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Original Article

TNF-α and IL-18 as diagnostic markers for acute myocardial infarction (AMI) and risk factors for AMI-related death

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Abstract: Background: This study aimed to explore the diagnostic values of tumor necrosis factor-α (TNF-α) and interleukin-18 (IL-18) in acute myocardial infarction (AMI). Methods: We recruited 48 patients with AMI at our hospital as the experimental group and 39 healthy examinees as the control group. Both groups were tested for serum TNF-α and IL-18 expressions using enzyme-linked immunosorbent assays and were analyzed for the diagnostic values of the TNF-α and IL-18 expressions for AMI using receiver operating characteristic (ROC) curves. Additionally, we explored the risk factors for AMI-related death using logistic regression. The experimental group had higher TNF-α and IL-18 expression levels compared with the control group ($P < 0.05$). According to the ROC curves, the cutoff values, sensitivities, and specialties for the AMI diagnosis were 0.679 pg/mL, 92.31%, and 70.83% for TNF-α and 133.50 pg/mL, 89.74%, and 68.75% for IL-18. Results: A multivariate analysis of survival revealed that the Killip classification, heart rate, and TNF-α and IL-18 levels were independent risk factors for AMI-related deaths ($P < 0.05$). TNF-α and IL-18 may have participated in the development and progression of AMI with comparatively acceptable sensitivities and specialties in its diagnosis based on their serum expression levels. Conclusions: the Killip classification, heart rate, and TNF-α and IL-18 levels are independent risk factors for AMI-related deaths and may be adopted as prediction indexes for evaluating patients' conditions and AMI prognoses.

Keywords: Acute myocardial infarction, TNF-α, IL-18, cardiovascular risk factors

Introduction

Coronary disease is the leading single cause of death [4] worldwide, with almost 60% of cases reported in developing countries, where the incidence and mortality rates continue to increase [5, 6]. The most severe consequence of coronary disease is myocardial infarction. Currently, approximately 290 million Chinese individuals have cardiovascular diseases, including approximately 2.5 million with myocardial infarction [7, 8]. Acute myocardial infarction (AMI) is a condition in which the blood supply is reduced or interrupted due to a narrow or blocked coronary artery, leading to acute myocardial ischemia and necrosis. The disease develops abruptly and progresses rapidly with a poor prognosis [3, 9], potentially resulting in cardiac dysfunction and sudden cardiac death.

Interleukin-18 (IL-18) and tumor necrosis factor-α (TNF-α) are cell factors that participate in various inflammatory reaction processes [1]. Animal experiments in recent years have proven that the microvascular dysfunction in the cardiac ischemia-reperfusion area is the result of an inflammatory reaction. Wu et al. [2] reported that patients with diastolic heart failure have comparatively high serum TNF-α and IL-6 expression levels. Additionally, AMI is thought to be an inflammatory reaction process to coronary artery intima injury, the rupture of unstable plaques, and the aggregation of adhesion factors due to external risks. AMI development and progression are closely associated with the rupture of unstable plaques, and inflammatory reactions are one of the major factors affecting plaque stability; thus, inflammatory reactions affect the development of AMI [10, 11]. Because interleukin-18 (IL-18) and tumor ne-

crosis factor-α (TNF-α) are cell factors that participate in AMI inflammatory reaction processes, the TNF-α and IL-18 levels in patients with AMI may be different than the levels in healthy people. However, studies on AMI diagnosis using serum TNF-α and IL-18 levels are limited [3].

Clinically, cardiac troponin (cTn) is the main AMI detection index, but its expression is reportedly elevated in the blood of patients with end-stage renal disease. Therefore, cTn can also be used as a biomarker of renal failure [12, 13], and exploring biomarkers that are closely related to AMI diagnosis can play a vital role in the timely diagnosis and treatment of the disease [14, 15].

In this study, we measured and discussed the expressions of TNF-α and IL-18 in patients with AMI and healthy people, their diagnostic values for AMI, and the risk factors of AMI-related deaths to provide references for its clinical treatment.

