evidence of poor fit ($\chi^2 = 13.47$, $df = 8$; $p = 0.097$), but the cross-validated calibration slope of 0.770 (intercept -0.019) indicates some overfitting, consistent with the EPV ratio; predicted probabilities would require recalibration before use in an independent cohort. These performance estimates are internal and should be interpreted as exploratory (Table 3).

3.13 Mortality burden and biomarker performance for in-hospital death

In-hospital mortality was substantially higher in ACS-CS patients than in ACS-noCS (35% vs 6.7%), confirming cardiogenic shock as the dominant adverse prognostic determinant in this setting and underscoring the critical need for robust early risk stratification in this population.

ROC analysis was performed to evaluate the individual discriminatory performance of conventional biomarkers and cytokines for predicting in-hospital mortality. Among conventional serum markers, ALT demonstrated the highest individual discrimination (AUC = 0.801), followed by ALP (AUC = 0.755), ejection fraction (AUC = 0.745), BNP (AUC = 0.742), CK-MB (AUC = 0.740) and CRP (AUC =

0.724). Although these markers individually achieved acceptable-to-moderate discrimination, their performance ceiling in the 0.72–0.80 range highlights inherent limitations when applied in isolation. Among cytokines evaluated individually, IL-8 yielded the highest discriminatory ability (AUC = 0.756) followed by IL-10 (AUC = 0.711), TNF- α (AUC = 0.663), IL-4 (AUC = 0.589) and IL-12p70 (AUC = 0.529) collectively reflecting modest individual predictive utility. Notably, while no single cytokine surpassed the best-performing conventional marker, the cytokine panel as a whole encoded complementary prognostic information, motivating construction of a combined multivariable model (Figure 4).

To formally quantify the incremental prognostic value of cytokine profiling over conventional clinical assessment, two multivariable predictive models were constructed and compared using cross-validated predicted probabilities from identical folds. The clinical-parameters model incorporating conventional serum markers and LVEF achieved moderate discriminatory performance with AUC of 0.731 (95% CI 0.627–0.835). The combined clinical-plus-cytokine model, which integrated inflammatory mediators including IL-8, IL-10, MCP-1, IL-12p70 and IL-4 alongside clinical variables, achieved an AUC of 0.737 (95% CI 0.634–0.841). The difference of 0.007 AUC units was not statistically significant (95% CI –0.037 to 0.050, $p = 0.766$). These analyses were based on 27 in-hospital deaths (EPV 4.5 for the clinical model and 2.5 for the combined model) and are therefore underpowered for formal model comparison; they are presented as exploratory (Figure 5).

4. Discussion

This observational study provides comprehensive description of cardiogenic shock complicating ACS as a dual crisis of haemodynamic failure and systemic immunological activation. The principal findings are: a distinctive clinical phenotype with female sex predominance and a higher prevalence of diabetes; a profound multi-organ dysfunction, extending well beyond the heart; significant upregulation of eleven of the thirteen analytes evaluated, with IL-4, IL-6, IL-1 β and GM-CSF showing the largest effect sizes; the independent association of IL-6, TNF- α and IL-10 with CS after adjustment; and high internal discrimination of a multi-cytokine ensemble model. We emphasize at the outset that the discrimination estimates are internal and exploratory, and that the study is designed to generate rather than to confirm hypotheses.

Clinical phenotype of ACS with cardiogenic shock

The over-representation of female patients in ACS-CS (46.7% vs 22.2%; $p = 0.002$) is consistent with prior reports highlighting sex-based differences in CS pathophysiology [18,19]. Female patients with ACS tend to have smaller coronary vessels, more diffuse atherosclerosis, a higher prevalence of microvascular dysfunction and sex-specific differences in inflammatory immune activation, collectively predisposing to more extensive myocardial dysfunction following acute ischaemia [20]. Male sex was associated with lower odds of CS in both the primary and Firth-penalized models. While the direction of this association is consistent with the unadjusted sex distribution and with prior literature, the magnitude of the point estimate should be interpreted with caution given the borderline events-per-variable ratio (8.6) and the wide confidence interval; the attenuation from OR 0.069 to 0.096 under penalization illustrates this instability directly.

Diabetes mellitus was more prevalent in ACS-CS [21]. Chronic hyperglycaemia impairs myocardial energy metabolism through mitochondrial dysfunction, suppresses ischaemic pre-conditioning, promotes endothelial dysfunction and chronically elevates baseline IL-6 and TNF- α production [22,23]. These mechanisms collectively reduce myocardial capacity to withstand and recover from acute ischaemic injury, amplifying vulnerability to haemodynamic decompensation. Smoking was significantly less frequent in the ACS-CS group. This inverse association most likely reflects the more predominantly female composition of the shock group in this cohort rather than a protective effect, and is consistent with the well-described “smoker’s paradox” reported in observational ACS series; it should not be interpreted causally. Hypertension and alcohol use did not differ significantly between groups. Taken together, the pattern of conventional risk factors does not explain the transition to shock, which appears to be determined principally by infarct extent, myocardial reserve and the magnitude of the inflammatory response.

Hepatic and multi-organ involvement

The marked hepatic biochemical abnormalities observed in ACS-CS warrant consideration of both reduced hepatic perfusion and venous congestion. The substantial elevations of ALT, AST and LDH are compatible with hypoperfusion-related hepatocellular injury whereas the concomitant elevation of ALP suggests that the hepatic disturbance may not represent isolated ischaemic hepatitis. In cardiogenic shock, reduced forward flow can coexist with elevated systemic venous pressure allowing hypoperfusion and hepatic congestion to occur simultaneously, so, a mixed hepatocellular-congestive/cholestatic pattern is plausible in our cohort. However, gamma-glutamyl transferase (GGT), ALP isoenzyme analysis and systematic hepatobiliary imaging were not performed, and the specific contribution of cholestasis or congestion to the observed ALP elevation therefore cannot be established. We interpret the liver abnormalities primarily as evidence of hepatic involvement in the setting of ACS-CS rather than assigning the ALP elevation to a specific aetiology.

