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SERUM CYTOKINE PANEL PREDICTS CARDIAC OUTCOMES FOLLOWING ACUTE MYOCARDIAL INFARCTION

SERUMSKI PANEL CITOKINA PREDVIĐA SRČANE ISHODE NAKON AKUTNOG INFARKTA MIOKARDA

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Summary

Background: Individual cytokines have been implicated in the pathogenesis of acute myocardial infarction (AMI). However, the predictive utility of a comprehensive serum cytokine panel for post-infarction outcomes remains underexplored.

Methods: We conducted a prospective cohort study of 184 patients presenting with ST-segment elevation myocardial infarction (STEMI). Blood samples were collected within 24 hours of primary percutaneous coronary intervention (PCI). We analysed a panel of 11 cytokines (GDF-15, IL-1β, IL-6, IL-8, IL-10, IFN-γ, VEGF, G-CSF, GM-CSF, TGF-β, and hs-cTnT) using a multiplex bead-based immunoassay. The primary endpoint was the occurrence of Major Adverse Cardiac Events (MACE) at 12 months. MACE was defined as cardiovascular death, recurrent MI, or heart failure hospitalisation.

Results: Elevated levels of IL-6, IL-8, GDF-15, and hs-cTnT were significantly associated with 12-month MACE. Multivariable logistic regression identified GDF-15 (OR 3.58, 95% CI 1.82–7.04, p<0.001) and hs-cTnT (OR 2.94, 95% CI 1.53–5.65, p=0.001) as independent predictors. In univariable analysis, IL-6, IL-8, GDF-15, and hs-cTnT were elevated. Still, only GDF-15 and hs-cTnT retained independent prognostic significance in the multivariable model. A composite biomarker score showed an AUC of 0.86 (95% CI 0.80–0.92) for predicting MACE.

Conclusion: A serum biomarker profile including GDF-15 and hs-cTnT may improve early risk assessment after primary PCI in STEMI, supporting routine biomarker profiling to enhance risk stratification beyond traditional variables.

Keywords: myocardial infarction, cytokines, GDF-15, high-sensitivity troponin, prognosis, inflammation

Kratak sadržaj

Uvod: Pojedinačni citokini su povezani sa patogenezom akutnog infarkta miokarda (AMI). Međutim, još uvek nije dovoljno istražena prognostička vrednost sveobuhvatnog serumskog citokinskog panela za ishode nakon infarkta.

Metode: Sprovedena je prospektivna kohortna studija na 184 pacijenta sa ST-elevacionim infarktom miokarda (STEMI). Uzorci krvi su uzeti u roku od 24 sata nakon primarne perkutane koronarne intervencije (PCI). Analiziran je panel od 11 citokina (GDF-15, IL-1β, IL-6, IL-8, IL-10, IFN-γ, VEGF, G-CSF, GM-CSF, TGF-β i hs-cTnT) pomožu multipleks imunotesta na bazi mikrozrnaca. Primarni ishod bio je pojava velikih neželjenih kardiovaskularnih događaja (MACE) u periodu od 12 meseci. MACE je definisan kao kardiovaskularna smrt, ponovni infarkt miokarda ili hospitalizacija zbog srčane insuficijencije.

Rezultati: Povišeni nivoi IL-6, IL-8, GDF-15 i hs-cTnT su bili značajno povezani sa MACE u 12 meseci. Multivarijantna logistička regresija identifikovala je GDF-15 (OR 3,58; 95% CI 1,82–7,04; p<0,001) i hs-cTnT (OR 2,94; 95% CI 1,53–5,65; p=0,001) kao nezavisne prediktore. U univarijantnoj analizi povišeni su bili IL-6, IL-8, GDF-15 i hs-cTnT, ali su samo GDF-15 i hs-cTnT zadržali nezavisni prognostički značaj u multivarijantnom modelu. Kombinovani biomarker skor pokazao je AUC od 0,86 (95% CI 0,80–0,92) za predikciju MACE.

Zaključak: Serumski biomarkerni profil koji uključuje GDF-15 i hs-cTnT može poboljšati ranu procenu rizika nakon primarne PCI kod STEMI pacijenata, podržavajuži rutinsko određivanje biomarkera radi boljeg stratifikovanja rizika iznad tradicionalnih kliničkih parametara.

Ključne reči: infarkt miokarda, citokini, GDF-15, visokoosetljivi troponin, prognoza, inflamacija

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Introduction

Despite improvements in medication and revascularisation, acute myocardial infarction (AMI) is still a major cause of death globally (1, 2). Troponin is the gold standard for diagnosis, but when used alone, its ability to predict Major Adverse Cardiac Events (MACE) and long-term unfavourable remodelling is limited (3, 4). Inflammation is a critical driver of atherosclerosis and post-infarction repair; however, excessive or prolonged inflammation exacerbates myocardial injury and fibrosis (5, 6).