Materials and methods

General materials

We included 48 patients with AMI admitted to the Department of Cardiovascular Medicine at our hospital from February 2017 to February 2019 as the experimental group and compared them with healthy examinees who underwent physical examinations at our hospital concurrently. The experimental group comprised 33 men and 15 women with a mean age of 57.28 ± 10.59 years, and the control group comprised 28 men and 11 women with a mean age of 59.84 ± 11.34 years. All the patients provided informed consents to participate in the study, which was approved by the ethics committee of our hospital. The inclusion criteria were as follows: at least four of the ACC/AHA diagnosis criteria for AMI were met [16], with typical ischemic chest pain lasting for more than 30 min; the ECG had a characteristic dynamic evolution; the biochemical markers of myocardial necrosis complied with the characteristic changes of myocardial infarction; and the coronary arteriography revealed the applicability of PIC for infarction-related artery anatomy. Conversely, the exclusion criteria were as follows: previous histories of myocardial infarction; use of anticoagulants, glucocorticoids, and/or immunosuppressants; a history of personal or family mental disorders; a history of receiving percutaneous coronary angioplasty or stent implantation; a history of inflammation, diseases of the thrombi, tumor trauma, hepatic and renal insufficiency, concurrent autoimmune diseases, acute and chronic infections, hematological diseases, malignant tumors, and chronic kidney disease, abnormal hepatic functions, severe cardiac insufficiency with an EF of < 30%, trauma, and/or surgeries and a severe infection in the previous 3 months; or currently pregnant or lactating.

Instruments and reagents

In this study, we used TNF-α enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Jingkang Bioengineering Co., Ltd., China, JKSJ-1857), IL-18 ELISA kits (Shanghai Haling Biological Technology Co., Ltd., China, HL10423), and ELISA detectors (Molecular Devices, USA, SpectraMaxiD5).

Detection methods

Morning fasting blood samples were extracted from the veins of the control and experimental groups before thrombolysis and then centrifuged at 3000/min following the routine procedures. The samples to be tested and the test kits were removed from the refrigerator 30 min prior to the analysis to bring them to room temperature. The serum TNF-α and IL-18 expression levels were measured using ELISA according to the following procedures: standard pores, blank pores (blank control pores had no sample and ELISA reagents, but the other steps remained the same), and the sample pores were gathered; 40 μL of diluted sample solution was added into the sample pores on the ELISA plate, followed by 10 μL of the sample to be tested (diluted 5-fold), wherein the sample was added to the pore bottom without touching the walls, and then shaken gently. The plate was then sealed with a film and incubated at 37°C for 30 min, Next, a 30× concentrated cleaning solution was diluted 30-fold with distilled water for future use. After removing the sealing film and the liquid, the plate was dried, and some cleaning solution was added to each pore for washing. The cleaning solution was removed again 30 s after standing still. These steps were repeated five times, and then the plate was dried. Then, 50 μL of ELISA reagent

Table 1. Comparison of the clinicopathological data in the two groups [n (%)]/(x ± sd)

Factor	Experimental group (n = 48)	Control group (n = 39)	t/χ^2	*P* value
Gender			0.095	0.758
Male	33 (68.75)	28 (71.79)		
Female	15 (31.25)	11 (28.21)		
Age (years)	57.28 ± 10.59	59.84 ± 11.34	1.086	0.280
BMI (kg/m^2)	23.18 ± 1.94	23.86 ± 2.19	1.535	0.129
Domicile			0.171	0.679
Urban	39 (81.25)	33 (84.62)		
Rural	9 (18.75)	6 (15.38)		
Previous history of disease			1.531	0.675
Hypertension	15 (31.25)	16 (41.03)		
Diabetes	4 (8.33)	4 (10.26)		
Hyperlipidemia	8 (16.67)	6 (15.38)		
AMI	7 (14.58)	3 (7.69)		
History of alcohol drinking			1.056	0.304
Yes	8 (16.67)	10 (25.64)		
No	40 (83.33)	29 (74.36)		
History of smoking			0.183	0.669
Yes	35 (72.92)	30 (76.92)		
No	13 (27.08)	9 (23.08)		
Creatinine (μmol/L)	70.45 ± 12.59	71.26 ± 11.12	0.314	0.754
Total cholesterol (mmol/L)	4.34 ± 1.12	4.27 ± 0.97	0.308	0.759
Triglyceride (mmol/L)	1.88 ± 1.26	1.93 ± 1.02	0.200	0.842
Low-density lipoprotein (mmol/L)	2.47 ± 0.92	2.38 ± 0.84	0.472	0.638
Blood urea nitrogen (mmol/L)	6.25 ± 1.48	6.11 ± 1.17	0.481	0.632
cTn (ng/mL)	0.67 ± 0.28	0.09 ± 0.05	12.760	< 0.001

was added to all pores except the blank pores and incubated for 30 min before washing again. Next, 50 μL of developer A was added into each pore, followed by 50 μL of developer B, then shaken gently and stored in a lucifugal environment at 37°C to develop the color. Thereafter, 50 μL of stop buffer was added to each pore to terminate the reaction (the color turned from blue to yellow). The optical density was measured at a wavelength of 450 nm to calculate the concentrations of IL-18 and TNF-α.