The elevations in CRP, procalcitonin and ferritin observed in ACS-CS are consistent with the sterile systemic inflammatory response that characterizes severe cardiogenic shock. Because patients with clinically overt infection or sepsis at presentation were excluded at enrolment (see Methods), and because sampling was performed within 24 hours of admission and before definitive therapy, these findings are unlikely to be driven by concurrent infection, although subclinical infection cannot be formally excluded in the absence of systematic microbiological surveillance in every patient.

The cytokine architecture of cardiogenic shock

The upregulation of 11 of 13 cytokines meeting both pre-specified criteria, with substantial effect sizes in ACS-CS, is the core observation of this study. This broad-spectrum activation reflects concurrent engagement of multiple immunological arms: innate myeloid activation (IL-1 β , TNF- α , IL-6, IL-8, MCP-1), myeloid growth factor signalling (GM-CSF, M-CSF), adaptive T-cell responses (IL-4, IFN- γ), immune counter-regulation (IL-10) and NLRP3 inflammasome activation (IL-18).

IL-6, the strongest individual discriminator (AUC 0.870; adjusted OR 1.81), is the central coordinator of acute-phase inflammatory responses. It activates JAK/STAT3 signalling in cardiomyocytes, drives CRP synthesis, promotes neutrophil and macrophage activation and contributes to endothelial dysfunction and vasoplegia [24,25]. Analyses from the CANTOS programme demonstrated that

modulation of the IL-6 signaling pathway is associated with reduced cardiovascular events [26] and IL-6 receptor blockade with tocilizumab increased myocardial salvage in ST-elevation myocardial infarction in the randomised ASSAIL-MI trial [27], providing translational context for this finding.

TNF- α carried the highest adjusted odds ratio (2.63; $p = 0.005$). It exerts direct negative inotropic effects through ceramide- and nitric oxide-dependent pathways, induces cardiomyocyte apoptosis and contributes to systemic vasoplegia [28]. Its independent significance beyond IL-6 suggests a mechanistically distinct pathogenic contribution. The apparently paradoxical independent association of IL-10 with CS (OR 2.01) is best understood as a counter-regulatory response to an overwhelming pro-inflammatory surge, analogous to the compensatory anti-inflammatory response described in septic shock [29]. Markedly elevated IL-10 in ACS-CS may simultaneously impair protective immune responses, consistent with reports of high IL-10 as an adverse prognostic marker in ACS and heart failure [30].

Significant upregulation of GM-CSF ($\log_2FC$ 2.08) and M-CSF ($\log_2FC$ 1.75) highlights the role of myeloid compartment activation. GM-CSF promotes granulocyte and macrophage proliferation and effector function, amplifying innate inflammation at the infarct site [31]. M-CSF, which regulates macrophage polarization and supports their survival, emerged as the joint second-highest individual discriminator (AUC = 0.847) suggesting that monocyte/macrophage-related processes represent a discriminating axis in CS. Elevated IL-4 ($\log_2FC$ 2.70), although primarily a Th2- and B-cell-associated cytokine, likely reflects adaptive immune engagement in the context of tissue damage, with potential influence on M2 macrophage polarisation and on the balance between inflammatory activation and resolution.

The strong inter-cytokine correlation network (IL-6-TNF- α -IL-1 β , $r=0.50-0.63$) and the highly interconnected STRING-based PPI network support the interpretation that the cytokine response in ACS-CS is a coordinated, mutually reinforcing inflammatory programme rather than isolated upregulation of individual mediators. The observed cytokine profile is consistent with activation of key inflammatory pathways such as NF- κ B, TNF- α and interleukin signalling. These pathways provide a plausible mechanistic basis for targeted anti-inflammatory approaches including anakinra (IL-1 blockade), tocilizumab (IL-6 receptor blockade) and infliximab (TNF- α inhibition), which have been explored in cardiovascular disease and in shock states [32,33]. Our data identify candidate targets; they do not test any therapeutic intervention.

Discriminatory performance and its limits

The random-forest model achieved an internally cross-validated AUC of 0.958 (95% CI 0.92-0.98) and accuracy of 86.7% from a single admission cytokine sample. This indicates that the admission inflammatory profile contains substantial information about the presence of shock. However, model development and evaluation were performed on the same cohort, and internal cross-validation does not remove optimism arising from a 13-feature model in 150 patients. The logistic model showed the same pattern: an apparent AUC of 0.951 fell to 0.932 on cross-validation, and the cross-validated calibration slope of 0.770 provides direct quantitative evidence of overfitting. We therefore make no claim of clinical readiness. External multi-centre validation with recalibration is required before any statement about clinical utility would be justified. For in-hospital mortality, adding cytokines to a clinical model increased the AUC by 0.007, a difference that was not statistically significant. With only 27 deaths, the analysis is underpowered to detect modest incremental discrimination. These findings are consistent with a possible contribution of

inflammatory pathways to mortality risk but do not establish an incremental prognostic role for cytokine profiling beyond conventional clinical assessment.

It is also relevant that all cytokine measurements were obtained from admission samples taken before definitive management, mechanical circulatory support or renal replacement therapy. This supports the practical feasibility of prospective evaluation of admission cytokine profiling for early risk stratification, which we regard as the appropriate next step.

Limitations

Several limitations should be considered when interpreting these findings.

First, the proportion of patients with cardiogenic shock in this cohort (40.0%) is much higher than the 5-10% frequency reported in broader hospitalized ACS populations. This reflects the deliberate two-group comparator sampling design at a tertiary referral center and is not an estimate of population prevalence or incidence. Because patients with CS were recruited alongside a comparison group rather than consecutively, the cohort does not represent an unselected ACS population; the generalizability of the observed associations and, in particular, the calibration of the models may therefore be limited.

