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Serum YKL-40 positively correlates with MMP-9 and CRP in patients with acute ST segment elevation myocardial infarction following emergency treatment

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Abstract

Objective: To investigate the role of YKL-40 in ST segment elevation myocardial infarction (STEMI) and its relationship to C-reactive protein (CRP) and matrix metalloproteinase-9 (MMP-9).

Methods: This prospective study included 358 STEMI patients who were sent to the Emergency Department of our hospital from April 2014 to December 2017. Serum levels of YKL-40, CRP and MMP-9 were determined using commercially available Enzyme linked immunosorbent assay (ELISA) kits. Major adverse cardiovascular events (MACE) and overall survival time were analyzed.

Results: GRACE scores ($P < .001$) and the levels of YKL-40 ($P < .001$), MMP-9 ($P < .001$), and CRP ($P < .001$) were significantly higher in deceased patients compared to those that survived. The levels of CRP ($P = .007$) and MMP-9 ($P = .022$) were significantly higher in the high YKL-40 group. The GRACE scores were also significantly elevated ($P = .011$, 95% CI 2.1 (-9.7 to -1.3)). Cumulative MACE rates and cardiac death rates were significantly higher in the high YKL-40 group ($P < .001$, 95% CI 3.9 (1.9–8.2)). Overall survival times were significantly longer in patients with lower YKL-40 levels ($P < .0001$).

Conclusion: Elevated YKL-40 levels positively correlate with CRP and MMP-9 levels and are associated with clinical outcomes including MACE and 6-month survival in STEMI patients.

Abbreviations: AMI = acute myocardial infarction, CRP = C-reactive protein, ELISA = enzyme linked immunosorbent assay, GRACE = Global Registry of Acute Coronary Events, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, MMP-9 matrix metalloproteinase-9, NSTEMI = non-ST segment elevation myocardial infarction, STEMI = ST segment elevation myocardial infarction.

Keywords: CRP, MMP-9, prognosis, STEMI, YKL-40

1. Introduction

Cardiovascular disease, one of the most severe diseases causing mortality and morbidity, has affected millions of people all over the world, accounting for almost 31% of deaths across the globe.[1,2] Acute myocardial infarction (AMI) is both a common and lethal disease that includes ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI)[3]. STEMI is a common cardiovascular disease associated with acute presentation of ischemic heart disease. Although STEMI is widely known and studied, the prevalence and incidence of STEMI worldwide are not well established. An early research showed the incidence of AMI decreased from 1987–2002 [4] but the mortality rates of STEMI patients remained high. The mortality rates of diabetic patients with STEMI are as high as 11.6% in a case-control study and was related to glucose levels.[5] A more recent study demonstrated the mortality rates of STEMI patients with atrial fibrillation were 22.7% amongst 14,329 patients in Korea.[6] Since AMI is typically sudden and severe, early diagnosis and treatment are important for infraction recovery. Thus, biomarkers for diagnosis and prognosis of AMI are important in the clinic.[7,8]

Studies have reported many biomarkers for AMI, such as creatine kinase MB (CK-MB),[9] troponin,[10] and NT-proBNP.[11] However, despite improved diagnostic methods, timely AMI treatment remains a problem in the clinic. A deeper understanding of the AMI mechanisms and its associated factors are still required for the identification of novel disease biomarkers. YKL-40, a member of the mammalian chitinase-like proteins, also known as chitinase-3-like-1,[12] is associated with many diseases, including diabetes,[13] stroke,[14] and

cancer.[15] It is also reported that YKL-40 is up-regulated during myocardial infarction.[16] However, the mechanisms of how YKL-40 influences AMI and its association with other known biomarkers including CRP and MMP-9 are unclear.

In this prospective study, we investigated the role of YKL-40 in STEMI patients and its association to CRP and MMP-9. These results may provide more clinical evidences for the diagnostic potential of YKL-40 in AMI.

