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RESEARCH ARTICLE

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Circulating tumor necrosis factor-α, interleukin-1β, and interleukin-17A estimates increased major adverse cardiac event risk in acute myocardial infarction patients

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Abstract

Background: Inflammatory cytokines are implicated in the development of atherosclerosis and cardiomyocyte injury during acute myocardial infarction (AMI). This study aimed to investigate the correlation of eight common inflammatory cytokines with major adverse cardiac event (MACE) risk and further establish a prognostic model in AMI patients.

Methods: Serum samples of 210 AMI patients and 20 angina pectoris patients were, respectively, collected at admission, to detect tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-17A, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM-1) via enzyme-linked immunosorbent assay.

Results: TNF-α, IL-6, IL-8, IL-17A, VCAM-1, and ICAM-1 were elevated (all $p < 0.050$); IL-10 ($p = 0.009$) was declined; IL-1β ($p = 0.086$) was not varied in AMI patients compared with angina pectoris patients. TNF-α ($p = 0.008$), IL-17A ($p = 0.003$), and VCAM-1 ($p = 0.014$) were elevated in patients with MACE occurrence compared to patients without MACE occurrence; meanwhile, they possessed a relatively good value for identifying MACE risk via receiver-operating characteristic (ROC) analysis. Subsequent multivariate logistic regression analysis revealed that the independent risk factors for MACE contained TNF-α (odds ratio (OR) = 1.038, $p < 0.001$), IL-1β (OR = 1.705, $p = 0.044$), IL-17A (OR = 1.021, $p = 0.009$), history of diabetes mellitus (OR = 4.188, $p = 0.013$), history of coronary heart disease (OR = 3.287, $p = 0.042$), and symptom-to-balloon time (OR = 1.064, $p = 0.030$), whose combination disclosed a satisfying prognostic value for MACE risk (area under the curve: 0.877, 95% CI: 0.817–0.936).

Conclusion: Elevated levels of serum TNF-α, IL-1β, and IL-17A independently correlated with MACE risk in AMI patients, which perhaps provide novel auxiliary for AMI prognostic prediction.

Jing Guo and Zhenfeng Hu contributed equally to this work.

KEYWORDS
acute myocardial infarction, biomarker, inflammatory cytokines, major adverse cardiac event, prognostic value

1 | INTRODUCTION

Acute myocardial infarction (AMI) is a common coronary artery disease, characterized by insufficient blood supply-induced myocardial injury and cardiomyocyte apoptosis.[1,2] Concerning the epidemiology of AMI, there are approximately 7.29 million AMI cases in 2015 worldwide, meanwhile, the in-hospital mortality of AMI patients ranges from 4% to 30%.[3–5] Of note, despite the administration of reperfusion therapies and postsurgery medications, the overall outcome of AMI patients is still unfavorable.[6,7] Therefore, exploring useful prognostic biomarkers is necessary for identifying AMI patients at high risk of inferior outcomes, providing more clinical evidence for clinicians to make proper treatment strategies timely.

Inflammation facilitates the initiation and development of atherosclerosis, and the latter is one of the core pathogenetic factors for AMI; meanwhile, inflammation worsens ischemic injury of cardiomyocytes and further exacerbates AMI severity.[8,9] Subsequently, inflammatory cytokines are supposed to be potential biomarkers for predicting AMI prognosis, which arise the interest of several researchers.[10–12] For instance, one previous study supports that elevated interleukin (IL)-1β is associated with increased coronary lesion severity and poor prognosis in AMI patients.[10] Another study shows that IL-6 possesses good predictive value for major adverse cardiac event (MACE) in ST-segment elevation myocardial infarction (STEMI) patients.[11] Nonetheless, the previous studies have either explored only a minority of inflammatory cytokines or only conducted in STEMI patients; the prognostic value of inflammatory cytokine patterns in AMI patients is rarely explored comprehensively.

Hence, this study quantified eight inflammatory cytokines in AMI patients, aiming to investigate their correlation with MACE risk and subsequently establish a comprehensive prognostic model based on these inflammatory cytokines and the main disease features of AMI.

2 | METHODS

2.1 | Subjects

A total of 210 AMI patients admitted from January 2018 to July 2021 were serially included in this prospective study. The inclusion criteria contained: (i) confirmed as AMI per the third universal definition of MI[13]; (ii) over 18 years old; (iii) received blood drawing immediately after admission. Patients who had the following conditions were ineligible: (i) previously underwent cardiothoracic surgery; (ii) complicated with systemic immune disease or inflammatory disease; (iii) had cancer or hematological malignant disease; (iv) pregnant or lactating female. Besides, 20 angina pectoris patients were enrolled as control. Enrollment criteria for angina pectoris patients contained: (i) diagnosis of angina pectoris[14]; (ii) more than 18 years old; (iii) had blood samples collected immediately after inclusion; (iv) without a history of AMI; (v) without cardiothoracic surgery, systemic immune disease, inflammatory disease cancer, and hematological malignancy; (vi) not during pregnancy and breastfeeding. The study had approval from the Institutional Review Board. Every subject or guardian had written informed consent.