Second, the discrimination models (random-forest AUC 0.958 and logistic AUC 0.951) were developed and evaluated on the same 150-patient cohort using internal five-fold cross-validation. Nested cross-validation or a true held-out test set was not feasible at this sample size. The 13-analyte panel itself was fixed a priori from external GEO data and was not derived from this cohort, which mitigates but does not eliminate optimism. Importantly, the five cytokines entered into the multivariable logistic model were chosen on the basis of their individual AUCs computed on the full dataset rather than within cross-validation folds; the cross-validated AUC and calibration statistics for that model are therefore themselves partially optimistic. All reported discrimination metrics must be regarded as exploratory.

Third, the multivariable logistic model had an EPV ratio of 8.6, below the conventional threshold of 10. Although no separation was detected and a Firth penalized sensitivity analysis gave consistent results, individual coefficient magnitudes, most notably that for male sex, should be regarded as imprecise.

Fourth, mortality analyses were based on 27 in-hospital deaths, which is insufficient for reliable multivariable modelling or for detecting modest differences in discrimination and these models are exploratory.

Fifth, cytokines were measured at a single time point, which precludes assessment of serial dynamics, response to therapy or the temporal relationship between inflammatory activation and haemodynamic deterioration. Cytokine concentrations and the derived cut-offs are specific to serum measured on the platform described and would require re-derivation for plasma or for other assay systems.

Sixth, serum lactate and formal SCAI shock-stage classification were not available in the dataset and could not be incorporated into the models; severity within the shock group could therefore not be

graded. Subclinical infection, while mitigated by the exclusion of patients with overt infection or sepsis, cannot be formally excluded.

Finally, this was a single-center study in a North Indian population; generalizability to other ethnic populations and healthcare settings requires assessment.

Despite these limitations, the comprehensive multi-domain phenotyping, the *a priori* bioinformatics-guided panel, FDR-corrected inference, pre-planned penalized sensitivity analysis and full code availability provide an internally coherent and reproducible description of a distinct immunological phenotype in ACS-CS.

5. Conclusion

This study indicates that cardiogenic shock complicating ACS is a multi-dimensional clinical crisis characterized by severe haemodynamic collapse, widespread multi-organ dysfunction, deranged coagulation, and a broad, coordinated systemic inflammatory cytokine response. Eleven of thirteen serum cytokines met both pre-specified significance criteria and were upregulated in ACS-CS, with IL-4, IL-6, IL-1 β and GM-CSF demonstrating the largest effect sizes. IL-6 was the strongest individual cytokine discriminator, and TNF- α , IL-10 and IL-6 were independently associated with CS in multivariable analysis. A multi-cytokine random-forest model showed high discrimination within this cohort, although this estimate is internal and requires external confirmation. These findings characterize ACS-CS as an immuno-inflammatory as well as a haemodynamic state and identify candidate cytokine targets for further investigation. Prospective, externally validated multi-center studies, and subsequently trials of targeted anti-inflammatory therapies in ACS-CS, are warranted.

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- **Ankur Mittal:** Data collection and analysis, patient recruitment, clinical data collection, drafting the manuscript, statistical analysis, critical revision, writing original draft, final approval.
- **Kraticka Singhal:** Substantial contribution to data acquisition, laboratory analysis, statistical analysis, drafting sections of the manuscript.
- **Monika Sharma:** Statistical analysis and interpretation of results, critical revision of the manuscript, final approval.
- **Akash Batta:** Interpretation of inflammatory/thrombotic markers, critical revision of the manuscript, final approval, Echocardiographic evaluation.
- **Yash Paul Sharma:** Conception and design of the study, critical revision of the manuscript for intellectual content, contribution to study design and interpretation of results, final approval, overall supervision.

The manuscript has been read and approved for submission by all authors.

Data availability: The complete annotated R analysis script that reproduces every reported result from the source data is provided as a Supplementary File (Analysis Code). Per-analyte summary statistics including AUCs for all thirteen cytokines are provided in Supplementary Table 3. The de-identified patient-level dataset containing all cytokine and clinical variables is available from the corresponding author on reasonable request.

Declaration of conflict of interest: The authors declare no conflict of interest.

AI / LLM Use Declaration: The complete annotated R analysis script that reproduces every reported result from the source data is provided as a Supplementary File (Analysis Code). Per-analyte summary statistics for all thirteen cytokines are provided in Supplementary Table 3. Claude was used for coding assistance only in generating figures 2-5 in R and all code and outputs were checked and verified by the authors. The de-identified patient-level dataset containing all cytokine and clinical variables is available from the corresponding author on reasonable request.

Ethical approval: All procedures contributing to this work were approved by the Institutional Ethics Committee (IEC-INT/2023/PhD-899) and comply with the ethical standards on human experimentation and with the Helsinki Declaration of 1975 as revised in 2013. Informed consent was obtained from all participants or their legally authorized representatives before enrollment.

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Figures and tables

Figure 1. Distribution of serum cytokine expression levels in ACS patients with and without cardiogenic shock. Box plots showing $\log_2$ -transformed serum cytokine levels in ACS patients with cardiogenic shock (ACS-CS) vs without (ACS-noCS). Boxes indicate IQR with median lines and whiskers represent $1.5 \times$ IQR. Cytokine levels were generally higher in ACS-CS reflecting enhanced systemic inflammation. Statistical significance was assessed using the Wilcoxon rank-sum test with Benjamini–Hochberg FDR correction.