2. Materials and methods

2.1. Patients and treatment

This prospective study included 358 STEMI patients who were sent to the Emergency Department of our hospital during April 2014 to December 2017. All patients were consecutively enrolled. The patients who met the inclusion criteria during the study period were all included. The diagnosis criteria of STEMI were defined as:

1. idiopathic chest pain >20 minutes and receiving oral glyceryl trinitrate did not release the pain;
2. typical ST segment elevation >1 mm in at least 2 contiguous leads;
3. transient increase in CK-MB or troponin I (TnI) higher than >2 times than the normal level.[17,18]

Patients with other severe diseases such as cancer, severe liver or renal disease, severe infection, and patients administered statins prior to the study were excluded. All patients received normal emergency treatment after admission. Treatments were performed according to local treatment guidelines for AMI.[19] Written informed consent was obtained from all patients. The study was approved by Ethic Committee of the Seventh Affiliated Hospital, Sun Yat-sen University.

2.2. Serum biomarkers

Blood samples were collected within 24 hours of admission. Serum levels of YKL-40 and other factors including C-reactive protein (CRP) and Matrix Metalloproteinase-9 (MMP-9) were determined using commercially available Enzyme linked immunosorbent assay (ELISA) kits (YKL-40 cat no. DC3L10, R & D Systems, Minneapolis, USA. CRP cat no. ab99995, Abcam Cambridge, MA, USA. MMP-9 cat no. ab246539, Abcam) according to the manufacturer's instructions.

2.3. Data collection and follow-up

The baseline characteristics of all patients were collected, including age, gender, body mass index (BMI), medical history (cardiovascular diseases, hypertension and diabetes), left ventricular ejection fraction (LVEF), and Global Registry of Acute Coronary Events (GRACE) risk score. Major adverse cardiovascular events (MACE) were defined as cardiovascular death, the recurrence of angina or malignant arrhythmia, re-hospitalization including surgical or percutaneous intervention. All deaths were recorded for survival analysis from admission to the end of the follow-up. Follow-up lasted 6 months.

2.4. Statistical analysis

Continuous data were expressed as mean ± SD or median (range) for normally and non-normally distributed data, respectively. Chi-Squared test was used to compare rates. Comparison between 2 groups was performed using a Student t test or Mann–Whitney U test. Spearman analysis was performed to analyze correlations. Kaplan–Meier curve was used for analysis of survival time. When P value <.05, it was considered as statistically significant. Data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, USA).

3. Results

3.1. Patient characteristics

A total of 358 STEMI patients were finally enrolled in the study, with mean age of 63.6 ± 7.1 years, and a mean follow-up duration of 6.9 ± 1.2 months (6–12 months). Amongst the patients, 31 died with mortality rates of 8.7%. As shown in Table 1, significant differences were observed regarding medical history, GRACE scores, and the levels of YKL-40 (P < .001), MMP-9 (P < .001), and CRP (P < .001) between deceased and surviving patients (P < .05 for all factors). No significant differences were observed for other indices.

3.2. Relationship between serum levels of YKL-40 and MMP-9 or CRP

Then, we determined the correlation amongst YKL-40, and STEMI biomarkers MMP-9 and CRP. The results showed that

Table 1
Basic clinical information for all STEMI patients.

Variables	All patients, n=358	Deceased, n=31	Survival, n=327	P*	95% CI
Age, year	63.6 ± 7.1	61.7 ± 7.4	63.8 ± 7.0	.113	1.3 (0.5–4.7)
Male: female	225: 133	20: 11	205: 122	.791	1.0 (0.6–1.9)
BMI	23.9 ± 2.6	24.7 ± 2.4	23.8 ± 2.6	.083	0.5 (−1.8 to 0.1)
Medical history, n (%)					
Cardiovascular diseases	105 (29.3)	12 (38.7)	93 (28.4)	.123	1.6 (0.9–2.9)
Hypertension	57 (15.9)	6 (19.4)	51 (15.6)	.479	1.3 (0.6–2.7)
Diabetes	68 (19.0)	5 (16.1)	63 (19.3)	.553	0.8 (0.4–1.7)
LVEF, (%)	56.7 ± 5.4	56.4 ± 5.2	56.8 ± 5.4	.671	1.0 (−1.6 to 2.4)
GRACE score	144.0 ± 20.4	167.0 ± 27.8	141.9 ± 18.1	<.001	3.6 (−32.2 to −18.0)
YKL-40, ng/ml	1.7 (1.4–2.7)	2.3 (1.6–2.7)	1.7 (1.4–2.0)	<.001	
MMP-9, ng/ml	2.5 (1.5–4.4)	3.5 (2.9–4.4)	2.4 (1.5–3.2)	<.001	
CRP, mg/L	7 (3–15)	11 (7–15)	7 (3–11)	<.001	