The role of cytokines in cardiovascular disease has evolved from observational associations to therapeutic targets, as evidenced by the CANTOS trial targeting IL-1β (7, 8). Yet single-cytokine approaches often fail to capture the complex immune network underlying plaque rupture and healing (9, 10). Specific cytokines, such as Interleukin-6 (IL-6), mediate the acute-phase response and correlate with infarct size (11, 12), while Interleukin-8 (IL-8) promotes neutrophil recruitment to ischemic tissue (13, 14).

Growth Differentiation Factor-15 (GDF-15) has emerged as a powerful prognostic biomarker in cardiovascular disease. Unlike traditional inflammatory cytokines, GDF-15 is induced by oxidative stress, ischemia, and pressure overload. It reflects both myocardial and systemic stress responses (15, 16). This biological profile may explain why GDF-15 can outperform individual inflammatory cytokines in the acute phase of myocardial infarction, particularly when evaluated head-to-head within a multiplex biomarker panel. Multiple studies have demonstrated that elevated GDF-15 independently predicts mortality and heart failure in acute coronary syndrome patients (17, 18). Similarly, high-sensitivity cardiac Troponin T (hs-cTnT) has revolutionised the diagnosis of MI, and emerging evidence suggests that even modest elevations beyond the acute event carry significant prognostic information (19, 20).

Despite this knowledge, routine clinical adoption of multi-marker prognostic panels is hindered by a lack of standardised panels and prospective validation (21, 22). Most existing studies focus on single biomarkers or fail to adjust for relevant confounders (23, 24). The advent of multiplex assay technology now permits simultaneous quantification of multiple mediators from small serum volumes, offering a pragmatic solution for risk prediction (25, 26).

While GDF-15 and hs-cTnT are both well-recognised prognostic biomarkers in cardiovascular disease, their prognostic performance relative to a wider array of inflammatory cytokines measured simultaneously in the setting of an acute STEMI event has not been fully elucidated. Therefore, this current study aimed to investigate whether an 11-plex serum biomarker panel measured acutely in STEMI can independently predict MACE at 12 months. The underlying hypothesis is that a collective biomarker signature focused on GDF-15 and hs-cTnT will provide incremental prognostic capability beyond traditional clinical risk markers. This current research aims to identify neither novel biomarkers nor their prognostic capability, but rather to measure the prognostic capability of a variety of cytokines simultaneously using a single multiplex approach and to ascertain whether a simplified biomarker score can identify the majority of prognostic data (27–30).

Materials and Methods

Study design and setting

From January 2024 to December 2025, the Department of Cardiology at [The Second Affiliated Hospital of Wenzhou Medical University] conducted this single-centre, prospective, observational cohort study. The Institutional Review Board approved the procedure, and the study followed the Declaration of Helsinki. All patients gave written informed consent before enrolment.

Study population

Consecutive patients presenting with ST-segment elevation myocardial infarction (STEMI) were screened for eligibility.

Inclusion criteria

1. Age ≥18 years.
2. Diagnosis of STEMI followed the Fourth Universal Definition of Myocardial Infarction (2). This required a rise or fall in cardiac troponin, with one value above the 99th percentile URL, plus symptoms of myocardial ischemia and new ST-elevation at the J-point in two contiguous leads (≥2.5 mm in men under 40, ≥2 mm in men 40 or older, or ≥1.5 mm in women for leads V2–V3, and/or ≥1 mm in other leads).
3. Presentation within 12 hours of symptom onset.
4. Successful primary PCI was defined as TIMI grade 3 flow with less than 30% residual stenosis. The treating interventional cardiologist adjudicated this using the final angiographic report. There was no core-laboratory adjudication.

Exclusion criteria

1. History of chronic inflammatory disease (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease).

2. Active malignancy or chemotherapy within 5 years.
3. Concurrent acute or chronic infection (temperature >38°C or white blood cell count >15,000/μL without relation to MI).
4. Prior myocardial infarction within 30 days.
5. End-stage renal disease (eGFR <15 mL/min/1.73 m^2) or requiring dialysis.
6. Cardiogenic shock at presentation (systolic BP <90 mmHg for >30 minutes requiring inotropes or intra-aortic balloon pump).
7. Use of immunosuppressive medications (oral corticosteroids, methotrexate, biologics) within 30 days.
8. Refusal or inability to provide informed consent.

Clinical data collection and definitions

Demographic data, cardiovascular risk factors, and medical history were obtained through standardised patient interviews and electronic medical record review. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic pressure≥90 mmHg on two occasions, or current antihypertensive therapy. Diabetes mellitus was defined as HbA1c ≥6.5%, fasting glucose ≥126 mg/dL, or use of glucose-lowering agents. Dyslipidaemia was defined as LDL-C ≥100 mg/dL or lipid-lowering therapy. Smoking status was categorised as current, former, or never.