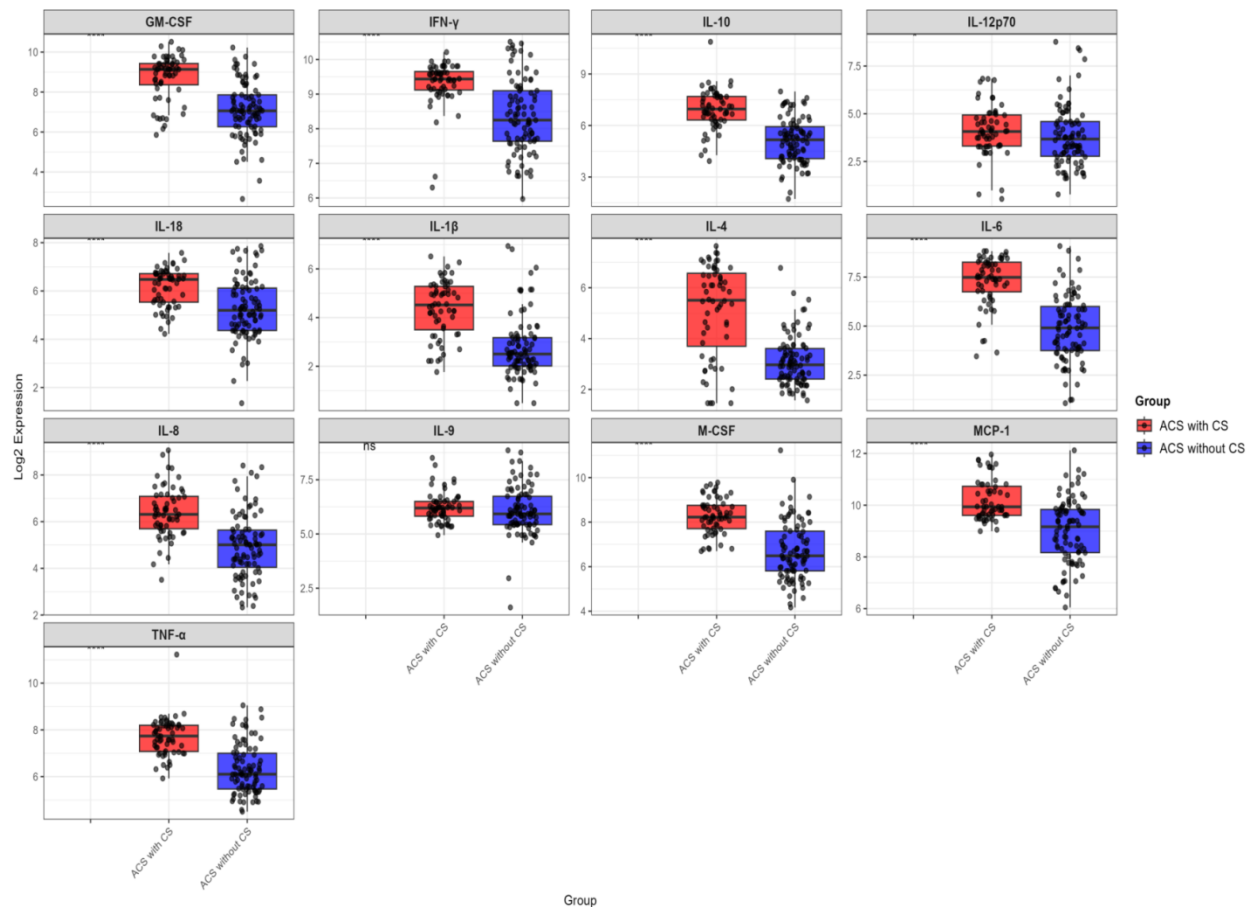


Figure 2. Significantly elevated key cytokines (IL-6, IL-1 β , TNF- α , GM-CSF and IL-10) in ACS patients with versus without cardiogenic shock. Box plots of log₂-transformed serum concentrations (pg/mL) with individual patient values overlaid, of IL-6, IL-1 β , TNF- α , GM-CSF and IL-10 in ACS patients with cardiogenic shock (ACS-CS) versus without (ACS-noCS). Boxes represent IQR with median lines and whiskers indicate 1.5 $\times$ IQR. All five cytokines were significantly elevated in ACS-CS indicating enhanced inflammatory and counter-regulatory responses; FDR values are shown above each panel. Statistical analysis was performed using the Wilcoxon rank-sum test with Benjamini–Hochberg FDR correction (FDR < 0.05; log₂FC > 0.5).