Statistical analysis

The statistical analysis was performed using SPSS 21.0 (IBM Corp, Armonk, NY, USA), and the data were visualized using GraphPad Prism 7 (Softhead Inc., Shenzhen, China). For the numerical data expressed as x ± sd, comparison studies were conducted using independent-sample *t* tests; for the nominal data expressed as [n (%)], comparison studies were conducted using χ^2 tests. Furthermore, the diagnostic values of IL-18 and TNF-α in AMI were evaluated using receiver operating characteristic (ROC) curves, the 3-year survival of patients was analyzed using the Kaplan-Meier method, and the multivariate analyses were performed using logistic regression. For all the statistical comparisons, $P < 0.05$ was considered significant.

Results

Clinical materials of the two groups

The two groups showed no significant differences in terms of gender, age, domicile, body mass index (BMI), history of alcohol drinking, history of smoking, or marital status, and the creatinine, total cholesterol, and triglyceride levels were comparable between the two groups ($P > 0.05$, **Table 1**).

The TNF-α and IL-18 expression levels in the two groups

The ELISA results showed that the TNF-α and IL-18 expression levels in the experimental

Table 2. Comparison of the TNF-α and IL-18 expressions (x ± sd) in the two groups

Group	N	TNF-α (pg/mL)	IL-18 (pg/mL)
Experimental group	48	0.81 ± 0.29	153.21 ± 44.78
Control group	39	0.49 ± 017	97.19 ± 31.61
t	-	6.874	6.589
P value	-	< 0.001	< 0.001

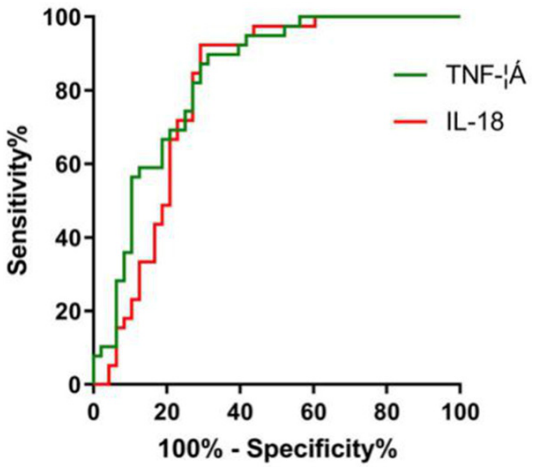

Figure 1. The ROC curve of the AMI diagnosis using TNF-α and IL-18. The AUC, cutoff value, sensitivity, and specialty were 0.801, 0.679 pg/mL, 92.31%, and 70.83% for the cervical carcinoma diagnoses based on the serum miR-214 levels and 0.832, 133.50 pg/mL, 89.74%, and 68.75% for the AMI diagnoses based on the serum IL-18 levels, respectively.

group were significantly elevated compared with the corresponding levels in the control group (P < 0.05, **Table 2** and **Figure 1**).

The diagnostic values of serum TNF-α and IL-18 in AMI-related death

An ROC curve describing the diagnosis of AMI based on the expressions of serum TNF-α and IL-18 was constructed. The AUC, cutoff value, sensitivity, and specialty were 0.801 (95% CI: 0.704-0.897), 0.679 pg/mL, 92.31%, and 70.83% for AMI diagnosis based on the serum TNF-α and 0.832 (95% CI: 0.747-0.918), 133.50 pg/mL, 89.74%, and 68.75% for AMI diagnosis based on the serum IL-18 (**Table 3** and **Figure 1**).

30-day survival of patients with AMI

The data from the 30-day survival of patients in the experimental group indicated that all patients were followed up. After 30 days, 11 died and 37 survived, for a of 77.08% survival (**Figure 2**).

Single-factor analysis of patient survival

On the basis of survival, the patients in the experimental group were further divided into the survival group (n = 37) and the death group (n = 11) for the collection of clinical materials and for the single-factor analysis. The analysis revealed that both groups showed no significant differences in terms of gender, BMI, previous history of disease, domicile, history of alcohol drinking, history of smoking, exercise habits, and triglyceride, creatinine, total blood urea nitrogen, and low-density lipoprotein levels (P > 0.05). However, they were statistically different in terms of age, Killip classification, heart rate, TNF-α, and IL-18 (P < 0.05) (**Table 4**).

Multivariate analysis of survival

Age, Killip classification, heart rate, TNF-α, and IL-18 were included and valued (**Table 5**) to move forward. Meanwhile, the LR was analyzed using a multivariate logistic regression. The results indicated that age was not an independent death factor affecting patient survival, but the Killip classification, heart rate, and TNF-α and IL-18 levels were independent death factors for patients with AMI (**Table 6**).