2.2 | Obtention of data and samples

Acute myocardial infarction patients' features were recorded, including gender, age, body mass index, history of smoke, history of chronic comorbidities, STEMI, symptom-to-balloon time, biochemical indexes, and infarct size. Infarct size was evaluated on the 3rd day after admission per a previous study.[15] Peripheral blood samples of AMI patients and angina pectoris patients were collected after enrollment (within 1 h at admission). Next, serum samples were isolated and stored at 4°C.

2.3 | Processing of samples

The collected samples were used to detect the levels of inflammatory cytokines by enzyme-linked immunosorbent assay (ELISA) using commercial ELISA kits (Thermo Fisher Scientific). The inflammatory cytokines included intercellular adhesion molecule 1 (ICAM-1) (cat. no. BMS241), vascular cell adhesion molecule-1 (VCAM-1) (cat. no. KHT0601), IL-1β (cat. no. KHC0011), IL-6 (cat. no. KHC0061), IL-8 (cat. no. KHC0081), IL-10 (cat. no. KHC0101), IL-17A (cat. no. BMS2017), and tumor necrosis factor-alpha (TNF-α) (cat. no. BMS2034). All procedures were in strict accordance with the manufacturer's instructions.

2.4 | Follow-up and assessment

The AMI patients were followed up routinely every 2–3 months after discharge until April 2022. The median follow-up was 21.2 months, and the range was 1.3–46.9 months. MACE was assessed and the accumulating MACE rate was calculated. MACE was considered as a composite of death, MI, and repeat revascularization.[16]

2.5 | Statistics

SPSS v.26.1 (IBM Corp.) was adopted for statistics. GraphPad Prism v.6.01 (GraphPad Software Inc.) was adopted for figure mappings.

The Wilcoxon rank-sum test was utilized for comparative analysis. The Spearman's rank correlation test was utilized for correlation analysis. The Kaplan–Meier curve was mapped to display the accumulating MACE rate. The receiver operating characteristic (ROC) curves were adopted to assess the predicted ability for MACE risk. Univariate logistic regression analyses were used for screening the predictive factors of MACE risk, and forward-stepwise multivariate logistic regression analysis was performed for screening the independent factors with all factors in the univariate logistic regression analysis included. A p value <0.05 indicated significance.

3 | RESULTS

3.1 | Clinical characteristics of AMI patients

Two hundred and ten AMI patients were composed of 53 (25.2%) females and 157 (74.8%) males, whose mean age was 62.8 ± 10.7 years (Table 1). Besides, 149 (71.0%) patients were assessed as STEMI, and the other 61 (29.0%) patients were recognized as non-STEMI (NSTEMI). The median (interquartile range (IQR)) symptom-to-balloon time was 4.3 (2.3–12.6) hours; the median (IQR) infarct size was 21.0% (16.0%–28.0%). Detailed AMI patients' information was exhibited in Table 1.

TABLE 1 Clinical characteristics of AMI patients.

Items	AMI patients (N = 210)
Age (years), mean ± SD	62.8 ± 10.7
Gender, no. (%)	
Female	53 (25.2)
Male	157 (74.8)
BMI (kg/m^2), mean ± SD	24.9 ± 3.2
History of smoke, no. (%)	99 (47.1)
History of hypertension, no. (%)	145 (69.0)
History of hyperlipidemia, no. (%)	86 (41.0)
History of diabetes mellitus, no. (%)	51 (24.3)
History of coronary heart disease, no. (%)	91 (43.3)
NSTEMI, no. (%)	61 (29.0)
STEMI, no. (%)	149 (71.0)
Symptom-to-balloon time (hours), median (IQR)	4.3 (2.3–12.6)
WBC (10^9/L), median (IQR)	10.4 (8.3–13.0)
FBG (mmol/L), median (IQR)	5.5 (4.6–6.3)
Scr (μmol/L), median (IQR)	78.2 (68.6–88.9)
TG (mmol/L), median (IQR)	1.8 (1.0–2.5)
TC (mmol/L), median (IQR)	4.7 (3.9–5.4)
LDL-C (mmol/L), median (IQR)	3.3 (2.6–3.9)
HDL-C (mmol/L), median (IQR)	0.9 (0.8–1.1)
CRP (mg/L), median (IQR)	5.7 (4.0–7.6)
cTnI (ng/mL), median (IQR)	3.7 (2.9–5.6)
CK-MB (ng/mL), median (IQR)	32.1 (19.0–48.4)
Infarct size (%), median (IQR)	21.0 (16.0–28.0)

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTnI, cardiac troponin I; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; Scr, serum creatinine; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

3.2 | Comparison of inflammatory cytokines between AMI and angina pectoris patients

TNF-α (p = 0.006), IL-6 (p = 0.011), IL-8 (p = 0.029), IL-17A (p = 0.008), VCAM-1 (p < 0.001), and ICAM-1 (p = 0.010) were elevated, while IL-10 (p = 0.009) was declined in AMI patients compared with angina pectoris patients; moreover, IL-1β (p = 0.086) was of no difference between AMI and angina pectoris patients (Table 2).

