SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45

DOI: 10.5937/jomb0-63175

UDK 577.1 : 61

ISSN 1452-8258

J Med Biochem 45: 1–7, 2026

Original paper
Originalni naučni rad

DYNAMIC PROFILING OF SERUM CYTOKINE NETWORKS PREDICT MAJOR ADVERSE CARDIAC EVENTS IN ST-ELEVATION MYOCARDIAL INFARCTION

DINAMIČKO PROFILISANJE MREŽA SERUMSKIH CITOKINA PREDVIĐA VELIKE NEŽELJENE SRČANE DOGAĐAJE KOD INFARKTA MIOKARDA SA ST-ELEVACIJOM

Jun Chen[1], Hui Ping Zheng[2]*

[1]Department of Basic Medical Sciences, Gannan Healthcare Vocational College, Ganzhoug 341000, Jiangxi, China
[2]Department of Nursing, Gannan Healthcare Vocational College, Ganzhoug 341000, Jiangxi, China

Summary

Background: The inflammatory cascade following ST-elevation myocardial infarction (STEMI) involves complex cytokine interactions whose clinical utility remains undefined. We characterized the temporal dynamics of serum cytokine networks and their prognostic value for major adverse cardiac events (MACE).
Methods: In this prospective observational study, 312 consecutive STEMI patients undergoing primary PCI were enrolled. Serial serum samples were obtained at admission (T0), 6 hours (T6), 24 hours (T24), and 72 hours (T72) post-PCI. A 15-plex cytokine panel was analyzed using high-sensitivity electrochemiluminescence. Patients were followed for 12 months for MACE (cardiac death, reinfarction, heart failure hospitalization).
Results: Distinct cytokine trajectories were identified. IL-6 peaked earliest at T6 (median 34.2 pg/mL, IQR 18.7–52.1), while IL-8 peaked at T24 (22.4 pg/mL, IQR 15.3–31.8). Patients who developed MACE (n=48, 15.4%) exhibited significantly higher IL-1β at T0 (3.2 vs 1.8 pg/mL, $p<0.001$), persistent IL-6 elevation, and a blunted IL-10 response. Network analysis revealed stronger pro-inflammatory connectivity in MACE patients.
Conclusion: Early-phase cytokine profiling, particularly IL-1β at presentation and IL-6 kinetics, provides incremental prognostic information beyond traditional risk markers. These findings support cytokine-guided risk stratification in acute MI.

Keywords: acute myocardial infarction, cytokines, inflammation, prognosis, biomarkers

Kratak sadržaj

Uvod: Inflamatorna kaskada koja sledi infarkt miokarda sa ST-elevacijom (STEMI) obuhvata složene interakcije citokina, čija klinička primenljivost još uvek nije u potpunosti definisana. Cilj rada bio je da se karakterišu vremenska dinamika serumskih citokinskih mreža i njihov prognostički značaj za velike neželjene srčane događaje (MACE).
Metode: U ovoj prospektivnoj opservacionoj studiji je uključeno 312 uzastopnih bolesnika sa STEMI, podvrgnutih primarnoj perkutanoj koronarnoj intervenciji (PCI). Serijski uzorci seruma su prikupljeni na prijemu (T0), nakon 6 sati (T6), 24 sata (T24) i 72 sata (T72) nakon PCI. Analiziran je panel od 15 citokina primenom visokosenzitivne elektrohemiluminiscentne metode. Bolesnici su praćeni tokom 12 meseci radi pojave MACE (srčana smrt, reinfarkt, hospitalizacija zbog srčane insuficijencije).
Rezultati: Identifikovane su različite putanje citokina tokom vremena. IL-6 je dostizao najraniji »pik« u T6 (medijana 34,2 pg/mL, IQR 18,7–52,1), dok je IL-8 dostizao u T24 (22,4 pg/mL, IQR 15,3–31,8). Bolesnici kod kojih se razvio MACE (n=48; 15,4%) imali su značajno više vrednosti IL-1β u T0 (3,2 naspram 1,8 pg/mL; $p<0,001$), perzistentno povišene vrednosti IL-6 i oslabljen odgovor IL-10. Analiza mreža je pokazala jaču proinflamatornu povezanost kod bolesnika sa MACE.
Zaključak: Profilisanje citokina u ranoj fazi, naročito vrednosti IL-1β pri prijemu i kinetika IL-6, pruža dodatne prognostičke informacije u odnosu na tradicionalne faktore rizika. Ovi nalazi podržavaju primenu citokinima vođene stratifikacije rizika kod akutnog infarkta miokarda.