Discussion

AMI is a common cardiac disease typically reported in clinical emergency treatments and is a key study point in cardiovascular diseases [17, 18] because of its complicated nosogenesis. Though the mortality rate has dropped remarkably after coronary intervention and thrombolysis as a reperfusion therapy, the time window thereto is 3-6 h after the chest pain begins [19]. Therefore, the early diagnosis of AMI plays a vital role in reducing the mortality rate [20]. To date, the major clinical diagnostic models of AMI have included the observation of the clinical characteristics, imaging, and traditional hematological tests, such as CK-MB and cardiac troponin T, which, however, are time consuming for AMI diagnoses based on blood draws and result in a low sensitivity for early diagnosis. Hence, proper diagnostic indexes are particularly important [21, 22].

Table 3. Diagnostic value of the serum TNF-α and IL-18 in AMI

Diagnosis index	AUC	95% CI	Standard error	Cutoff value (pg/mL)	Sensitivity (%)	Specialty (%)
TNF-α	0.801	0.704-0.897	0.049	0.679	92.31	70.83
IL-18	0.832	0.747-0.918	0.044	133.50	89.74	68.75

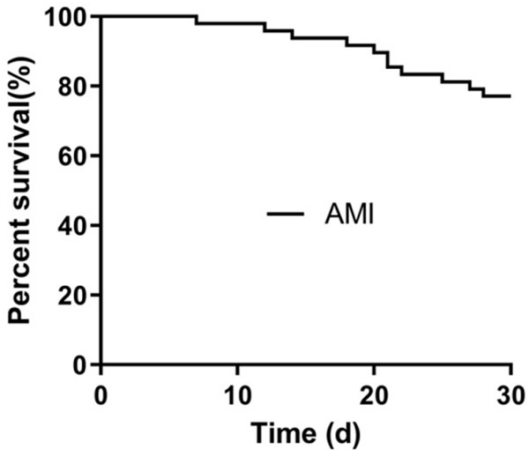

Figure 2. The 30-day survival of patients with AMI. Within 30 days, 11 patients died and 37 survived, for a survival rate of 77.08%.

AMI involves a complicated nosogenesis, and the inflammatory reaction plays an important role in the pathogenesis of atherosclerosis according to some previous studies [23]. TNF-α is a multifunctional inflammatory cell factor produced by activated monocytes/macrophages, with a considerable promoting effect for the formation and development of thrombi and atherosclerotic plaques and a close relationship with immunological reactions [24, 25]. Meanwhile, IL-18 is an important proinflammatory factor that can induce IFN-γ production to participate in the inflammatory reaction in atherosclerotic plaques, promote MMP expression in VSMCs and monocytes, accelerate the decomposition of extracellular matrix of plaques, and reduce the stability of atherosclerotic plaques [26]. In the present study, the expression levels of IL-18 and TNF-α in the serum of patients with AMI (experimental group) and healthy examinees (control group) were measured. The experimental group had higher serum IL-18 and TNF-α expression levels than the control group. Other similar studies also confirmed the close relationship between IL-18, TNF-α, and the development of AMI. For instance, Somasuntharam et al. [27] established an anti-inflammatory therapy for myocardial infarction by knocking out TNF-α with DNAzyme particles, Hua et al. [28] demonstrated the significant interactions between the TNF-αG-308A polymorphism and the AMI-related risks through a meta-analysis, and O'Brien et al. [29] revealed that IL-18 can be a treatment target for AMI and heart failure.

The diagnostic values of the serum TNF-α and IL-18 expression levels in AMI were demonstrated by a further analysis of the ROC curves, which indicated a sensitivity and a specialty of 92.31% and 70.83%, respectively, for the AMI diagnosis using serum TNF-α and 89.74% and 68.75%, respectively, for the AMI diagnosis using serum IL-18, thereby demonstrating the sensitivity and specialty of serum TNF-α and IL-18 in diagnosing AMI.