Blood sampling protocol

Peripheral venous blood was collected from the antecubital vein immediately following PCI (median 4.2 hours, IQR 2.8–6.1 hours post-reperfusion). Samples were collected in serum separator tubes (Becton Dickinson, Franklin Lakes, NJ, USA). Blood was allowed to clot at room temperature for 30 minutes, followed by centrifugation at 1,500×g for 15 minutes at 4 °C. Serum was aliquoted into 1.5 mL cryovials and stored at -80 °C within 2 hours of collection. No samples underwent more than one freeze-thaw cycle before analysis.

Multiplex biomarker assay

Biomarker concentrations were determined using the Bio-Plex Pro™ Human Cytokine 11-plex Panel (Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions. The panel included the following analytes: Interleukin (IL)-1β, IL-6, IL-8, IL-10, Interferon-gamma (IFN-γ), Vascular Endothelial Growth Factor (VEGF), Granulocyte Colony-Stimulating Factor (G-CSF), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Transforming Growth Factor-beta (TGF-β), Growth Differentiation Factor-15 (GDF-15), and high-sensitivity cardiac Troponin T (hs-cTnT).

Assay procedure

1. Magnetic beads coated with capture antibodies were vortexed and added to a 96-well plate.
2. Serum samples were thawed on ice and diluted 1:4 in sample diluent.
3. Standards and quality controls were prepared via a 4-fold serial dilution.
4. Fifty microliters of standards, controls, and samples were added to designated wells and incubated on a plate shaker (850 rpm) for 60 minutes at room temperature.
5. Plates were washed three times with wash buffer using a magnetic plate washer.
6. Detection antibodies were added and incubated for 30 minutes with shaking.
7. Streptavidin-phycoerythrin (PE) was added and incubated for 10 minutes.
8. Plates were washed three times, and beads were resuspended in assay buffer.
9. Plates were read on the Bio-Plex 200 Suspension Array System.

Quality control

All samples were assayed in duplicate. The mean coefficient of variation (CV) for duplicate samples was <8%. Lower limits of detection (LOD) ranged from 0.1 to 5.0 pg/mL depending on the analyte. Values below the LOD were imputed as LOD/√2.

Echocardiography

Transthoracic echocardiography was performed within 48 hours of admission using a Vivid E95 system (GE Healthcare, Chicago, IL, USA). Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson's method from apical 4- and 2-chamber views. Measurements were performed by two independent cardiologists blinded to clinical outcomes. Inter-observer variability (ICC 0.92, 95% CI 0.88–0.95) was acceptable.

Follow-up and outcome ascertainment

Patients were followed for 12 months post-discharge. Follow-up visits were scheduled at 1 month (±7 days), 6 months (±14 days), and 12 months (±30 days). Visits included clinical assessment, electrocardiography, and medication reconciliation. For patients unable to attend in-person visits, structured telephone interviews were conducted.

Primary endpoints

Major Adverse Cardiac Events (MACE) were defined as the first occurrence of any of the following:

- Cardiovascular death: Death resulting from acute MI, heart failure, cardiac arrest, or other cardiovascular causes.
- Recurrent myocardial infarction: Defined by the Fourth Universal Definition (2) with rise/fall of troponin and either symptoms, new ischemic ECG changes, or imaging evidence of new viability loss.
- Hospitalisation for heart failure: Unplanned hospital admission with symptoms of heart failure (dyspnoea, orthopnoea, oedema) and objective evidence of congestion (pulmonary oedema on imaging, elevated natriuretic peptides, or invasive hemodynamic evidence) requiring intravenous diuretic or vasoactive therapy.

Secondary endpoints

- Individual components of the primary composite endpoint.
- All-cause mortality.
- Target vessel revascularisation (TVR).

Outcome events were adjudicated by two independent cardiologists unaware of biomarker results. Disagreements were resolved by consensus or third-party adjudication.

Statistical analysis

Sample size calculation

Based on a predicted MACE rate of 20% at 12 months and an anticipated odds ratio of 2.8 for high versus low GDF-15 (17), a minimum of 160 patients was required to achieve 80% power at $\alpha=0.05$, assuming a binary predictor prevalence of 40%. To account for 15% loss to follow-up, we targeted enrolment of 184 patients. Although the sample size was estimated based on a binary classification of GDF-15, the final analyses used continuous biomarker values, which provided greater statistical power and supported the adequacy of the planned sample size.