Ključne reči: akutni infarkt miokarda, citokini, inflamacija, prognoza, biomarkeri

Address for correspondence:
Dr. Jun Chen
Department of Basic Medical Sciences, Gannan Healthcare Vocational College
Ganzhoug 341000, Jiangxi, China
e-mail: chen_jun@gnhvc.edu.cn
e-mail: cjzhp@163.com

Introduction

The inflammatory response to acute myocardial infarction represents a critical determinant of both infarct healing and subsequent ventricular remodeling (1). While troponins provide diagnostic confirmation of myocyte necrosis, they offer limited insight into the inflammatory milieu that dictates long-term outcomes (2). Recent advances in immunocardiology have highlighted serum cytokines as pivotal mediators of ischemia-reperfusion injury, yet their precise temporal relationships and clinical utility remain incompletely characterized (3).

Previous studies have primarily examined individual cytokines in isolation, overlooking the complex network interactions that define the inflammatory response (4, 5). Furthermore, the optimal timing for cytokine assessment and their incremental prognostic value beyond established risk scores requires clarification (6). The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) demonstrated that targeting interleukin-1β reduces cardiovascular events, validating cytokines as therapeutic targets, yet practical biomarkers to guide such therapy are lacking (7).

Accordingly, to address these gaps in understanding of the temporal evolution, coordinated inflammatory signatures, and clinical relevance of cytokine responses following acute STEMI, the present study was designed to (i) characterize longitudinal changes in circulating cytokines, (ii) identify network-level inflammatory patterns associated with clinical and imaging outcomes, and (iii) evaluate the incremental prognostic value of these inflammatory signatures beyond established clinical risk models.

We conducted the CYTORE-AMI (Cytokine Response in Acute Myocardial Infarction) study to address these gaps. Our primary objectives were: (1) to define the temporal evolution of a comprehensive cytokine panel following STEMI, (2) to identify cytokine signatures associated with adverse outcomes, and (3) to evaluate the incremental prognostic value of cytokine measurements over traditional risk factors.

Materials and Methods

Study design and population

This prospective, single-center cohort study enrolled consecutive patients presenting with STEMI between January 2023 and December 2024. Inclusion criteria were: (1) diagnosis of STEMI per current guidelines (8), (2) successful primary PCI within 12 hours of symptom onset, and (3) age ≥18 years. Exclusion criteria included active infection, autoimmune disease, malignancy, steroid therapy, and cardiogenic shock at presentation.

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board. All participants provided written informed consent.

Blood sampling and cytokine analysis

Venous blood samples were collected in serum separator tubes at four timepoints: admission before PCI (T0), 6 hours post-PCI (T6), 24 hours (T24), and 72 hours (T72). Samples were processed within 30 minutes, aliquoted, and stored at -80 °C until batch analysis.

A custom 15-plex cytokine panel (IL-1β, IL-1ra, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, TNF-α, IFN-γ, MCP-1, G-CSF, VEGF) was measured using the Meso Scale Discovery V-PLEX platform (9). The assay sensitivity ranged from 0.05 to 0.5 pg/mL, depending on the analyte. High-sensitivity troponin T (Roche Diagnostics) and CRP (Siemens Healthcare) were measured concurrently.

The cytokines included in the custom 15-plex panel were selected a priori based on their established roles in acute myocardial ischemia–reperfusion injury, innate and adaptive immune activation, and post-infarction remodeling. Specifically, the panel captures key upstream inflammasome-related mediators (IL-1β, IL-18), central downstream amplifiers (IL-6, TNF-α), chemokines involved in leukocyte recruitment (IL-8, MCP-1, G-CSF), counter-regulatory anti-inflammatory pathways (IL-10, IL-1ra), T-helper cell–associated cytokines (IL-2, IL-4, IL-12p70, IL-17A, IFN-γ), and vascular or reparative signaling (VEGF). This balanced selection was designed to enable network-level assessment of both pro- and anti-inflammatory interactions rather than isolated cytokine effects.

Clinical outcomes and follow-up

The primary endpoint was MACE at 12 months, a composite of cardiac death, recurrent myocardial infarction, or hospitalization for heart failure (10). Secondary endpoints included individual components of MACE and left ventricular ejection fraction (LVEF) at 6 months, assessed by cardiac MRI in a subset (n=180).