3.3 | Prognostic value of inflammatory cytokines in AMI patients

The 1-, 2-, and 3-year accumulating MACE rates of AMI patients in this study were 4.1%, 9.9%, and 17.6%, respectively (Figure 1). TNF-α (p = 0.008), IL-17A (p = 0.003), and VCAM-1 (p = 0.014) were elevated in patients with MACE occurrence compared to patients without MACE occurrence; while IL-1β (p = 0.071), IL-6 (p = 0.231), IL-8 (p = 0.182), IL-10 (p = 0.564), and ICAM-1 (p = 0.076) were not varied between patients with and without MACE occurrence (Figure 2A). Furthermore, the ROC curves showed that IL-17A (area under the curve (AUC): 0.701, 95% confidence interval (CI): 0.583–0.818) possessed good value for identifying MACE risk; TNF-α (AUC: 0.680, 95% CI: 0.537–0.823) and VCAM-1 (AUC: 0.667, 95% CI: 0.552–0.782) only presented a weak potency for predicting MACE risk (Figure 2B,C). Besides, other inflammatory cytokines (including IL-1β, IL-6, IL-8, IL-10, and ICAM-1) could not identify MACE risk.

Moreover, IL-17A and VCAM-1 were elevated in patients with MACE occurrence (vs. without MACE occurrence) within 1, 2, and 3 years (all p < 0.050); they both possessed a favorable value for predicting 1-, 2-, and 3-year MACE risk via ROC analysis. TNF-α was increased in patients with MACE occurrence (vs. without MACE occurrence) within 2 and 3 years (both p < 0.050), with a pleasing predictive value on 2- and 3-year MACE risk revealed by ROC curves, but it could not estimate 1-year MACE occurrence (Table 3).

3.4 | Independent prognostic factors in AMI patients

The univariate logistic regression analysis showed that TNF-α (p < 0.001), IL-1β (p = 0.021), IL-8 (p = 0.031), IL-17A (p = 0.007),

TABLE 2 Comparison of inflammatory cytokines between AMI patients and angina pectoris patients.

	AMI patients ($N = 210$)			Angina pectoris patients ($N = 20$)			
Items	Median	IQR	Range	Median	IQR	Range	p Value
TNF-α (pg/mL)	57.2	46.5–74.8	33.2–159.8	44.7	38.8–63.2	22.3–75.6	0.006
IL-1β (pg/mL)	1.7	1.1–2.4	0.4–5.0	1.5	0.6–1.9	0.2–3.6	0.086
IL-6 (pg/mL)	23.7	20.0–30.0	11.7–78.9	18.9	13.0–27.0	7.8–39.6	0.011
IL-8 (pg/mL)	47.5	36.4–63.2	19.5–143.8	38.5	28.0–57.4	19.8–88.2	0.029
IL-10 (pg/mL)	92.0	69.6–120.9	40.8–215.6	120.4	80.6–158.7	42.0–231.8	0.009
IL-17A (pg/mL)	58.8	45.7–82.9	26.4–205.3	45.7	32.2–69.1	25.1–96.7	0.008
VCAM-1 (ng/mL)	734.0	599.3–980.2	315.7–2389.5	518.4	381.5–728.7	269.2–1000.9	<0.001
ICAM-1 (ng/mL)	142.7	108.6–190.3	52.7–515.3	112.1	83.1–151.1	48.1–252.6	0.010

Abbreviations: AMI, acute myocardial infarction; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; IQR, interquartile range; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1.

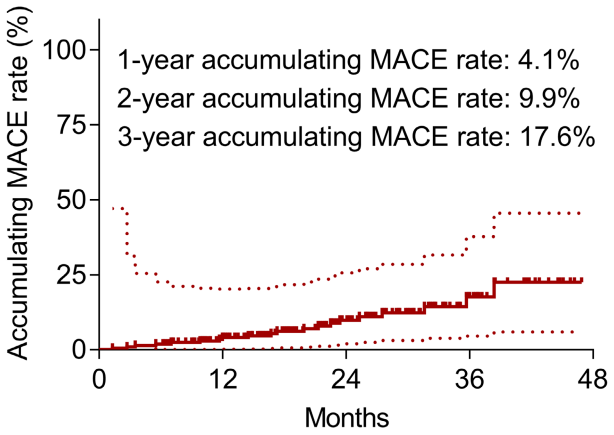


FIGURE 1 One-, two-, and three-year accumulating MACE rates in AMI patients. The dots represented the upper and lower limits of the 95% CI.

VCAM-1 ($p = 0.005$), ICAM-1 ($p = 0.010$), age ($p = 0.013$), history of diabetes mellitus ($p = 0.028$), serum creatinine (Scr) ($p = 0.044$), total cholesterol (TC) ($p = 0.014$), low-density lipoprotein cholesterol (LDL-C) ($p = 0.024$), C-reactive protein (CRP) ($p = 0.003$), cardiac troponin I (cTnI) ($p = 0.043$), and infarct size ($p = 0.018$) were positively correlated with MACE occurrence. After adjusted by the multivariate logistic regression analysis, the independent risk factors for MACE contained TNF-α ($p < 0.001$), IL-1β ($p = 0.044$), IL-17A ($p = 0.009$), history of diabetes mellitus ($p = 0.013$), history of coronary heart disease ($p = 0.042$), and symptom-to-balloon time ($p = 0.030$) (Table 4).