Descriptive statistics

Continuous variables were assessed for normality using the Shapiro-Wilk test and visual inspection of Q-Q plots. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared using Student's independent t-test. Non-normally distributed variables were reported as medians with interquartile ranges (IQRs) and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies (percentages) and compared using the Chi-square test or Fisher's exact test (for expected cell counts <5).

Biomarker data transformation

Due to non-normal distribution, raw biomarker concentrations were natural log-transformed (ln) before regression analyses. For descriptive tables, median (IQR) values are presented in original units (pg/mL).

Univariable and multivariable logistic regression

Univariable logistic regression was performed to identify predictors of 12-month MACE. Variables with a p-value <0.10 in univariable analysis were considered candidates for multivariable analysis. To avoid multicollinearity, the variance inflation factor (VIF) was calculated; variables with a VIF >5 were excluded or combined.

Multivariable logistic regression was performed using backward stepwise elimination (likelihood ratio method). Two models were constructed:

Model 1 (Clinical): Adjusted for age, sex, diabetes, hypertension, LVEF, and GRACE score.

Model 2 (Biomarker + Clinical): Adjusted for Model 1 covariates plus log-transformed biomarkers.

Results are reported as odds ratios (OR) with 95% confidence intervals (CI).

Predictive accuracy

Receiver operating characteristic (ROC) curves were generated to evaluate discriminative ability. The area under the curve (AUC) was reported with 95% CI. Comparisons between AUCs were performed using the DeLong test.

To derive a composite biomarker score, logistic regression coefficients for significant independent biomarkers (GDF-15 and hs-cTnT) were used to weight individual values. The score was calculated as: (1.28 × ln[GDF-15]) + (1.08 × ln[hs-cTnT]), based on the β-coefficients from multivariable analysis.

Subgroup and sensitivity analyses

Pre-specified subgroup analyses were performed by age (<65 vs≥65), sex, diabetes status, and LVEF (<50% vs≥50%). Interaction testing was conducted using likelihood ratio tests.

Sensitivity analyses were performed: (1) excluding patients with extreme biomarker values (>99th percentile); (2) using multiple imputation by chained equations (MICE) for missing follow-up data; (3) analysing biomarkers as tertiles rather than continuous variables.

Software

Statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) with packages: pROC, glm2, and mice. A two-tailed p-value <0.05 was considered statistically significant.

Results

Study population and baseline characteristics

A total of 239 patients with STEMI were screened. After applying exclusion criteria, 184 patients were enrolled and included in the final analysis. Reasons for exclusion included: active infection (n=18), chronic inflammatory disease (n=12), cardiogenic shock (n=11), immunosuppressive therapy (n=8), and refusal to participate (n=6).

The mean age of the cohort was 62.3±11.4 years, and 134 patients (72.8%) were male. Complete 12-month follow-up was achieved in 177 patients (96.2%); seven patients (3.8%) were lost to follow-up and censored at the time of last contact.

During the 12-month follow-up period, 44 patients (23.9%) experienced at least one MACE event. The breakdown of primary endpoint events was as follows: cardiovascular death (n=11, 6.0%), recurrent myocardial infarction (n=19, 10.3%), and hospitalisation for heart failure (n=28, 15.2%). Some patients experienced more than one event; only the first event was counted for the composite endpoint.

Comparison of baseline characteristics by MACE status

Patients who developed MACE were significantly older (67.1±10.2 vs 60.5±11.8 years, p=0.002) and more likely to have diabetes mellitus (43.2% vs 23.6%, p=0.011). No significant differences were observed in sex distribution, hypertension, or smoking status.

Patients with MACE had more extensive myocardial injury, as evidenced by significantly lower LVEF (41.2±8.7% vs 50.1±9.8%, p<0.001) and higher GRACE risk scores (159.4±31.2 vs 137.2±27.8, p<0.001).

Medication prescriptions at discharge were generally similar between groups, although patients with MACE were numerically less frequently prescribed dual antiplatelet therapy and beta-blockers; these differences did not reach statistical significance.

Serum biomarker profiles

Overall biomarker detectability

All 11 biomarkers were detectable in >95% of samples. IL-1β and GM-CSF had the lowest absolute concentrations (median <5 pg/mL), while GDF-15 had the highest among the novel biomarkers (median >1800 pg/mL).

Comparison of biomarker levels by MACE status

Patients who developed MACE demonstrated significantly elevated levels of four biomarkers: IL-6 (14.8 vs 6.1 pg/mL, p<0.001), IL-8 (19.3 vs 9.4 pg/mL, p<0.001), GDF-15 (2456.7 vs 1245.3 pg/mL, p<0.001), and hs-cTnT (58.3 vs 38.4 ng/mL, p=0.008).

No significant differences were observed between groups for IL-1β, IL-10, IFN-γ, VEGF, G-CSF, GM-CSF, or TGF-β. Notably, the anti-inflammatory cytokines IL-10 and TGF-β showed nearly identical distributions between groups, suggesting that an impaired anti-inflammatory response does not distinguish outcomes in this cohort.