A subset of participants (n=180) underwent MRI examinations based on clinical indications and availability rather than random selection. Therefore, analyses involving MRI-derived variables were conducted as post-hoc exploratory analyses and were not prespecified in the primary study design.

Follow-up was conducted through clinic visits at 1, 6, and 12 months, with telephone contact at 3 and 9 months. Events were adjudicated by an independent committee blinded to cytokine data.

Statistical analysis

Continuous variables are presented as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables are presented as counts (percentages) and compared using the chi-square test. Cytokine trajectories were analyzed using linear mixed models. Receiver operating characteristic (ROC) analysis was performed to assess discriminative ability. Multivariable Cox regression included traditional risk factors (age, diabetes, anterior MI, peak troponin, LVEF) and significant cytokines. Network analysis was performed using Spearman correlations with Bonferroni correction. A two-sided $p<0.05$ was considered significant. Analyses used R version 4.2.0.

Results

Patient characteristics

Of 350 screened patients, 312 met the inclusion criteria and completed follow-up (*Table I*). The median age was 62 years (IQR 54–71), with 73% males. Median door-to-balloon time was 45 minutes (IQR 32–68). Forty-eight patients (15.4%)

Table I Baseline characteristics of study population.

Characteristic	Overall (n=312)	No MACE (n=264)	MACE (n=48)	p-value
Age, years	62 (54–71)	61 (53–69)	68 (60–76)	0.002
Male sex	228 (73%)	196 (74%)	32 (67%)	0.34
Diabetes	94 (30%)	72 (27%)	22 (46%)	0.012
Hypertension	198 (63%)	162 (61%)	36 (75%)	0.08
Current smoker	136 (44%)	120 (45%)	16 (33%)	0.14
Anterior MI	142 (46%)	112 (42%)	30 (63%)	0.01
Door-to-balloon, min	45 (32–68)	43 (30–65)	58 (40–82)	0.003
Peak troponin T, ng/L	2,450 (1,120–4,850)	2,210 (980–4,320)	3,980 (2,150–6,740)	<0.001
LVEF at admission, %	48 (40–55)	50 (42–57)	40 (35–45)	<0.001
CRP at 24h, mg/L	18.4 (8.2–35.6)	16.2 (7.1–31.4)	32.8 (18.5–52.1)	<0.001

Table II Temporal cytokine concentrations (pg/mL) in all patients.

Cytokine	T0 (Admission)	T6 (6h post-PCI)	T24 (24h)	T72 (72h)	p-trend
IL-1β	2.1 (1.2–3.4)	3.8 (2.1–6.2)	2.6 (1.5–4.1)	1.8 (1.0–2.9)	<0.001
IL-6	8.4 (4.2–15.1)	34.2 (18.7–52.1)	28.5 (14.8–46.3)	12.6 (6.4–21.8)	<0.001
TNF-α	4.2 (2.8–6.1)	6.8 (4.1–9.5)	5.9 (3.7–8.4)	4.5 (3.0–6.7)	<0.001
IL-8	10.2 (6.4–15.8)	18.9 (11.2–27.4)	22.4 (15.3–31.8)	14.7 (9.1–22.5)	<0.001
IL-10	3.1 (1.8–5.0)	8.4 (4.9–13.2)	5.2 (3.0–8.1)	9.1 (5.3–14.6)	<0.001
IL-1ra	185 (112–298)	420 (245–685)	580 (340–920)	720 (425–1,150)	<0.001
MCP-1	85 (52–134)	210 (145–325)	185 (120–290)	140 (95–220)	<0.001
IL-18	245 (168–380)	320 (210–485)	280 (185–425)	260 (175–400)	0.003

Table III Cytokine differences between outcome groups.

Cytokine	Timepoint	No MACE (n=264)	MACE (n=48)	p-value	AUC (95% CI)
IL-1β	T0	1.8 (1.0–2.9)	3.2 (2.1–5.0)	<0.001	0.72 (0.64–0.80)
IL-6	T6	30.1 (16.4–48.2)	52.8 (34.6–78.4)	<0.001	0.75 (0.68–0.82)
IL-6	T72	10.8 (5.6–18.9)	18.7 (11.2–30.5)	<0.001	0.69 (0.61–0.77)
IL-10	T24	5.6 (3.3–8.7)	3.8 (2.1–6.2)	0.004	0.65 (0.56–0.74)
IL-1ra	T72	780 (460–1,240)	520 (310–850)	0.002	0.66 (0.57–0.75)
IL-8	T24	20.8 (14.1–29.5)	28.4 (19.8–39.2)	0.001	0.68 (0.60–0.76)

experienced MACE within 12 months, including 8 cardiac deaths, 15 recurrent MIs, and 25 heart failure hospitalizations.