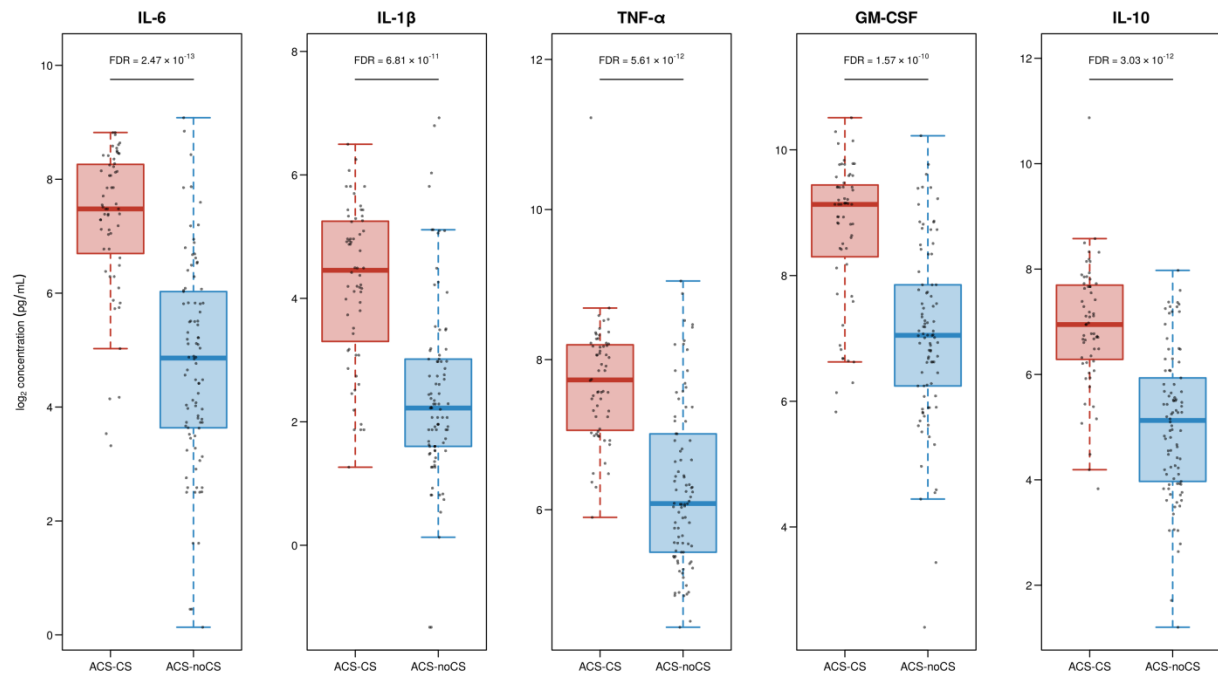


Figure 3. Receiver operating characteristic (ROC) curves for individual cytokine discrimination of cardiogenic shock in ACS patients. IL-6 showed the highest AUC (0.870; sensitivity 85.0%, specificity 78.9% at 68.22 pg/mL) followed by IL-10 (AUC 0.847; sensitivity 86.7%, specificity 74.4% at 60.63 pg/mL), M-CSF (AUC 0.847; sensitivity 88.3%, specificity 73.3% at 169.91 pg/mL), TNF- α (AUC 0.841; sensitivity 90.0%, specificity 72.2% at 116.78 pg/mL) and IL-1 β (AUC 0.822; sensitivity 81.7%, specificity 76.7% at 8.45 pg/mL). All showed good discriminatory performance (AUC 0.822–0.870). Empirical ROC curves were computed from patient-level data (pROC), filled circles mark the Youden-index cut-off on each curve and the dashed line indicates no discrimination (AUC = 0.50).

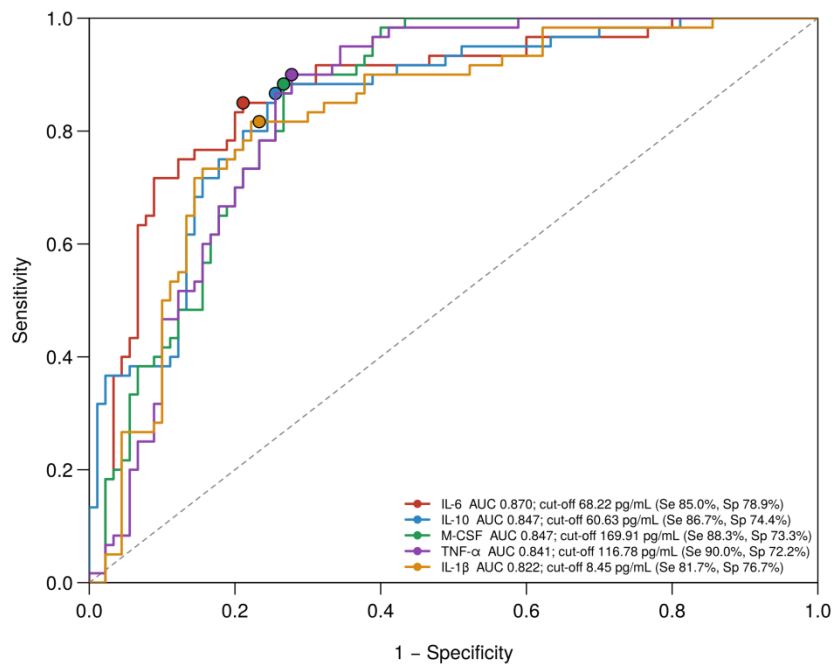


Figure 4. In-hospital mortality in ACS with cardiogenic shock, and individual discriminatory performance of conventional biomarkers and cytokines for mortality prediction. (A) In-hospital mortality was significantly higher in ACS-CS compared to ACS-noCS (35.0% [21/60] vs 6.7% [6/90]; $p < 0.001$); (B) Empirical ROC curves for mortality prediction in the whole cohort (27 deaths) shown in separate panels for conventional markers and cytokines, showed highest discrimination with ALT (AUC 0.801) followed by ALP (0.755), ejection fraction (0.745), BNP (0.742), CK-MB (0.740) and CRP (0.724). Among cytokines, IL-8 had the highest AUC (0.756), followed by IL-10 (0.711), TNF- α (0.663), IL-4 (0.589) and IL-12p70 (0.529). No individual cytokine outperformed the best conventional marker. The dashed line indicates AUC = 0.50.