Correlation matrix

Among the four significant biomarkers, moderate positive correlations were observed. The strongest correlation was between GDF-15 and IL-6 (Spearman's ρ=0.49, p<0.001), followed by GDF-15 and hs-cTnT (ρ=0.45, p<0.001). This suggests overlapping but distinct pathophysiological pathways.

Univariable logistic regression analysis

Univariable logistic regression identified the following significant predictors ($p<0.10$) of 12-month MACE:

Clinical variables: Age (OR per 10-year increase: 1.72, 95% CI 1.24–2.38, p=0.001), diabetes mellitus (OR 2.46, 95% CI 1.22–4.95, p=0.012), LVEF (OR per 5% decrease: 1.62, 95% CI 1.31–2.01, p<0.001), Killip class ≥II (OR 2.43, 95% CI 1.21–4.88, p=0.013), GRACE score (OR per 10-point increase: 1.31, 95% CI 1.12–1.53, p<0.001).

Biomarker variables (log-transformed): IL-6 (OR 2.41, 95% CI 1.57–3.70, p<0.001), IL-8 (OR 2.12, 95% CI 1.38–3.26, p=0.001), GDF-15 (OR 3.89, 95% CI 2.34–6.47, p<0.001), hs-cTnT (OR 1.84, 95% CI 1.18–2.87, p=0.007).

Variables with $p\geq0.10$ (sex, hypertension, dyslipidaemia, smoking, multi-vessel disease, IL-1β, IL-10, IFN-γ, VEGF, G-CSF, GM-CSF, TGF-β) were not advanced to multivariable analysis.

Multivariable logistic regression analysis

Model building

To avoid overfitting, the multivariable model was constructed with one predictor per 10 events (44 MACE events allowed approximately 4–5 predictors). Backward stepwise elimination was performed.

Final multivariable model

After adjustment for age, diabetes, LVEF, and GRACE score, two biomarkers remained independently associated with 12-month MACE:

GDF-15 (log): OR 3.58 (95% CI 1.82–7.04), p<0.001

hs-cTnT (log): OR 2.94 (95% CI 1.53–5.65), p=0.001

IL-6 and IL-8 were retained in the multivariable model a priori to assess whether their apparent univariable associations remained independent after adjustment for GDF-15 and hs-cTnT. Their coefficients were attenuated and no longer remained statistically significant in the final model. The variance inflation factor (VIF) for all retained variables was <2.3, indicating acceptable multicollinearity.

Independent effect of biomarkers

The addition of GDF-15 and hs-cTnT to the clinical model significantly improved model fit (Likelihood ratio $\chi^2 = 24.3$, $p<0.001$), indicating independent and incremental prognostic value.

Predictive performance of biomarker panel

Individual biomarker discriminative ability

ROC analysis was performed to assess the ability of individual biomarkers to discriminate MACE status:

GDF-15: AUC 0.81 (95% CI 0.74–0.88)

hs-cTnT: AUC 0.73 (95% CI 0.65–0.81)

IL-6: AUC 0.71 (95% CI 0.63–0.79)

IL-8: AUC 0.69 (95% CI 0.61–0.77)

Composite biomarker score

A weighted composite biomarker score was derived from the β-coefficients of GDF-15 and hs-cTnT:

Biomarker Score = (1.28 × ln[GDF-15, concentration in pg/mL]) + (1.08 × ln[hs-cTnT, concentration in ng/mL])

The composite biomarker score demonstrated an AUC of 0.86 (95% CI 0.80–0.92).

Incremental value

The addition of the composite biomarker score to a clinical base model (age, diabetes, LVEF, GRACE score) increased the AUC from 0.77 (95% CI 0.69–0.85) to 0.89 (95% CI 0.83–0.95), representing a 15.6% relative improvement in discriminatory capacity (p=0.004).

Risk reclassification

Continuous Net Reclassification Improvement (NRI) for the addition of the composite biomarker score to the clinical model was 0.62 (95% CI 0.41–0.83, p<0.001), and the Integrated Discrimination Improvement (IDI) was 0.14 (95% CI 0.08–0.20, p<0.001), indicating excellent improvement in risk classification.

Subgroup analyses

The prognostic value of the composite biomarker score was consistent across all pre-specified subgroups:

Table I Baseline demographic and clinical characteristics stratified by 12-month MACE status.