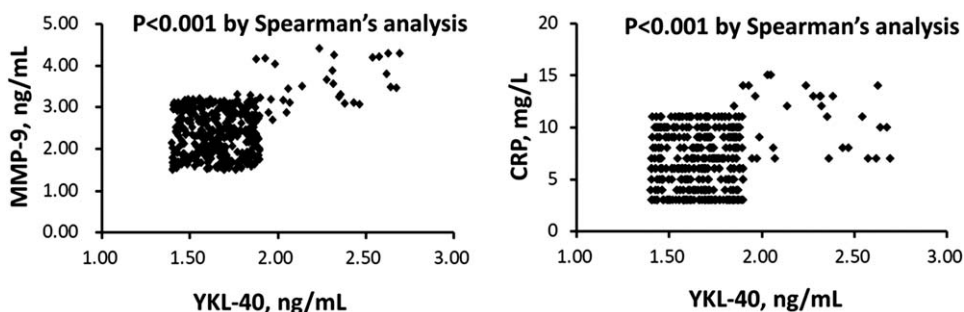* Comparison between deceased and survival patients.

Figure 1. Correlation between serum levels of YKL-40 and MMP-9 or CRP.

the levels of YKL-40 positively correlated with MMP-9 and CRP ($P < .05$, Fig. 1). The levels of MMP-9 and CRP also positively correlated ($P < .05$).

3.3. Relationship between serum levels of YKL-40 and the outcomes of STEMI patients

Patients were further divided into 2 groups, YKL-40 high and YKL-40 low groups, according to the median value of YKL-40 (1.7 ng/ml). The clinical outcomes of the groups of patients were further compared. As shown in Table 2, the levels of both CRP and MMP-9 were significantly higher in YKL-40 high level group, as well as GRACE score ($P < .05$ for all factors). The cumulative MACE rates and cardiac death rates were significantly higher in the YKL-40 high level group ($P < .001$, 95%CI 3.9 (1.9–8.2).

3.4. Association of serum YKL-40 levels and overall survival time

Finally, we analyzed the association between serum YKL-40 levels and overall survival time using K–M curves. The overall survival time was dramatically longer in patients with lower YKL-40 levels (Fig. 2, $P < .05$), suggesting that YKL-40

expression was associated with the 6-month survival of STEMI patients.

4. Discussion

Despite recent developments in the treatment of AMI, it remains a severe disease with high morbidity and mortality rates. Early predictors of STEMI are thus urgently required. Typical biomarkers for AMI include CK-MB, troponin and BNP.[20,21] Amongst these biomarkers, YKL-40 is elevated in STEMI patients.[22] However, a deeper insight into YKL-40 and STEMI in the clinic are required. In this study, we demonstrate for the first time that elevated YKL-40 levels positively correlate with MMP-9, and confirm that YKL-40 correlates with CRP and its associated clinical outcomes including MACE and the 6-month survival rates of STEMI patients.

Several studies have reported the relationship between YKL-40, cardiovascular disease and related diseases such as hypertension and diabetes. Harutyunyan et al demonstrated that serum YKL-40 was significantly higher in stable coronary artery disease but not a proper biomarker for myocardial ischemia.[23] Xu et al found that YKL-40 was associated with hypertension incidence in Chinese males.[24] Rathcke et al also showed that YKL-40 was elevated in patients with type 2 diabetes

Table 2

Clinical outcomes between patients with high/low serum levels of YKL-40.

