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Serum YKL-40 predicts long-term outcome in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

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Abstract

Serum YKL-40, a potential inflammatory marker, is greatly increased at the early stage of ST-segment elevation myocardial infarction (STEMI). Here, we hypothesized that YKL-40 levels at admission could predict the long-term outcomes after STEMI.

A total of 324 patients with acute STEMI undergoing primary percutaneous coronary intervention (PCI) were consecutively enrolled and followed for 24 months. The baseline clinical and procedural data were recorded, and serum YKL-40 levels at admission were measured using ELISA method. The endpoint of interest was major adverse cardiac event (MACE), including all-cause death, recurrent myocardial infarction, and hospitalization for heart failure.

Patients with elevated serum YKL-40 levels (≥ 126.8 ng/mL) were more likely to be older and smoker and to present with type 2 diabetes, advanced Killip class, multivessel disease and intra-aortic balloon pump, with increased levels of admission glucose, triglyceride, and high-sensitivity C-reactive protein and decreased level of high-density lipoprotein cholesterol. During the follow-up period, the incidence of MACE was notably higher in the high than in the low YKL-40 groups (28.4% vs 11.1%, $P < .001$). Kaplan–Meier curve showed that elevated YKL-40 levels were associated with reduced MACE-free survivals (log-rank $P < .001$). In multivariate Cox regression analysis, we found that high serum YKL-40 level was an independent predictor of MACE after controlling for clinical and angiographic variables (hazard ratio: 1.65, 95% confidence interval: 1.14–2.39, $P = .008$).

The results of our study indicate that serum YKL-40 may be used as a biomarker to predict the long-term outcome after PCI in patients with STEMI.

Abbreviations: CI = confidence interval, HF = heart failure, HR = hazard ratio, hs-CRP = high-sensitivity C-reactive protein, MACE = major adverse cardiac events, MI = myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction, TIMI = Thrombolysis in Myocardial Infarction, VSMCs = vascular smooth muscle cells.

Keywords: myocardial infarction, prognosis, risk stratification, YKL-40

1. Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is a severe heart attack resulting from the rapture of a vulnerable atherosclerotic lesion in coronary vessels. Despite the advances in

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diagnosis and treatment, STEMI remains the leading cause of morbidity and cardiovascular mortality worldwide.[1] Moreover, even after successful reperfusion therapy, patients with STEMI are still at great risks of developing acute heart failure (HF), cardiac shock, and mechanical complications.[2] Thus, identification of high-risk patients is critical to improve the management and prognosis of STEMI. In addition to thrombosis and platelet activation, a number of studies suggest that inflammatory response also plays an important role in the occurrence and progression of STEMI.[3–5]

YKL-40, also known as human cartilage glycoprotein-39 or chitinase-like protein 1, is a heparin- and chitin-binding glycoprotein secreted by macrophages, neutrophils, vascular smooth muscle cells (VSMCs), and cancer cells.[6] To date, YKL-40 has been considered as a novel biomarker of inflammation that contributes to cell proliferation and differentiation, angiogenesis, and tissue remodeling.[7,8] In addition, previous studies have demonstrated that serum YKL-40 level was increased at the early stage of STEMI,[9] and YKL-40 can predict the long-term mortality in patients with stable coronary disease.[10] However, it is unclear whether YKL-40 is associated with the long-term prognosis after STEMI. In this study, we hypothesized that YKL-40 may be an effective biomarker to predict the long-term outcomes in STEMI patients undergoing percutaneous coronary intervention (PCI).

2. Materials and methods

2.1. Study population

This prospective cohort study initially recruited 407 consecutive patients with STEMI who received primary PCI in Wuhan Third Hospital (Wuhan, China) between April 2012 and December 2015. Acute STEMI at admission was diagnosed based on the following criteria: >20 minutes of persistent chest pain, >1.0 mm of a new ST-segment elevation in ≥2 contiguous electrocardiography leads, and a cardiac troponin I level >the 99th percentile upper reference limit.[11] The diagnosis of STEMI was further confirmed by detection of the culprit lesion via coronary angiography. Subjects with known history of coronary heart disease, previous myocardial infarction and previous coronary revascularization including PCI and coronary artery bypass grafting were not included. Moreover, we also excluded patients with malignancy, hematological disorders, active infection, chronic inflammatory disease, severe hepatic or renal dysfunction, chronic HF, treatment with steroid or chemotherapeutic drugs, and loss of follow-up. As a result, 324 patients were included into the final analysis.