Additionally, the aforementioned independent factors were combined to build a prognostic model, which disclosed a satisfying value for identifying MACE risk in AMI patients (AUC: 0.877, 95% CI: 0.817–0.936, Figure 3).

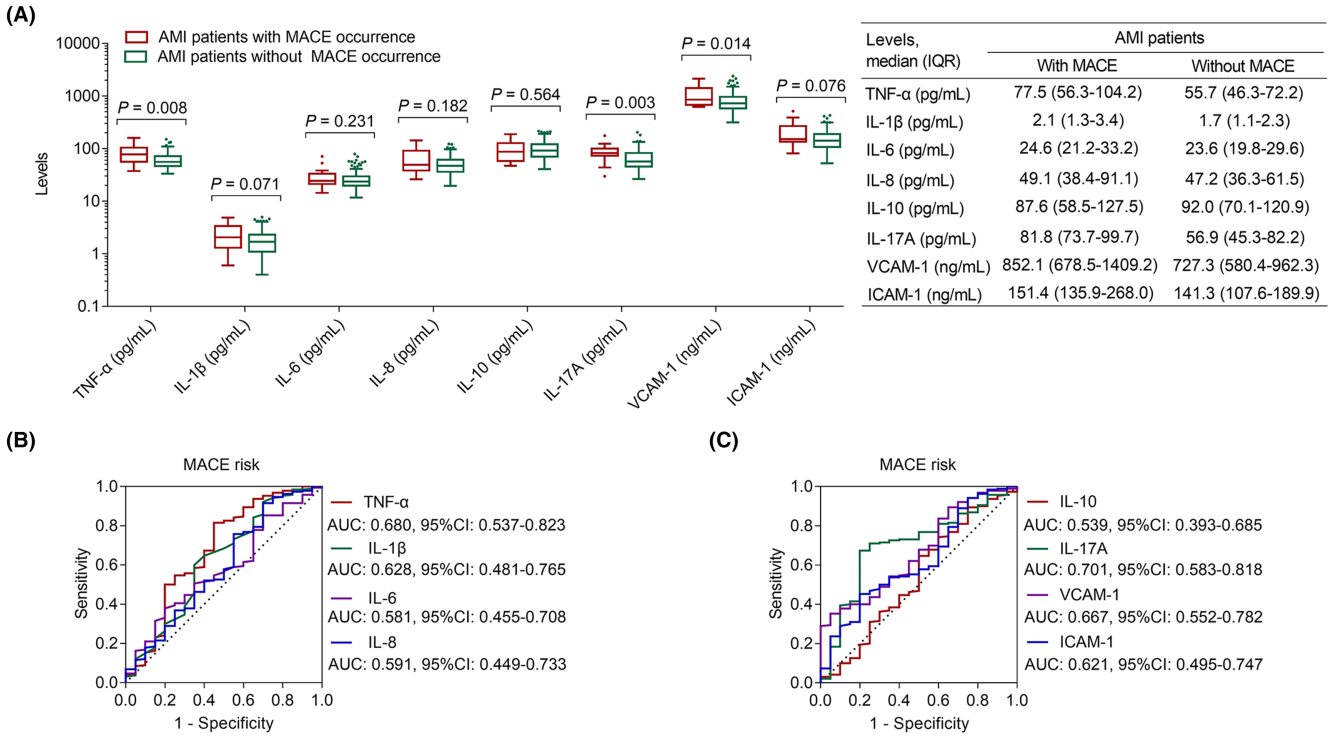
Furthermore, the combination of all inflammatory cytokines possesses a relatively good predicting value for MACE risk (AUC: 0.790, 95% CI: 0.686–0.894, Figure S1). The combination of TNF-α, IL-1β, and IL-17A exerted a moderate predicting value for MACE risk (AUC: 0.778, 95% CI: 0.668–0.889, Figure S2).

3.5 | Correlation of TNF-α, IL-1β, IL-17A with lipid indexes in AMI patients

TNF-α was positively linked with TG ($p = 0.022$), TC ($p = 0.005$), and LDL-C ($p = 0.002$), but it was not linked with HDL-C ($p = 0.405$); IL-1β was not related to TG ($p = 0.636$), TC ($p = 0.829$), LDL-C ($p = 0.455$), or HDL-C ($p = 0.406$); IL-17A was positively associated with LDL-C ($p = 0.033$), while it was not correlated with the other three lipid indexes (TG, TC, and HDL-C) (all $p > 0.050$) (Table S1).