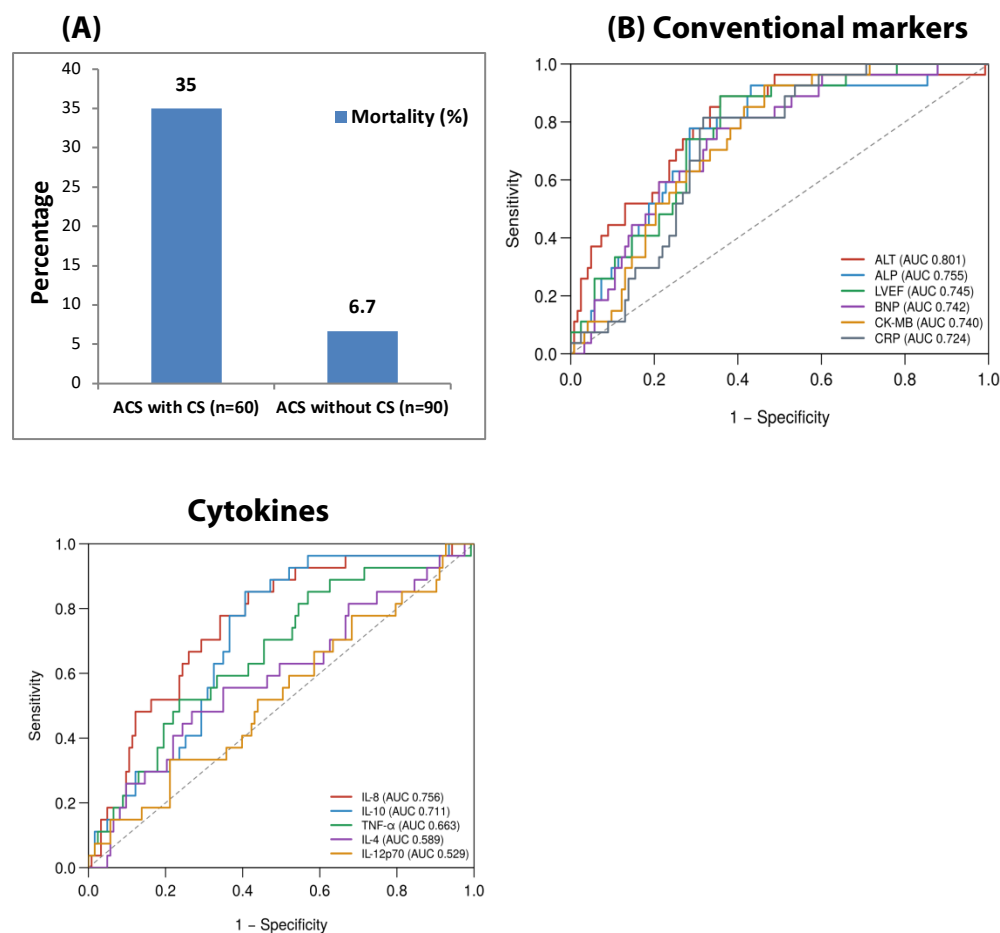


Figure 5 Comparison of ROC curves for the combined clinical–cytokine model versus the clinical-parameters model alone for prediction of in-hospital mortality. The combined clinical + cytokine model (IL-8, IL-10, MCP-1, IL-12p70, IL-4) achieved an AUC of 0.737 compared with 0.731 for the clinical-only model. The difference of 0.007 AUC units was not statistically significant (95% CI -0.037 to 0.050, $p = 0.766$). Both models were evaluated using cross-validated predicted probabilities from identical folds and were based on 27 in-hospital deaths. The dashed line indicates AUC = 0.50.

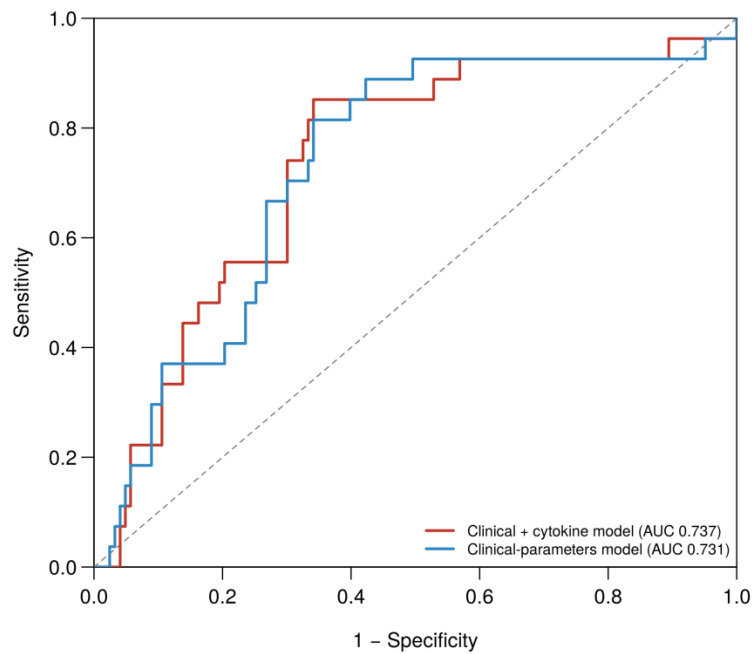


Table 1. Clinical profile of ACS patients with and without cardiogenic shock

Parameter / Symptom	ACS with CS (n = 60)	ACS without CS (n = 90)	p - value
A. Demographic characteristics			
Age (years, mean $\pm$ SD)	59.95 $\pm$ 11.69	59.17 $\pm$ 10.72	0.679
Male sex, n (%)	32 (53.3)	70 (77.8)	0.002*
Female sex, n (%)	28 (46.7)	20 (22.2)	—
B. Clinical symptoms			
Chest pain, n (%)	54 (90)	44 (48.9)	<0.001*
Syncope, n (%)	53 (88.3)	20 (22.2)	<0.001*
Shortness of breath, n (%)	51 (85)	41 (45.6)	<0.001*
Palpitations, n (%)	38 (63.3)	33 (36.7)	0.001*
C. Comorbidities, risk factors and In-hospital mortality			
In-hospital mortality, n (%)	21 (35)	6 (6.7)	<0.001*
Diabetes mellitus, n (%)	41 (68.3)	34 (37.8)	<0.001*
Hypertension, n (%)	38 (63.3)	50 (55.6)	0.343
Smoking, n (%)	15 (25)	40 (44.4)	0.016*
Alcohol use, n (%)	11 (18.3)	21 (23.3)	0.464
D. Haemodynamic parameters (Median [IQR])			
Systolic BP (mmHg)	85 [80 – 90]	127 [112 – 140]	<0.001*
Diastolic BP (mmHg)	60 [56 – 62]	80 [70 – 90]	<0.001*
Pulse rate (bpm)	104 [98 – 112.5]	84.5 [78 – 93.75]	<0.001*
Shock index	1.23 [1.15 – 1.36]	0.66 [0.57 – 0.81]	<0.001*
Respiratory rate (/min)	22 [20 – 22]	20 [18 – 20]	<0.001*
E. Cardiac biomarkers and LV function (Median [IQR])			
Ejection fraction (%)	27.5 [23 – 32]	44.5 [37 – 52]	<0.001*
CK-MB (U/L)	54.55 [46.88 – 61]	6.25 [2.10 – 23.13]	<0.001*
Troponin I (ng/mL)	8.96 [1.33–18.49]	1.02 [0.04–7.67]	<0.001*
Myoglobin (ng/mL)	349.5 [214.75–510]	283 [119.25–506]	0.364
BNP (pg/mL)	1009 [348.75 – 1680.5]	237.5 [65.28 – 481.5]	<0.001*
D-dimer (ng/mL)	1050 [487.75 – 2195.75]	432.5 [163.25 – 878.75]	<0.001*
LDH (U/L)	964 [810.25 – 1282.25]	190.21 [145.45 – 278.02]	<0.001*
F. Hepatic, renal, inflammatory and electrolyte parameters (Median [IQR])			
ALT (U/L)	418 [345.75 – 509.5]	45 [29.58 – 63.5]	<0.001*
AST (U/L)	434.5 [347.25 – 542.25]	61 [45.3 – 121.75]	<0.001*
ALP (U/L)	414.5 [299.5 – 540]	91.5 [76.5 – 106.5]	<0.001*
Albumin (g/dL)	3.19 [2.91 – 3.53]	3.6 [3.2 – 3.91]	<0.001*
Total Protein (g/dL)	6.16 [5.56 – 6.85]	6.70 [6.10 – 7.19]	0.002*
Urea (mg/dL)	65.8 [39.38 – 95.5]	36.5 [28.78– 47.53]	<0.001*
Creatinine (mg/dL)	1.05 [0.92 – 1.18]	0.98 [0.86 – 1.10]	0.008*