Temporal cytokine profiles

The kinetic profiles revealed distinct patterns (*Table II*). Pro-inflammatory cytokines showed early peaks: IL-6 reached maximum at T6 (34.2 pg/mL, IQR 18.7–52.1), while IL-8 peaked later at T24 (22.4 pg/mL, IQR 15.3–31.8). The anti-inflammatory cytokine IL-10 showed a biphasic pattern with peaks at T6 and T72. IL-1 receptor antagonist (IL-1ra), a natural antagonist, increased progressively, peaking at T72.

Cytokine associations with clinical outcomes

Patients who developed MACE exhibited significantly different cytokine profiles (*Table III*). At presentation (T0), IL-1β was already elevated in MACE patients (3.2 vs 1.8 pg/mL, p<0.001). The IL-6 response was both higher and more sustained, with median levels 58% higher at T6 and 73% higher at T72. Conversely, the anti-inflammatory response was attenuated, with lower IL-10 at T24 (3.8 vs 5.6 pg/mL, p=0.004) and T72 (6.2 vs 9.8 pg/mL, p<0.001).

In multivariable Cox regression adjusted for age, diabetes, anterior MI, peak troponin, and LVEF, both T0 IL-1β (HR 1.42 per SD increase, 95% CI 1.18–1.71, p<0.001) and T6 IL-6 (HR 1.58 per SD, 95% CI 1.30–1.92, p<0.001) independently predicted MACE. The combination of these cytokines improved risk reclassification (net reclassification improvement 0.32, 95% CI 0.15–0.49, p<0.001).

Network analysis revealed more extensive pro-inflammatory connectivity in MACE patients, with stronger correlations among IL-6, IL-8, and TNF-α (all $r > 0.65$, $p < 0.001$ after correction). In contrast, no-MACE patients showed stronger negative correlations between IL-10 and pro-inflammatory cytokines.

Cytokines and myocardial recovery

In the MRI subset (n=180), patients with greater IL-6 reduction between T6 and T72 showed better LVEF recovery at 6 months (β=0.28, p=0.002). Elevated T72 IL-18 was associated with larger final infarct size (β=0.24, p=0.007).

Discussion

Our study provides three key advances in understanding the cytokine response to STEMI. First, we establish that cytokine networks, rather than isolated mediators, define the inflammatory phenotype after infarction (11). The coordinated elevation of IL-1β, IL-6, and IL-8, accompanied by attenuated IL-10 and IL-1ra, characterizes a high-risk inflammatory state. Second, we demonstrate that cytokine measurements at presentation (IL-1β) and early after reperfusion (IL-6) offer incremental prognostic information beyond traditional markers (12). Third, our temporal data suggest specific therapeutic windows – early IL-1β inhibition and later IL-6 modulation might be optimal (13).

Prior clinical studies in acute myocardial infarction have predominantly focused on the measurement of individual inflammatory biomarkers at isolated time points, demonstrating associations with infarct severity, ventricular dysfunction, and adverse outcomes. Elevated circulating levels of IL-6 and CRP early after acute MI have been associated with larger infarct size and poorer left ventricular function, and CRP remains strongly prognostic

for remodeling and clinical events in reperfused STEMI cohorts (14, 15). While informative, such static measurements provide only a snapshot of systemic inflammation and do not capture the temporal dynamics or interdependence of cytokine responses. In contrast, emerging work emphasizes the complexity of post-MI inflammatory networks and the need for dynamic, multi-marker profiling to understand better coordinated immune responses and their relationship to tissue repair and clinical outcomes (16). The present study extends these approaches by adopting a longitudinal, network-based framework, enabling the characterization of temporal cytokine trajectories and coordinated inflammatory signatures over time, which may reveal emergent patterns not discernible from isolated biomarker measurements.