4 | DISCUSSION

Considering that the etiology of AMI contains a characteristic inflammatory infiltrate, TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-17A, VCAM-1, and ICAM-1 are mostly recognized to involve in the initiation and development of AMI, and their abnormal levels have been explored in AMI patients in some studies.[11,17–20] For instance, one prior study discloses that compared with angina pectoris patients, IL-6 is increased in AMI patients, while IL-10 is of no difference.[17] Another study exhibits that IL-17 is elevated, while IL-10 is declined in AMI patients compared with the controls.[18] Although the included eight inflammatory cytokines in the current study were quite common, limited evidence has comprehensively explored their levels in AMI patients. Therefore, the current study was further conducted to clarify the aberrant level of the aforementioned eight inflammatory cytokines in AMI patients, which suggested that TNF-α, IL-6, IL-8, IL-17A, VCAM-1, and ICAM-1 were elevated, but IL-10 was declined in AMI patients compared with angina pectoris patients. The possible reasons were those: (i) Atherosclerosis in AMI patients would induce leukocyte infiltration and chronic inflammation.[21–23] (ii) The severe artery stenosis or occlusion condition and the subsequent myocardial ischemia promoted the release of proinflammatory cytokine in neutrophils and further exacerbated the acute inflammatory pattern in AMI patients.[19,24] (iii) Macrophage, known to be a major contributor of inflammatory response, dominated the leukocyte population



Levels, median (IQR)	AMI patients	
	With MACE	Without MACE
TNF-α (pg/mL)	77.5 (56.3-104.2)	55.7 (46.3-72.2)
IL-1β (pg/mL)	2.1 (1.3-3.4)	1.7 (1.1-2.3)
IL-6 (pg/mL)	24.6 (21.2-33.2)	23.6 (19.8-29.6)
IL-8 (pg/mL)	49.1 (38.4-91.1)	47.2 (36.3-61.5)
IL-10 (pg/mL)	87.6 (58.5-127.5)	92.0 (70.1-120.9)
IL-17A (pg/mL)	81.8 (73.7-99.7)	56.9 (45.3-82.2)
VCAM-1 (ng/mL)	852.1 (678.5-1409.2)	727.3 (580.4-962.3)
ICAM-1 (ng/mL)	151.4 (135.9-268.0)	141.3 (107.6-189.9)

FIGURE 2 TNF-α, IL-17A, and VCAM-1 possessed good prognostic value for MACE risk in AMI patients. Comparison of inflammatory cytokines between AMI patients with and without MACE occurrence (A). The ROC curves of TNF-α, IL-1β, IL-6, and IL-8 for predicting MACE risk in AMI patients (B). The ROC curves of IL-10, IL-17A, VCAM-1, and ICAM-1 for predicting MACE risk in AMI patients (C).

in atherosclerotic plaques and secreted several inflammatory cytokines (such as TNF-α, IL-6, IL-8, etc.) in AMI patients.[25,26] In that case, the proinflammatory cytokines (TNF-α, IL-6, IL-17A, IL-8, ICAM-1, and VCAM-1) were elevated in AMI patients than those in angina pectoris patients, while the anti-inflammatory cytokine (IL-10) presented a reverse trend. Besides, it was worth to mention that: the current study enrolled angina pectoris patients as controls rather than healthy controls were in order to evaluate the inflammatory cytokine level in AMI patients and to remove the interference of other cardiac complications on the results.

Concerning the prognostic value of inflammatory cytokines for MACE risk in AMI patients, one previous study displays that IL-6 and IL-8 are positively linked with the emergence of MACE in AMI patients.[27] Another study finds that VCAM-1 and IL-17A are independent risk factors for MACE in STEMI patients.[28] Partially consistent with the former study, this study noticed that TNF-α, IL-1β, and IL-17A were independently linked with increased MACE risk in AMI patients. Probable reasons were listed as follows: (i) TNF-α, IL-1β, and IL-17A triggered the development of atherosclerotic plaque and vascular lesions, which greatly increased the infarction degree and MACE risk in AMI patients.[29–31] (ii) TNF-α, IL-1β, and IL-17A were considered as proinflammatory mediators that elicited the acute phase response and aggravated ischemia–reperfusion injury, while the latter factors would lead to poor prognosis in AMI patients.[32,33] (iii) Excessive inflammatory response limited the improvement in left ventricular function, leading to an inferior prognosis in AMI patients.[24,34] (iv) The secretion of proinflammatory cytokines (such as TNF-α and IL-1β) would induce hypoxic condition and lead to cellular death, which inhibited the potential of stem cells for regenerating the injured myocardium; subsequently, the prognosis of AMI patients was impacted.[35] Combining the above four aspects, TNF-α, IL-1β, and IL-17A were therefore independent predicting factors for MACE risk in AMI patients. Moreover, it was noticed that VCAM-1 correlated with AMI prognosis, while ICAM-1 did not, which could be explained by that: VCAM-1 facilitated endothelial dysfunction of cardiovascular and increased the risk of plaque fragmentation, it played a more vital and direct role in AMI patients compared with ICAM-1.[36] Hence, it was observed that only VCAM-1 was associated with AMI prognosis, while ICAM-1 was not linked with the prognosis.

Apart from the aforementioned inflammatory cytokines (TNF-α, IL-1β, and IL-17A), three disease features (the history of diabetes mellitus, history of coronary heart disease, and increased symptom-to-balloon time) were also recognized as the independent prognostic factors for MACE risk in AMI patients, which were pooled to establish a prognostic model. Based on the ROC curve, it was noticed that the comprehensive model exhibited excellent predictive potency on MACE risk with an AUC value of 0.877, which might provide more assistance in risk stratification and management for AMI patients, clinically. While further studies were warranted to validate or refine the prognostic model.