Risk factors related to AMI have always been gaining considerable interest in clinical studies, and their exploration plays a key role in preventing infections, controlling patients' conditions, and alleviating clinical syndromes. For instance, Sun et al. [30] demonstrated that the use of diuretics and postoperative low cardiac output syndrome were independent risk factors leading to acute renal injuries in patients with AMI who received a coronary artery bypass graft. Jin et al. [31] found that age, elevated CRP expression and NT-proBNF, and the elimination of reflow were risk factors causing atrial fibrillation in hospitalized patients with AMI. However, little attention has been paid to TNF-α and IL-18, which are the two risk factors for AMI-related death. In the current study, the experimental group reported a 30-day survival rate of only 77.08%; additionally, the multivariate survival analysis revealed that TNF-α and IL-18 were independent risk factors for AMI-related deaths. Moreover, Formanowicz et al. [32] found that IL-18 was an important indicator and a predictive factor of cardiovascular death in a 2-year follow-up, and Kitagawa et al. [33] discovered that TNF-α can possibly be relied on to predict the deterioration of left ventricular systolic function, heart failure, and death, so TNF-α and IL-18 may contribute significantly to the development and prognosis of AMI.

Table 4. Comparison of the single-factor analysis of survival in the two groups

Factor	Survival group (n = 37)	Death group (n = 11)	t/c^2	*P* value
Age (years)			5.779	0.016
≥ 60	15 (40.54)	9 (81.82)		
< 60	22 (59.46)	2 (18.18)		
Gender			0.385	0.535
Male	24 (64.86)	6 (54.55)		
Female	13 (35.14)	5 (45.45)		
Previous history of disease				
Hypertension	11 (29.73)	4 (36.36)	0.174	0.677
Diabetes	3 (8.11)	1 (9.09)	0.011	0.918
Hyperlipidemia	4 (10.81)	2 (18.18)	0.421	0.516
AMI	4 (10.81)	1 (9.09)	0.027	0.870
Domicile			0.637	0.425
Urban	22 (59.46)	8 (72.73)		
Rural	15 (40.54)	3 (27.27)		
History of alcohol drinking			0.105	0.746
Yes	25 (67.57)	8 (72.73)		
No	12 (32.43)	3 (27.27)		
History of smoking			0.174	0.677
Yes	26 (70.27)	7 (63.64)		
No	11 (29.73)	4 (36.36)		
Exercise habit			1.134	0.287
Yes	13 (35.14)	2 (18.18)		
No	24 (64.86)	9 (81.82)		
BMI (kg/m^2)	23.19 ± 1.58	24.09 ± 1.43	1.692	0.097
Triglyceride (mmol/L)	1.94 ± 0.72	1.85 ± 0.88	0.346	0.731
Creatinine (μmol/L)	72.12 ± 12.18	71.26 ± 10.47	0.238	0.813
Blood urea nitrogen (mmol/L)	6.25 ± 1.48	6.64 ± 1.24	0.794	0.432
Low-density lipoprotein (mmol/L)	2.34 ± 0.82	2.18 ± 0.75	0.579	0.566
Killip classification			21.650	< 0.001
≥ class 3	4 (10.81)	9 (81.82)		
< class 3	33 (89.19)	2 (18.18)		
Heart rate (beats/min)	83.49 ± 12.49	93.73 ± 14.65	2.295	0.026
TNF-α (pg/mL)	0.75 ± 0.14	1.21 ± 0.29	7.305	< 0.001
IL-18 (pg/mL)	95.65 ± 32.17	161.18 ± 45.23	5.387	< 0.001

Table 5. Valuation table

Factor	Valuation
Age (years)	≥ 60 = 1, < 60 = 0
Killip classification	≥ class 3 = 1, < class 3 = 0
Heart rate (beats/min)	Raw data analysis in case of continuity variables
TNF-α (pg/mL)	Raw data analysis in case of continuity variables
IL-18 (pg/mL)	Raw data analysis in case of continuity variables
Death	Death = 1, survival = 0

The current study analyzed the serum expression levels of TNF-α and IL-18 in patients with AMI and healthy examinees and their roles in the diagnosis and prognosis of AMI. However,

Table 6. Multivariate analysis of survival

Factor	B	SE	Wald χ^2	OR (95% CI)	*P* value
Killip classification	0.656	0.174	7.524	2.91 (2.26-5.52)	0.006
Heart rate (beats/min)	0.714	0.289	12.114	3.63 (2.57-7.61)	< 0.01
TNF-α (pg/mL)	1.263	0.428	14.592	5.31 (3.41-7.58)	< 0.01
IL-18 (pg/mL)	1.178	0.329	15.554	3.67 (1.46-9.87)	< 0.01

the study had some weaknesses. The weaknesses include the failure to explore the regulation mechanism of TNF-α and IL-18 in AMI and the failure to study their roles in AMI monitoring and treatment. These gaps should be addressed in future studies.

Conclusions

In conclusion, TNF-α and IL-18 play a role in the development of AMI and may serve as new biomarkers for AMI and as independent risk factors for AMI-related death.

Disclosure of conflict of interest

None.

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