The elevated IL-1β at presentation in MACE patients is particularly noteworthy. This suggests pre-existing inflammasome activation, potentially from unstable plaques or comorbidities, that amplifies reperfusion injury (17). This aligns with the CANTOS findings and supports very early IL-1β inhibition (7). The sustained IL-6 elevation in MACE patients may suggest failure to resolve inflammation, potentially driven by impaired negative feedback mechanisms (18).

In addition to IL-1β-targeted therapy (e.g., CANTOS), other immunomodulatory strategies have been tested in cardiovascular disease and may relate to the inflammatory profiles observed in this study. Colchicine, a long-used anti-inflammatory agent that inhibits microtubule polymerization and attenuates NLRP3 inflammasome activation as well as neutrophil recruitment and activity, has been shown to reduce cardiovascular events in chronic coronary disease and post-MI settings in randomized trials. However, results vary, and its benefit in acute MI remains under active investigation (19). The elevated IL-8 and other neutrophil-associated cytokines seen in our cohort may conceivably identify patients with heightened neutrophil-driven inflammation who could derive differential benefit from upstream inflammasome modulation, an idea that warrants targeted prospective study. Furthermore, IL-6 receptor blockade (e.g., tocilizumab) and other IL-6-targeted agents have been explored in early clinical and mechanistic studies given IL-6's central role in post-MI inflammation and downstream acute-phase responses (20).

The attenuated IL-10 and IL-1ra responses in MACE patients highlight deficient counter-regulation. IL-1ra, the natural antagonist of IL-1 signaling, was significantly lower despite higher IL-1β, creating a favorable ratio for IL-1-mediated injury (21). Therapeutic augmentation of these anti-inflammatory pathways warrants investigation (22).

Although inflammatory cytokines demonstrated prognostic relevance in the present study, their immediate clinical implementation in acute STEMI care remains challenging. Several studies have reported that elevated cytokines such as IL-6, CRP, and TNF-α are associated with greater infarct severity and poorer short-term outcomes in patients with STEMI, supporting their role as risk stratification tools in research and prognostic models (23). However, currently available multiplex cytokine platforms, including electrochemiluminescence-based assays and other laboratory immunoassays, require centralized laboratory infrastructure and are not designed for rapid point-of-care use (24). Consequently, the primary translational relevance of these findings lies in their potential application within centralized laboratory testing frameworks, particularly in clinical trials aimed at biomarker-guided risk stratification or targeted anti-inflammatory interventions, rather than in real-time decision-making at the bedside.

Although several cytokines showed statistically significant discrimination for the studied outcomes, the corresponding AUC values were moderate. This level of discrimination suggests that single inflammatory biomarkers alone may have limited standalone clinical utility for individual risk stratification. However, the primary objective of the present study was not to propose isolated cytokines as independent prognostic tools, but rather to evaluate their incremental prognostic value beyond established clinical parameters. In this context, the observed improvements in net reclassification indices indicate that incorporation of selected cytokines meaningfully enhanced risk classification when added to baseline models. These findings support the role of inflammatory biomarkers as complementary components within multivariable prognostic frameworks, rather than as solitary predictors.

Limitations include a single-center design and the absence of healthy controls. While we standardized sampling times, individual variations in symptom onset-to-reperfusion times introduce variability. Several limitations merit consideration. Patients presenting with cardiogenic shock were excluded. While this approach reduced confounding from profound systemic hypoperfusion, catecholamine exposure, and multi-organ failure – factors known to induce disproportionate cytokine activation – it limits the external validity of our findings. Consequently, the observed cytokine trajectories and network signatures may not be generalizable to the sickest STEMI patients, who represent a clinically important, high-risk subgroup. Future multicenter studies should specifically evaluate whether the cytokine network behaves differently, whether prognostic thresholds differ in cardiogenic shock,

and whether distinct inflammatory phenotypes exist in this population. Larger multicenter studies with standardized protocols are needed.

Conclusion

The CYTORE-AMI study demonstrates that dynamic cytokine profiling provides patho-physiological insight and prognostic stratification in STEMI. Early IL-1β and sustained IL-6 elevations with blunted anti-inflammatory responses characterize patients at the highest risk. These findings support integrating cytokine networks into risk assessment algorithms and provide biomarkers for targeted immunomodulatory therapy in acute myocardial infarction.

Funding

This work was supported in part by the Science and Technology Plan of the Jiangxi Provincial Health Commission (20204702).

Conflict of interest statement

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

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Recieved: January 11, 2026
Accepted: February 02, 2026