A few limitations of this study should be acknowledged. First, the inflammatory level would significantly change after the acute phase, while this study only collected the serum samples of AMI patients at admission, and the vertical change of inflammatory cytokines during

TABLE 3 Comparison of inflammatory cytokines between AMI patients with and without MACE occurrence.

	Inflammatory cytokines, median (IQR)							
Items	**TNF-α (pg/mL)**	**IL-1β (pg/mL)**	**IL-6 (pg/mL)**	**IL-8 (pg/mL)**	**IL-10 (pg/mL)**	**IL-17A (pg/mL)**	**VCAM-1 (ng/mL)**	**ICAM-1 (ng/mL)**
1-year MACE								
No	56.6 (46.5–74.5)	1.7 (1.1–2.4)	23.7 (20.0–30.0)	47.3 (36.3–62.5)	91.3 (69.6–120.9)	58.3 (45.5–82.4)	727.3 (596.5–966.7)	142.5 (108.3–190.3)
Yes	61.5 (47.0–98.8)	2.0 (1.0–3.8)	23.5 (19.2–31.1)	55.9 (38.7–86.3)	98.0 (58.4–127.5)	90.6 (79.4–119.9)	993.6 (768.0–1409.2)	146.0 (115.1–249.0)
p Value	0.380	0.639	0.884	0.332	0.991	0.002	0.021	0.687
AUC of ROC	0.592	0.549	0.485	0.601	0.501	0.825	0.741	0.542
95% CI	0.373–0.810	0.315–0.783	0.285–0.685	0.393–0.809	0.290–0.713	0.738–0.913	0.605–0.878	0.355–0.729
2-year MACE								
No	55.9 (46.3–72.7)	1.7 (1.1–2.4)	23.7 (19.9–29.9)	47.2 (36.3–61.6)	91.4 (69.9–120.8)	58.2 (45.5–82.3)	727.4 (583.8–961.8)	142.3 (108.1–190.0)
Yes	77.6 (57.9–105.8)	2.0 (1.1–2.8)	24.0 (20.7–30.7)	50.0 (37.6–93.1)	94.1 (55.9–133.1)	82.5 (76.8–108.8)	914.2 (692.7–1699.4)	146.5 (116.4–280.3)
p Value	0.029	0.450	0.869	0.271	0.695	0.008	0.009	0.299
AUC of ROC	0.669	0.558	0.513	0.585	0.530	0.706	0.703	0.581
95% CI	0.501–0.838	0.397–0.720	0.369–0.657	0.421–0.750	0.358–0.703	0.561–0.851	0.574–0.833	0.431–0.730
3-year MACE								
No	55.5 (46.2–72.0)	1.7 (1.1–2.4)	23.6 (19.8–29.6)	47.2 (36.3–61.5)	92.5 (70.2–120.8)	56.8 (45.4–82.2)	727.2 (581.2–961.8)	140.4 (107.8–189.9)
Yes	77.6 (57.9–105.8)	2.0 (1.3–3.3)	24.4 (21.1–33.2)	50.0 (37.6–93.1)	81.0 (56.3–133.1)	82.5 (76.8–100.0)	883.3 (692.7–1449.8)	153.5 (135.2–280.3)
p Value	0.003	0.136	0.250	0.178	0.525	0.002	0.007	0.064
AUC of ROC	0.704	0.604	0.580	0.594	0.544	0.718	0.689	0.629
95% CI	0.561–0.846	0.459–0.749	0.447–0.713	0.445–0.742	0.391–0.697	0.599–0.836	0.576–0.802	0.498–0.760

Abbreviations: AMI, acute myocardial infarction; AUC, area under the curve; CI, confidence interval; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; IQR, interquartile range; MACE, major adverse cardiac events; ROC, receiver-operating characteristics; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1.

TABLE 4 Logistic regression analysis for MACE risk among AMI patients.

Items	*p* Value	OR	95% CI	
			Lower	Upper
Univariate logistic regression analysis				
TNF-α	<0.001	1.031	1.013	1.048
IL-1β	0.021	1.645	1.079	2.509
IL-6	0.227	1.023	0.986	1.060
IL-8	0.031	1.020	1.002	1.039
IL-10	0.705	0.998	0.985	1.010
IL-17A	0.007	1.018	1.005	1.032
VCAM-1	0.005	1.001	1.000	1.002
ICAM-1	0.010	1.007	1.002	1.012
Age	0.013	1.065	1.013	1.119
Male	0.276	2.024	0.569	7.200
BMI	0.091	1.130	0.981	1.301
History of smoke	0.231	1.776	0.694	4.542
History of hypertension	0.272	1.891	0.607	5.898
History of hyperlipidemia	0.185	1.874	0.741	4.739
History of diabetes mellitus	0.028	2.883	1.120	7.419
History of coronary heart disease	0.120	2.108	0.823	5.395
STEMI vs. NSTEMI	0.354	1.714	0.549	5.353
Symptom-to-balloon time	0.370	1.021	0.976	1.068
WBC	0.169	1.093	0.963	1.240
FBG	0.150	1.323	0.904	1.938
Scr	0.044	1.024	1.001	1.049
TG	0.106	1.559	0.910	2.673
TC	0.014	1.680	1.109	2.545
LDL-C	0.024	1.628	1.068	2.483
HDL-C	0.547	0.551	0.079	3.832
CRP	0.003	1.189	1.062	1.330
cTnI	0.043	1.186	1.005	1.400
CK-MB	0.181	1.012	0.995	1.029
Infarct size	0.018	1.073	1.012	1.138
Multivariate logistic regression analysis				
TNF-α	<0.001	1.038	1.018	1.058
IL-1β	0.044	1.705	1.014	2.868
IL-17A	0.009	1.021	1.005	1.037
History of diabetes mellitus	0.013	4.188	1.351	12.977
History of coronary heart disease	0.042	3.287	1.046	10.332
Symptom-to-balloon time	0.030	1.064	1.006	1.126