Characteristic	Total (n=184)	MACE (n=44)	No MACE (n=140)	p-value
Age, years (mean ± SD)	62.3±11.4	67.1±10.2	60.5±11.8	0.002
Male sex, n (%)	134 (72.8)	30 (68.2)	104 (74.3)	0.431
Body mass index, kg/m^2 (mean ± SD)	27.8±4.5	27.9±4.8	27.7±4.4	0.798
Cardiovascular risk factors, n (%)				
Hypertension	98 (53.3)	27 (61.4)	71 (50.7)	0.212
Diabetes mellitus	52 (28.3)	19 (43.2)	33 (23.6)	0.011
Dyslipidaemia	86 (46.7)	23 (52.3)	63 (45.0)	0.396
Current smoker	81 (44.0)	17 (38.6)	64 (45.7)	0.409
Prior MI	18 (9.8)	6 (13.6)	12 (8.6)	0.324
Prior stroke/TIA	11 (6.0)	4 (9.1)	7 (5.0)	0.308
Killip class, n (%)				0.018
Class I	129 (70.1)	25 (56.8)	104 (74.3)	
Class II	41 (22.3)	13 (29.5)	28 (20.0)	
Class III	14 (7.6)	6 (13.6)	8 (5.7)	
LVEF, % (mean ± SD)	48.5±9.3	41.2±8.7	50.1±9.8	<0.001
LVEF <50%, n (%)	88 (47.8)	31 (70.5)	57 (40.7)	<0.001
Infarct-related artery, n (%)				0.554
LAD	89 (48.4)	23 (52.3)	66 (47.1)	
LCx	32 (17.4)	8 (18.2)	24 (17.1)	
RCA	63 (34.2)	13 (29.5)	50 (35.7)	
Multi-vessel disease, n (%)	71 (38.6)	21 (47.7)	50 (35.7)	0.151
Symptom-to-balloon time, min (median, IQR)	189 (135–278)	201 (142–301)	182 (130–268)	0.118
GRACE risk score (mean ± SD)	142.6±29.8	159.4±31.2	137.2±27.8	<0.001
Medications at discharge, n (%)				
Aspirin	181 (98.4)	43 (97.7)	138 (98.6)	0.692
P2Y12 inhibitor	173 (94.0)	40 (90.9)	133 (95.0)	0.318
DAPT	172 (93.5)	39 (88.6)	133 (95.0)	0.135
Statin	176 (95.7)	41 (93.2)	135 (96.4)	0.367
Beta-blocker	162 (88.0)	36 (81.8)	126 (90.0)	0.149
ACE-I/ARB	148 (80.4)	33 (75.0)	115 (82.1)	0.294
Aldosterone antagonist	31 (16.8)	10 (22.7)	21 (15.0)	0.230

Abbreviations: SD, standard deviation; IQR, interquartile range; MI, myocardial infarction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; GRACE, Global Registry of Acute Coronary Events; DAPT, dual antiplatelet therapy; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table II Serum biomarker concentrations stratified by 12-month MACE status.

Biomarker	Total (n=184) Median (IQR)	MACE (n=44) Median (IQR)	No MACE (n=140) Median (IQR)	p-value
IL-1β (pg/mL)	0.7 (0.2–2.2)	0.8 (0.2–2.1)	0.7 (0.2–2.3)	0.891
IL-6 (pg/mL)	8.1 (3.5–19.8)	14.8 (7.2–31.5)	6.1 (2.9–15.3)	<0.001
IL-8 (pg/mL)	11.8 (5.6–25.4)	19.3 (10.1–38.7)	9.4 (4.8–20.1)	<0.001
IL-10 (pg/mL)	2.3 (1.0–5.7)	2.1 (0.9–5.4)	2.4 (1.1–5.9)	0.612
IFN-γ (pg/mL)	6.0 (2.4–14.8)	5.8 (2.1–14.3)	6.2 (2.5–15.1)	0.723
VEGF (pg/mL)	34.5 (17.2–69.8)	32.1 (15.4–67.2)	35.8 (18.9–71.4)	0.441
G-CSF (pg/mL)	40.8 (17.3–85.6)	42.3 (18.9–88.4)	39.8 (16.7–84.2)	0.502
GM-CSF (pg/mL)	3.3 (0.9–9.8)	3.1 (0.8–9.4)	3.4 (0.9–10.1)	0.668
TGF-β (pg/mL)	1812.5 (1178.3–2589.7)	1850.2 (1201.5–2543.8)	1798.4 (1154.9–2612.3)	0.817
GDF-15 (pg/mL)	1542.8 (987.3–2541.6)	2456.7 (1783.4–3987.2)	1245.3 (876.5–1987.4)	<0.001
hs-cTnT (ng/mL)	42.5 (18.2–89.1)	58.3 (31.4–110.2)	38.4 (15.1–79.3)	0.008

Abbreviations: IL, interleukin; IFN, interferon; VEGF, vascular endothelial growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; TGF, transforming growth factor; GDF, growth differentiation factor; hs-cTnT, high-sensitivity cardiac troponin T.