CRP (mg/L)	153.86 [132.10 – 195.75]	9.36 [3.13 – 23.38]	<0.001*
Procalcitonin (ng/mL)	0.76 [0.67 – 0.84]	0.50 [0.40 – 0.83]	<0.001*
Ferritin (ng/mL)	488.5 [225.4–1159]	271 [206.6–311.9]	<0.001*
Sodium (mEq/L)	135.5 [132.0 – 140.25]	139 [137 – 143]	<0.001*
Potassium (mEq/L) (mean ± SD)	4.52 ± 0.93	4.20 ± 0.61	0.022*
Chloride (mEq/L)	99.15 [95–103]	103 [100.4–104]	<0.001*
Calcium (mg/dL) (mean ± SD)	8.80 ± 0.85	9.07 ± 0.74	0.047*
G. Haematological profile and coagulation (Median [IQR])			
Neutrophils (%)	79.30 [71.50–85.75]	71.15 [66.62–76.53]	<0.001*
Lymphocytes (%)	10.55 [6.60–18.10]	19.40 [12.68–22.98]	<0.001*
Monocytes (%)	7.35 [5.30–9.80]	7.50 [6.80–8.67]	0.556
Eosinophils (%)	0.65 [0.20–1.5]	1.10 [0.70–1.80]	0.015*
Basophils (%)	0.30 [0.18–0.50]	0.40 [0.30–0.50]	0.013*
ANC (×10 ⁹ /L)	7.50 [5.42–9.17]	7.01 [5.82–9.56]	0.867
ALC (×10 ⁹ /L)	1 [0.67–1.69]	1.82 [1.33–2.13]	<0.001*
TLC (×10 ⁹ /L)	9.50 [7.97–11.05]	9.85 [8.80–12.39]	0.079
Haemoglobin (g/dL)	11.85 [10.17–13.33]	12.75 [11.40–13.67]	0.008*
Platelets (×10 ⁹ /L)	193 [150.50–247.50]	186.5 [144.25– 237.25]	0.548
PT (s)	13.75 [11.88–18.62]	11.55 [10.90–12.97]	<0.001*
INR	1.18 [1.00–1.55]	1 [0.93–1.10]	<0.001*
PTI (%)	87.5 [68.12–100]	99.5 [90.25–100]	<0.001*
aPTT (s)	29.86 [28–35.95]	28.60 [26.55–31.60]	0.016*
H. Metabolic, endocrine and lipid parameters (Median [IQR])			
HbA1c (%)	7.50 [5.90–8.53]	6.10 [5.70–7.20]	<0.001*
Uric acid (mg/dL)	8.55 [6.20–11.88]	7 [6.22–7.86]	0.003*
Serum iron (µg/dL)	91.50 [60.30–118]	74.24 [60.83–85.75]	0.022*
PTH (pg/mL)	45 [28.80–52.42]	62 [46.50–69.55]	<0.001*
Vitamin D3 (ng/mL)	24 [15–37.24]	22.50 [16.72–27]	0.341
Vitamin B12 (pg/mL)	560 [450–806.75]	480 [418.81–828.82]	0.582
TSH (µIU/mL)	2.73 [1.50–3.77]	2.55 [1.48–3.10]	0.287
T3 (ng/mL)	0.93 [0.68–1.30]	1.14 [0.92–1.27]	0.012*
T4 (µg/dL)	7.84 [6.21–9.22]	7.90 [6.86–8.40]	0.980
Total cholesterol (mg/dL)	148.5 [119.75– 184.50]	174.0 [157.25– 189.75]	<0.001*
Triglycerides (mg/dL)	160.5 [105.25– 210.25]	150.5 [141.25– 161.75]	0.524
HDL (mg/dL)	38.05 [27.90–48.28]	41.35 [37.10–46]	0.027*
LDL (mg/dL)	75.55 [60.90–100.84]	100.25 [82.81– 116.50]	<0.001*
VLDL (mg/dL)	32.10 [21.05–42.05]	30.10 [28.25–32.35]	0.524
Magnesium (mg/dL)	2.02 [1.73–2.39]	2.11 [2–2.35]	0.110