Demographic, clinical, and laboratory data of all eligible patients were collected. The study protocol was approved by the Institutional Ethics Committee, and informed consent was obtained from each participant.

2.2. Measurement of serum YKL-40

The blood samples for serum YKL-40 measurement were obtained immediately after admission (before PCI treatment), centrifuged for 10 minutes at 3000 g and then stored at −80°C until further analysis. Serum YKL-40 levels were measured using ELISA method with a commercially available kit (BOSTER Biological Technology co.ltd, Wuhan, China), according to the manufacturer's instructions. A standard curve was depicted to determine the YKL-40 concentration of unknown sample. The coefficients of variation of intra- and inter-assay were <6% and 8%, respectively.

2.3. Primary PCI and follow-up

All patients received a loading dose of 300-mg aspirin and 300 to 600-mg clopidogrel immediately after admission. Primary PCI was performed using standard approaches according to the established guidelines. Blood flow of the culprit artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification. Selection of stents and use of tirofiban were based on the discretion of operators, as was the application of additional techniques such as thrombus aspiration and intra-aortic balloon pump. After PCI procedure, all patients were transferred to Intensive Care Unit and were followed for 24 months after discharge by a return visit to the clinic or by telephone interviews. The endpoint was the incidence of major adverse cardiac events (MACE), defined as a composite of all-cause death, recurrent myocardial infarction (MI), and hospitalization for HF.[12]

2.4. Statistical methods

Continuous variables were expressed as mean±SD or median (interquartile range) according to their distribution, and categorical variables were reported as counts (percentage). For data presentation, patients were divided into 2 groups according to their median levels of YKL-40. Between-group comparisons were carried out using Student's t-test, Mann–Whitney U test or Chi-square test, when appropriate. Kaplan–Meier analysis with

Table 1

Clinical and laboratory data in patients with higher and lower YKL-40 levels.

Variables	Higher YKL-40 (n = 162)	Lower YKL-40 (n = 162)	P
Age, years	63.1 ± 10.4	58.0 ± 9.7	<.001
Male gender, n (%)	116 (71.6)	122 (75.3)	.63
BMI, kg/m^2	25.2 ± 3.9	25.4 ± 3.6	.34
Hypertension, n (%)	78 (48.1)	70 (43.2)	.37
Type 2 diabetes, n (%)	52 (32.1)	33 (20.4)	.016
Current smokers, n (%)	92 (56.8)	73 (42.1)	.035
Family histories of CHD, n (%)	29 (17.9)	20 (12.3)	.16
Systolic BP, mm Hg	134.4 ± 27.6	133.8 ± 30.2	.85
Diastolic BP, mm Hg	83.7 ± 19.1	81.6 ± 18.9	.32
LVEF, %	48.1 ± 12.5	49.0 ± 11.2	.50
eGFR, mL/min/1.73 m^2	85.7 ± 21.2	89.1 ± 18.5	.13
Killip class ≥2, n (%)	58 (35.8)	36 (22.2)	.007
Peak troponin I, ng/mL	37.4 ± 8.3	36.8 ± 9.6	.55
Leukocyte, ×10^9/L	10.4 ± 3.9	9.7 ± 3.5	.09
Hemoglobin, g/L	138.7 ± 23.1	142.0 ± 21.1	.18
Platelet count, ×10^6/L	245.9 ± 62.6	238.2 ± 65.8	.28
Admission glucose, mmol/L	8.38 ± 4.32	7.49 ± 3.14	.034
Triglyceride, mmol/L	1.85 ± 0.93	1.65 ± 0.71	.030
Total cholesterol, mmol/L	4.61 ± 0.98	4.71 ± 1.20	.41
LDL-C, mmol/L	3.03 ± 0.79	2.94 ± 0.82	.32
HDL-C, mmol/L	0.98 ± 0.36	1.10 ± 0.39	.004
hs-CRP, mg/L	4.33 ± 2.91	3.18 ± 2.04	<.001

BMI = body mass index, BP = blood pressure, CHD = coronary heart disease, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction.

log-rank test was conducted to compare the MACE-free survival among the 2 groups. The predictive value of baseline variables for MACE was determined by a stepwise multivariable Cox regression analysis; and, variables with P-value <.1 in univariate analysis were included in the model. All statistical analyses were realized with SPSS 21.0 software (SPSS Inc., Chicago, IL), and P-values of <.05 were used as significance threshold.