Table III Multivariable logistic regression analysis for prediction of 12-month MACE.

Variable	β Coefficient	Standard Error	Odds Ratio (OR)	95% Confidence Interval	p-value
Age (per 10-year increase)	0.341	0.148	1.41	1.05–1.89	0.022
Diabetes mellitus (yes vs no)	0.612	0.338	1.84	0.95–3.57	0.071
LVEF (per 5% decrease)	0.398	0.124	1.49	1.17–1.90	0.001
GRACE score (per 10-point increase)	0.254	0.131	1.29	0.99–1.67	0.054
IL-6 (log)	0.412	0.249	1.51	0.93–2.46	0.098
IL-8 (log)	0.341	0.264	1.41	0.84–2.36	0.197
GDF-15 (log)	1.275	0.345	3.58	1.82–7.04	<0.001
hs-cTnT (log)	1.078	0.334	2.94	1.53–5.65	0.001

Model fit: Hosmer-Lemeshow $\chi^2=5.91$, p=0.657; Nagelkerke $R^2=0.45$; AUC=0.89.

Sensitivity analyses

Exclusion of extreme values

Exclusion of patients with GDF-15 >5000 pg/mL (n=12) and hs-cTnT >200 ng/mL (n=9) did not materially alter the association between the composite biomarker score and MACE (OR 2.59, 95% CI 1.78–3.77, p<0.001).

Multiple imputation

Analysis using multiply imputed datasets for the 7 patients lost to follow-up yielded consistent results (pooled OR for composite biomarker score: 2.71, 95% CI 1.84–3.99, p<0.001).

Table IV Receiver operating characteristic (ROC) analysis for prediction of 12-month MACE.

Predictor Model	AUC	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
GRACE Risk Score	0.71	0.63–0.79	68	65	38	87
Clinical Model (Age, DM, LVEF)	0.77	0.69–0.85	72	70	43	89
IL-6 alone	0.71	0.63–0.79	64	68	38	86
IL-8 alone	0.69	0.61–0.77	61	66	36	85
GDF-15 alone	0.81	0.74–0.88	79	75	50	92
hs-cTnT alone	0.73	0.65–0.81	70	68	41	88
Composite Biomarker Score (GDF-15 + hs-cTnT)	0.86	0.80–0.92	82	80	56	94
Combined Model (Clinical + Biomarker Score)	0.89	0.83–0.95	86	84	63	95

Abbreviations: AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; GRACE, Global Registry of Acute Coronary Events; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; IL, interleukin; GDF, growth differentiation factor; hs-cTnT, high-sensitivity cardiac troponin T.

Table V Subgroup analysis for the association of composite biomarker score with 12-month MACE.

Subgroup	n	MACE Rate (%)	OR (per 1-SD increase)	95% CI	p-value	p-interaction
Age						0.324
<65 years	98	17.3	2.89	1.71–4.89	<0.001	
≥65 years	86	31.4	2.41	1.54–3.77	<0.001	
Sex						0.451
Male	134	22.4	2.67	1.82–3.92	<0.001	
Female	50	28.0	2.98	1.63–5.44	<0.001	
Diabetes						0.612
Non-diabetic	132	19.7	2.71	1.79–4.10	<0.001	
Diabetic	52	36.5	2.54	1.41–4.58	0.002	
LVEF						0.178
≥50%	96	17.7	2.81	1.67–4.73	<0.001	
<50%	88	35.2	2.23	1.44–3.45	<0.001	

Biomarker tertiles

When analysed by tertiles, patients in the highest tertile of the composite biomarker score had a significantly higher risk of MACE compared to those in the lowest tertile (OR 5.89, 95% CI 2.91–11.92, p<0.001).

Secondary endpoint analysis

The composite biomarker scores significantly predicted each component of the primary endpoint:

Cardiovascular death: OR 3.12 (95% CI 1.67–5.83, p<0.001)

Recurrent MI: OR 2.41 (95% CI 1.48–3.92, p<0.001)

Heart failure hospitalisation: OR 2.89 (95% CI 1.81–4.62, p<0.001)

The score also predicted all-cause mortality (OR 2.54, 95% CI 1.39–4.64, p=0.002) but not target vessel revascularisation (OR 1.32, 95% CI 0.84–2.07, p=0.228).

Discussion

The key finding of this study is not the identification of GDF-15 or hs-cTnT as novel biomarkers, but rather their dominance over other inflammatory cytokines in a head-to-head comparison within a single multiplex panel measured in the acute phase of STEMI. The key findings are threefold. First, patients who develop adverse outcomes exhibit significantly higher serum concentrations of IL-6, IL-8, GDF-15, and hs-cTnT. Second, GDF-15 and hs-cTnT remain robust predictors after extensive multivariable adjustment for clinical risk factors. Third, a composite biomarker score provides incremental prognostic value when added to established clinical risk models (31, 32).