All continuous variables were compared using the Mann–Whitney U (Wilcoxon rank-sum) test; variables shown as mean ± SD are presented in that format for description only and were tested by the same method. Categorical variables were compared using the Pearson chi-square test without continuity correction. p-

values below 0.001 are reported as < 0.001. ACS: acute coronary syndrome; CS: cardiogenic shock; SD: standard deviation; IQR: interquartile range; n: number; BP: blood pressure; bpm: beats per minute; LV: left ventricular; LVEF: left ventricular ejection fraction; CK-MB: creatine kinase-MB; BNP: B-type natriuretic peptide; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; CRP: C-reactive protein; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; TLC: total leucocyte count; NLR: neutrophil-to-lymphocyte ratio; PT: prothrombin time; INR: international normalized ratio; PTI: prothrombin time index; aPTT: activated partial thromboplastin time; HbA1c: glycated haemoglobin; PTH: parathyroid hormone; TSH: thyroid-stimulating hormone; T3: triiodothyronine; T4: thyroxine; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; VLDL: very-low-density lipoprotein cholesterol. Units: mmHg (millimetres of mercury); bpm (beats per minute); U/L (units per litre); ng/mL (nanograms per millilitre); pg/mL (picograms per millilitre); mg/L (milligrams per litre); mg/dL (milligrams per decilitre); g/dL (grams per decilitre); µg/dL (micrograms per decilitre); mEq/L (milliequivalents per litre); µIU/mL (micro-international units per millilitre); ×10⁹/L (cells per litre); s (seconds), *: statistically significant.

Table 2. Differential serum cytokine expression: ACS with CS versus ACS without CS.

Cytokine	ACS-CS (n = 60), median [IQR], pg/mL	ACS-noCS (n = 90), median [IQR], pg/mL	log ₂ median (CS)	log ₂ median (noCS)	log ₂ FC	p-value	FDR
GM-CSF	561.22 [329.08– 687.22]	132.44 [75.97– 231.19]	9.13	7.05	2.08	7.22×10^{-11}	1.57×10^{-10}
IFN- γ	691.31 [554.79– 802.79]	303.30 [198.45– 546.31]	9.43	8.24	1.19	6.18×10^{-9}	8.92×10^{-9}
IL-1 β	21.93 [10.33– 37.93]	4.67 [3.04–8.04]	4.45	2.22	2.23	2.62×10^{-11}	6.81×10^{-11}
IL-4	44.51 [12.12– 94.08]	6.83 [4.31–11.20]	5.48	2.77	2.70	3.82×10^{-10}	6.22×10^{-10}
IL-6	178.39 [106.60– 305.35]	29.05 [12.50–63.15]	7.48	4.86	2.62	1.90×10^{-14}	2.47×10^{-13}
IL-8	78.47 [50.90– 134.63]	31.18 [15.51–48.82]	6.29	4.96	1.33	1.82×10^{-10}	3.38×10^{-10}
IL-9	72.31 [55.55– 89.45]	59.77 [42.20– 105.66]	6.18	5.90	0.27	0.245	0.245 (NS)
IL-10	123.38 [78.92– 205.35]	34.95 [15.81–59.92]	6.95	5.13	1.82	6.07×10^{-13}	3.03×10^{-12}
IL-12p70	15.78 [8.90–29.61]	11.77 [5.84–23.11]	3.98	3.56	0.42	0.044	0.047 (M)
IL-18	88.12 [45.45– 104.21]	35.75 [19.59–68.55]	6.46	5.16	1.30	1.24×10^{-6}	1.47×10^{-6}
MCP-1	978.43 [777.95– 1697.06]	573.43 [286.34– 912.39]	9.93	9.16	0.77	1.75×10^{-8}	2.27×10^{-8}
M-CSF	298.55 [208.27– 431.26]	88.75 [55.09– 192.31]	8.22	6.47	1.75	6.98×10^{-13}	3.03×10^{-12}
TNF- α	212.23 [134.06– 292.41]	67.75 [43.35– 127.04]	7.73	6.08	1.65	1.73×10^{-12}	5.61×10^{-12}

Concentrations are group medians [IQR] in pg/mL, measured in serum. The log₂ median columns are the base-2 logarithms of those medians, and log₂FC is their difference, so that all columns are mutually reconcilable. Groups were compared using the Wilcoxon rank-sum test with Benjamini–Hochberg FDR correction across all 13 analytes. Pre-specified significance criteria were FDR < 0.05 and log₂FC > 0.5; eleven analytes met both. NS: not significant; M: marginal (FDR < 0.05 but log₂FC < 0.5). log₂FC: log₂ fold change. FDR: Benjamini-Hochberg false discovery rate. AUC for all 13 cytokines are given in Supplementary Table 3 while cut-offs, sensitivity and specificity for the five leading cytokines are given in Supplementary Table 1.

Table 3. Multivariable logistic regression: factors independently associated with cardiogenic shock.

Variable	Adjusted OR	95% CI	p-value	Firth OR	Firth 95% CI
log ₂ IL-6	1.81	1.18-2.77	0.006*	1.72	1.12-2.65
log ₂ IL-10	2.01	1.13-3.56	0.017*	1.89	1.08-3.31
log ₂ TNF-α	2.63	1.33-5.20	0.005*	2.41	1.24-4.68
log ₂ M-CSF	1.34	0.72-2.50	0.352	1.29	0.70-2.38
log ₂ IL-1β	1.10	0.66-1.83	0.720	1.08	0.65-1.79
Male sex	0.069	0.014-0.34	0.001*	0.096	0.024-0.383
Age (years)	1.007	0.96-1.05	0.774	1.006	0.96-1.05
Model performance and calibration					
AUC (apparent)	0.951	0.919–0.984	–	–	–
AUC (5-fold cross-validated)	0.932	–	–	–	–
Hosmer–Lemeshow goodness-of-fit	χ ² = 13.47	df = 8	0.097	–	–
Calibration slope (cross-validated)	0.770	–	–	–	–
Calibration intercept (cross-validated)	–0.019	–	–	–	–

Model: CS ~ age + sex + log₂(IL-6) + log₂(IL-10) + log₂(TNF-α) + log₂(M-CSF) + log₂(IL-1β).

Events per variable = 8.6 (60 events, 7 predictors). No complete or quasi-separation was detected. Firth penalised logistic regression was fitted as a pre-planned sensitivity analysis. All performance estimates are internal and should be interpreted as exploratory. *: statistically significant. χ²: chi-square; df: degrees of freedom.