3. Results

3.1. Baseline characteristics

The median concentration of serum YKL-40 in STEMI patients was 126.8 ng/mL (interquartile range: 85.9–183.3 ng/mL). Based on the median level, patients were divided into the higher (n = 162) and lower (n = 162) YKL-40 groups. The baseline clinical and laboratory data are shown in Table 1. Compared with patients with low YKL-40, patients with high YKL-40 were more likely to be older (P < .001) and smoker (P = .035) and to present with type 2 diabetes (P = .016) and advanced Killip class (P = .007), with increased levels of admission glucose (P = .034), triglyceride (P = .03), high-sensitivity C-reactive protein (hs-CRP) (P < .001), and decreased level of high-density lipoprotein cholesterol (HDL-C) (P = .004). Moreover, serum YKL-40 levels were also significantly higher in patients with old age, type 2 diabetes, smoking habits, advanced Killip class, elevated triglyceride and hs-CRP, and decreased HDL-C (Table S1, http://links.lww.com/MD/C884).

3.2. Angiographic and procedural data

Angiographic and procedural characteristics are summarized in Table 2. Serum YKL-40 level was associated with the number of diseased arteries (P = .017) and the application of intra-aortic

Table 2

Angiographic and procedural data in patients with high and low YKL-40 levels.

Variables	Higher YKL-40 (n = 162)	Lower YKL-40 (n = 162)	P
Door-to-balloon time, min	108 ± 41	105 ± 36	.48
Culprit vessel, n (%)			.67
LAD	84 (51.8)	76 (46.9)	
LCX	21 (13.0)	24 (14.8)	
RCA	57 (35.2)	62 (38.3)	
Number of diseased vessels, n (%)			.017
Single vessel	89 (54.9)	110 (67.9)	
Multivessel	73 (45.1)	52 (32.1)	
Pre-PCI TIMI flow, n (%)			.43
0–1	156 (96.3)	153 (94.4)	
2–3	6 (3.7)	9 (5.6)	
Stent implanted, n (%)	159 (98.1)	158 (97.5)	.70
Stent length, mm	22.4 ± 6.9	21.7 ± 6.5	.35
Stent diameter, mm	3.08 ± 0.43	3.12 ± 0.49	.44
Use of tirofiban, n (%)	58 (35.8)	54 (33.3)	.64
Thrombectomy, n (%)	34 (21.0)	42 (25.9)	.29
Post-PCI TIMI flow, n (%)			.12
0–1	11 (6.8)	5 (3.1)	
2–3	151 (93.2)	157 (96.9)	
IABP, n (%)	21 (13.0)	10 (6.2)	.038

IABP = intra-aortic balloon pump, LAD = left anterior descending artery, LCX = left circumflex artery, PCI = percutaneous coronary intervention, RCA = right coronary artery, TIMI = Thrombolysis in Myocardial Infarction.

balloon pump (P = .038), but not with the door-to-balloon time, culprit vessel, TIMI flow grade, stent parameters and uses of tirofiban and thrombectomy (all P > .05). In addition, we found that serum YKL-40 levels were also remarkably higher in patients

Table 3

Incidence of MACE in patients with higher and lower YKL-40 levels.

Events	Higher YKL-40 (n = 162)	Lower YKL-40 (n = 162)	P
All-cause death	14	5	.033
Recurrent MI	6	2	.15
Hospitalization for HF	26	11	.009
MACE (total)	46	18	<.001

HF = heart failure, MI = myocardial infarction.

with multivessel disease and intra-aortic balloon pump treatment (Table S1, http://links.lww.com/MD/C884).

3.3. Incidence of MACE

A total of 64 patients who experienced MACE were identified during the 24-month follow-up, including 19 deaths, 8 recurrent MI, and 37 hospitalizations for HF. Compared with the lower YKL-40 group, the higher YKL-40 group showed an increased incidence of MACE (28.4% vs 11.1%, P < .001; Table 3). Likewise, Kaplan–Meier analysis indicated that an elevated YKL-40 level was correlated with a shorter MACE-free survival (log-rank P < .001; Fig. 1).