Variables	YKL-40 high, n=173	YKL-40 low, n=185	P value	95% CI
Age, year	64.0±7.2	63.3±6.9	.349	0.7 (−2.2 to 0.8)
Male: female	63:51	69:51		1.0 (0.5–1.7)
BMI	23.9±2.5	23.9±2.7	.790	0.3 (−0.5 to 0.6)
Medical history, n (%)				
Cardiovascular diseases	54 (31.2)	51 (27.8)	.642	1.2 (0.6–2.1)
Hypertension	29 (16.8)	28 (15.1)	.700	1.2 (0.5–2.8)
Diabetes	32 (18.5)	36 (19.5)	.859	0.9 (0.5–1.9)
LVEF, (%)	56.3±5.0	57.1±5.6	.167	1.0 (−1.6~2.4)
GRACE score	146.9±22.2	141.4±18.1	.011	2.1 (−9.7 to −1.3)
CRP, mg/L	8 (3–15)	7 (3–11)	.007	
MMP-9, ng/mL	2.5 (1.5–4.4)	2.4 (1.5–3.2)	.022	
MACE, n (%)*				
Cardiac death	29 (16.8)	2 (1.1)	.047	
Rehospitalization	18 (10.4)	11 (5.9)		
Recurrence of angina or malignant arrhythmia	14 (8.1)	9 (4.9)		
Cumulative MACE	61 (35.3)	22 (11.9)	<.001	3.9 (1.9–8.2)

* $P < .05$, compared with the group of low YKL-40.
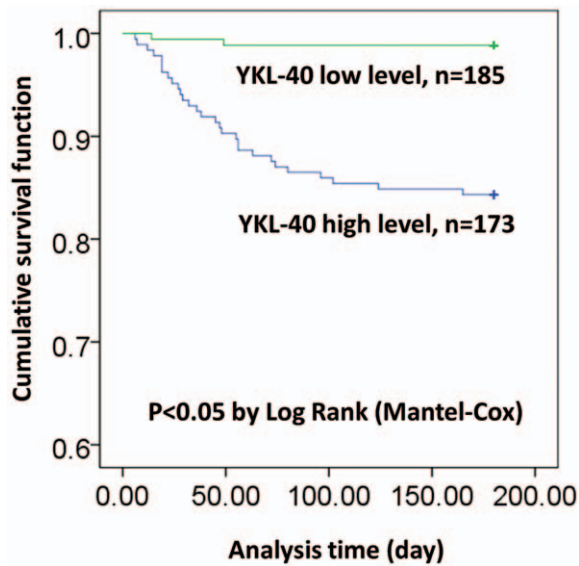
Figure 2. Survival analysis for patients with high/low YKL-40 levels by K–M curve.

and was related to insulin resistance.[25] In a recent study, elevated YKL-40 levels have been shown to be associated with reduced MACE-free survival.[26] In this study, we found that YKL-40 was up-regulated in STEMI patients, which was consistent with previous findings.

The relationship between CRP, MMP-9 and AMI has been confirmed in many researches. In an early research in 2008, authors investigated 73 patients with STEMI and coronary artery disease and found YKL-40 was significantly increased in both STEMI and coronary artery disease patients and was correlated with CRP.[27] Milwidsky et al recently demonstrated that CRP velocity was significantly higher amongst patients who died within 30 days.[28] MMP-9 was also found to be elevated in AMI and could be used as a potential biomarker for stroke mortality and myocardial infarction.[29] However, despite these studies, the relationship between CRP or MMP-9 and YKL-40 is undefined. In this study, we showed for the first time that elevated YKL-40 levels positively correlated with MMP-9 and CRP.

This study also had some limitations. Firstly, the study was of a limited size and single centered. Secondly, we used only a short follow-up duration. Thirdly the molecular mechanisms for YKL-40 and its relationship with CRP and MMP-9 in AMI are unknown. Further studies in this area are now required.

In conclusion, we conducted a prospective study to investigate the role of YKL-40 in STEMI patients. The results showed the serum YKL-40 was elevated in STEMI patients and positively correlated with CRP and MMP-9 levels. YKL-40 was also associated with clinical outcomes including MACE and 6-month survival of STEMI patients. These findings provide further clinical evidence for the role of YKL-40 in AMI.

Author contributions

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