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; CI, confidence interval; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTnI, cardiac troponin I; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac events; OR, odds ratio; Scr, serum creatinine; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; WBC, white blood cell.

the follow-up period in AMI patients remained unclear. Second, the mean age of AMI patients in this study was 62.8 ± 10.7 years, while AMI affected more and more younger populations in recent years; hence, a further study was warranted to determine the inflammatory cytokines in younger AMI patients.[37,38] Third, the present study determined eight common inflammatory cytokines in AMI patients, whereas many other inflammatory cytokines (such as transforming growth factor-beta (TGF-β), IL-8, IL-23, and other IL family members)

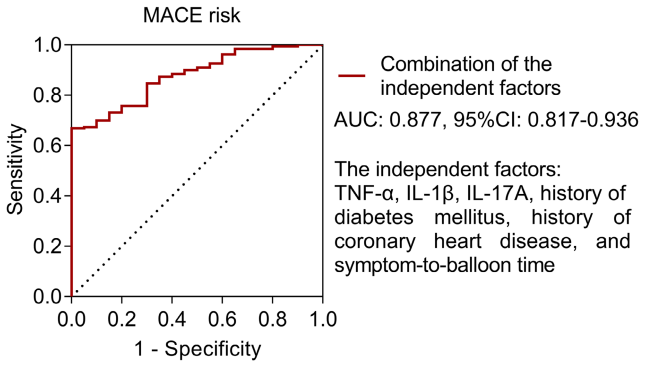


FIGURE 3 Combination of the independent factors for predicting MACE risk in AMI patients.

deserved further explorations in AMI patients. Fourth, only 20 patients in this study experienced MACE, which would reduce the statistical power. Fifth, the predictive model obtained in this study lacked further internal and external validation.

Collectively, increased serum TNF-α, IL-1β, and IL-17A levels are independently related to elevated MACE risk in AMI patients, whose combination with the history of diabetes mellitus, history of coronary heart disease, and increased symptom-to-balloon time possess satisfying prognostic discrimination for AMI. However, the verification in further large-scale studies is warranted.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

CONSENT TO PARTICIPATE

Every subject or guardian had written informed consent.

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REFERENCES

1. Anderson JL, Morrow DA. Acute myocardial infarction. *N Engl J Med*. 2017;376(21):2053-2064.
2. Heusch G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat Rev Cardiol*. 2020;17(12):773-789.
3. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70(1):1-25.
4. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639.
5. Castro-Dominguez Y, Dharmarajan K, McNamara RL. Predicting death after acute myocardial infarction. *Trends Cardiovasc Med*. 2018;28(2):102-109.
6. Harrington DH, Stueben F, Lenahan CM. ST-elevation myocardial infarction and non-ST-elevation myocardial infarction: medical and surgical interventions. *Crit Care Nurs Clin North Am*. 2019;31(1):49-64.
7. Johansson S, Rosengren A, Young K, Jennings E. Mortality and morbidity trends after the first year in survivors of acute myocardial infarction: a systematic review. *BMC Cardiovasc Disord*. 2017;17(1):53.
8. Libby P. Inflammation in atherosclerosis-no longer a theory. *Clin Chem*. 2021;67(1):131-142.
9. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. *Nat Rev Cardiol*. 2014;11(5):255-265.
10. Oprescu N, Micheu MM, Scafa-Udriste A, Popa-Fotea NM, Dorobantu M. Inflammatory markers in acute myocardial infarction and the correlation with the severity of coronary heart disease. *Ann Med*. 2021;53(1):1041-1047.
11. Scarlatescu AI, Micheu MM, Popa-Fotea N, et al. IL-6, IL-1RA and resistin as predictors of left ventricular remodelling and major adverse cardiac events in patients with acute ST elevation myocardial infarction. *Diagnostics (Basel)*. 2022;12(2):266.
12. Zykov MV, Barbarash OL, Kashtalap VV, Kutikhin AG, Barbarash LS. Interleukin-12 serum level has prognostic value in patients with ST-segment elevation myocardial infarction. *Heart Lung*. 2016;45(4):336-340.
13. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60(16):1581-1598.
14. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477.
15. Yun KH, Rhee SJ, Ko JS. Comparison of the infarct size between the loading of ticagrelor and clopidogrel in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Korean Circ J*. 2017;47(5):705-713.
16. Hong D, Choi KH, Song YB, et al. Prognostic implications of post-percutaneous coronary intervention neutrophil-to-lymphocyte ratio on infarct size and clinical outcomes in patients with acute myocardial infarction. *Sci Rep*. 2019;9(1):9646.
17. Dizdarevic-Hudic L, Kusljugic Z, Barakovic F, et al. Correlation between interleukin 6 and interleukin 10 in acute myocardial infarction. *Bosn J Basic Med Sci*. 2009;9(4):301-306.
18. Li Q, Liu Y, Xia X, et al. Activation of macrophage TBK1-HIF-1alpha-mediated IL-17/IL-10 signaling by hyperglycemia aggravates the complexity of coronary atherosclerosis: an in vivo and in vitro study. *FASEB J*. 2021;35(5):e21609.
19. Ong SB, Hernandez-Resendiz S, Crespo-Avilan GE, et al. Inflammation following acute myocardial infarction: multiple players, dynamic roles, and novel therapeutic opportunities. *Pharmacol Ther*. 2018;186:73-87.
20. Lino DOC, Freitas IA, Meneses GC, et al. Interleukin-6 and adhesion molecules VCAM-1 and ICAM-1 as biomarkers of post-acute myocardial infarction heart failure. *Braz J Med Biol Res*. 2019;52(12):e8658.
21. Casarotti ACA, Teixeira D, Longo-Maugeri IM, et al. Role of B lymphocytes in the infarcted mass in patients with acute myocardial infarction. *Biosci Rep*. 2021;41(2):BSR20203413.
22. Mora-Ruiz MD, Blanco-Favela F, Chavez Rueda AK, Legorreta-Haquet MV, Chavez-Sanchez L. Role of interleukin-17 in acute myocardial infarction. *Mol Immunol*. 2019;107:71-78.
23. Marchini T, Mitre LS, Wolf D. Inflammatory cell recruitment in cardiovascular disease. *Front Cell Dev Biol*. 2021;9:635527.