Our results are consistent with the growing recognition of GDF-15 as a potent prognostic biomarker in acute coronary syndromes. A member of the transforming growth factor-β superfamily, GDF-15 is expressed at very low levels in normal tissues but is significantly increased in response to pressure overload, oxidative stress, and ischemia (33, 34). In contrast to conventional inflammatory cytokines, GDF-15 reflects the cumulative burden of cardiovascular disease by integrating signals from multiple stress pathways (35, 36). Our work validates and extends the findings to a modern STEMI population treated with primary PCI. Elevated GDF-15 levels have been consistently linked to mortality and heart failure across the spectrum of ACS (37, 38).

Particular attention should be paid to the independent predictive value of hs-cTnT assessed within 24 hours following PCI. Although peak troponin is a reliable indicator of infarct size, its ability to predict outcomes independently of LVEF and GRACE score has been questioned (39, 40). The idea that the degree of myocardial necrosis, as measured with high-sensitivity assays, provides distinct prognostic information is supported by our findings, which show that hs-cTnT remains an independent predictor of MACE even after thorough correction (41, 42).

Interestingly, while IL-6 and IL-8 were significantly elevated in the MACE group in univariable analysis, they lost significance in the multivariable model after inclusion of GDF-15. This observation has several potential explanations. First, GDF-15 may capture both inflammatory and non-inflammatory stress pathways, rendering isolated cytokine measurements redundant (43, 44). Second, IL-6 and IL-8 exhibit significant temporal variability in the immediate post-infarction period, whereas GDF-15 demonstrates greater stability (45, 46). Third, collinearity between these biomarkers suggests overlapping biological signals (47, 48). This lack of independent predictive value of IL-6 and IL-8 might also be explained by the high temporal variability of these cytokines in the early post-infarction phase. These cytokines exhibit rapid, dynamic responses to acute inflammatory signalling, and their measurement may not adequately capture their prognostic profile. On the contrary, GDF-15 is a marker of a more integrated stress response that combines ischemic, inflammatory, and oxidative stress pathways, which might account for the greater temporal stability of this biomarker and its independent predictive value. Thus, a single measurement might not adequately capture the prognostic impact of dynamically regulated cytokines such as IL-6 and IL-8 (45, 46).

The failure of anti-inflammatory cytokines (IL-10, TGF-β) to predict outcomes underscores the concept that the magnitude of the pro-inflammatory and myocardial stress responses, rather than the compensatory anti-inflammatory response, is the dominant determinant of poor prognosis in the acute phase (49, 50).

Current risk stratification following STEMI relies heavily on LVEF and GRACE scores, which lack direct biological insight into the extent of myocardial injury and systemic stress (51, 52). Our data suggest that adding a targeted biomarker panel including GDF-15 and hs-cTnT to routine post-PCI assessment could identify high-risk patients who might benefit from more intensive follow-up, advanced imaging, or emerging cardioprotective therapies (53, 54). Contemporary reviews suggest that only a limited number of biomarkers, particularly natriuretic peptides and GDF-15, consistently add prognostic information beyond troponin in ACS, although their role in routine treatment decision-making remains incompletely defined (55, 56).

While the composite biomarker score demonstrated strong discriminative performance in this cohort, it should currently be considered a proof-of-concept tool. Further validation in larger, multi-centre cohorts is required to establish clinically actionable risk categories and to determine their incremental value in guiding treatment decisions (56, 57).

Several limitations should be acknowledged. First, this is a single-centre study with a modest sample size and requires external validation in larger, multicentre cohorts. Second, biomarkers were measured at a single time point; serial sampling may reveal dynamic patterns with greater predictive utility (58, 59). Third, causality cannot be inferred from an observational design. Fourth, we did not measure natriuretic peptides (BNP/NT-proBNP), which are established cornerstone biomarkers for prognosis in heart failure and acute coronary syndromes. Their inclusion would have allowed a more direct comparison with the cytokine panel and may have improved risk discrimination (60–62). Fifth, although we adjusted for multiple confounders, residual confounding cannot be ruled out.

Conclusion

Importantly, our findings demonstrate that the majority of prognostic information contained within a broader cytokine panel can be captured by a simplified two-marker model, supporting the feasibility of translating multiplex biomarker data into clinically applicable tools. A serum biomarker panel quantifying GDF-15 and hs-cTnT levels within 24 hours of primary PCI independently predicts 12-month MACE in STEMI patients. This biomarker signature offers additive prognostic value over conventional clinical risk scores. Routine multiplex biomarker profiling may facilitate the identification of patients at the highest risk for adverse events following myocardial infarction.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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