24. Chaar D, Dumont B, Vulesevic B, et al. Neutrophils pro-inflammatory and anti-inflammatory cytokine release in patients with heart failure and reduced ejection fraction. *ESC Heart Fail*. 2021;8(5):3855-3864.
25. Duncan SE, Gao S, Sarhene M, et al. Macrophage activities in myocardial infarction and heart failure. *Cardiol Res Pract*. 2020;2020:4375127.
26. Boyle JJ. Macrophage activation in atherosclerosis: pathogenesis and pharmacology of plaque rupture. *Curr Vasc Pharmacol*. 2005;3(1):63-68.
27. Kristono GA, Holley AS, Hally KE, et al. An IL-6-IL-8 score derived from principal component analysis is predictive of adverse outcome in acute myocardial infarction. *Cytokine X*. 2020;2(4):100037.
28. Zhang J, Xu H, Yao M, Jia H, Cong H. The abnormal level and prognostic potency of multiple inflammatory cytokines in PCI-treated STEMI patients. *J Clin Lab Anal*. 2022;36(11):e24730.
29. Mai W, Liao Y. Targeting IL-1beta in the treatment of atherosclerosis. *Front Immunol*. 2020;11:589654.
30. Poznyak AV, Bharadwaj D, Prasad G, Grechko AV, Sazonova MA, Orekhov AN. Anti-inflammatory therapy for atherosclerosis: focusing on cytokines. *Int J Mol Sci*. 2021;22(13):7061.
31. Abbate A, Toldo S, Marchetti C, Kron J, Van Tassell BW, Dinarello CA. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. *Circ Res*. 2020;126(9):1260-1280.
32. Kozel M, Kocka V, Lisa L, Budesinsky T, Tousek P. Immune-inflammatory response after bioresorbable vascular scaffold implantation in patients with acute myocardial infarction with ST elevation in a long-term perspective. *Heart Vessels*. 2019;34(4):557-563.
33. Algoet M, Janssens S, Himmelreich U, et al. Myocardial ischemia-reperfusion injury and the influence of inflammation. *Trends Cardiovasc Med*. 2022. doi:10.1016/j.tcm.2022.02.005 [Online ahead of print]
34. Shahrivari M, Wise E, Resende M, et al. Peripheral blood cytokine levels after acute myocardial infarction: IL-1beta- and IL-6-related impairment of bone marrow function. *Circ Res*. 2017;120(12):1947-1957.
35. Khodayari S, Khodayari H, Amiri AZ, et al. Inflammatory microenvironment of acute myocardial infarction prevents regeneration of heart with stem cells therapy. *Cell Physiol Biochem*. 2019;53(5):887-909.
36. Skerk V, Markotic A, Delic Brkljacic D, et al. The association of ventricular tachycardia and endothelial dysfunction in the setting of acute myocardial infarction with ST elevation. *Med Sci Monit*. 2013;19:1027-1036.
37. Gulati R, Behfar A, Narula J, et al. Acute myocardial infarction in young individuals. *Mayo Clin Proc*. 2020;95(1):136-156.
38. Zasada W, Bobrowska B, Plens K, et al. Acute myocardial infarction in young patients. *Kardiol Pol*. 2021;79(10):1093-1098.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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