3.4. Independent predictors of MACE

Univariate and multivariate Cox regression analyses were performed to determine the potential predictors of MACE. In the univariate regression analysis, age, male gender, presence of hypertension and diabetes, the presence of advanced Killip class, left ventricular ejection fraction, estimated glomerular filtration
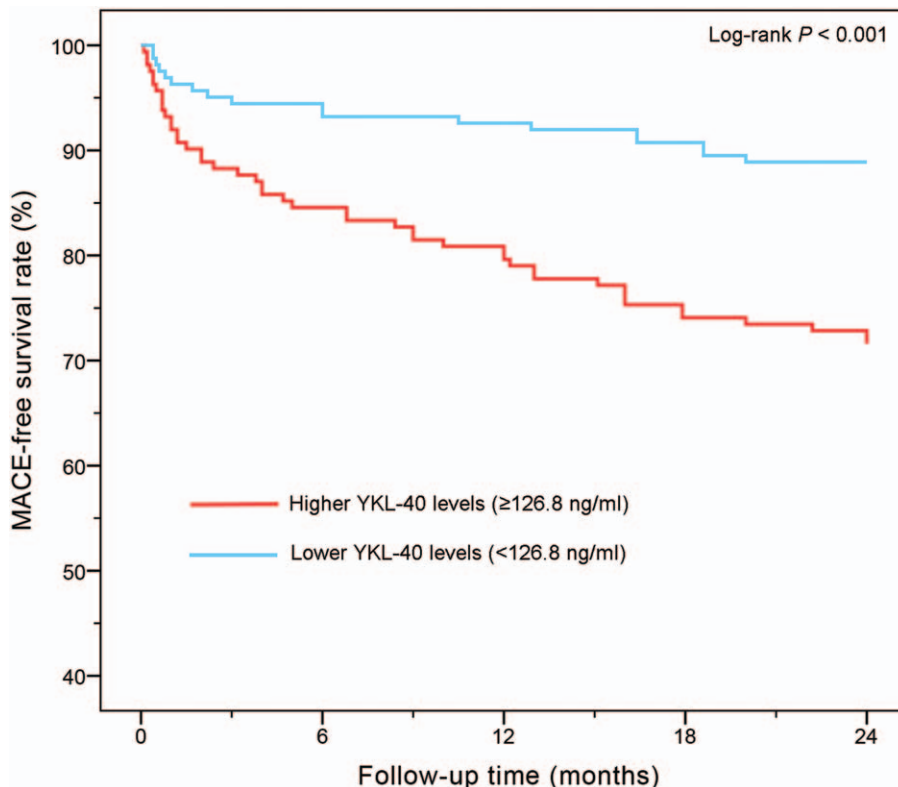

Figure 1. Kaplan–Meier analysis of MACE according to the serum YKL-40 levels. MACE = major adverse cardiac events.

Table 4

Univariate and multivariate Cox regression analyses for MACE.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age	1.12	1.07–1.18	<.001	1.09	1.02–1.16	.005
Male gender	0.62	0.41–0.95	.026	0.77	0.45–1.32	.34
Hypertension	1.74	1.13–2.69	.012	1.34	0.80–2.25	.27
Type 2 diabetes	2.16	1.29–3.61	.003	1.48	0.92–2.38	0.11
Killip class ≥2	2.91	1.58–5.36	<.001	2.08	1.35–3.21	<0.001
LVEF	0.78	0.63–0.96	.021	0.87	0.69–1.10	0.24
eGFR	0.95	0.92–0.98	<.001	0.99	0.96–1.02	0.52
Peak troponin I	1.89	1.18–3.03	.008	1.72	1.08–2.75	0.023
hs-CRP	1.59	1.12–2.26	.003	1.40	1.03–1.92	0.038
Multi-vessel disease	1.33	0.97–1.82	.076	1.06	0.91–1.23	0.45
YKL-40	1.74	1.25–2.41	<.001	1.65	1.14–2.39	0.008

CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio, hs-CRP = high-sensitivity C-reactive protein, LVEF = left ventricular ejection fraction.

rate, peak troponin I, hs-CRP, multivessel disease, and serum YKL-40 levels were associated with MACE. In the multivariate regression analysis with adjustment of the aforementioned parameters, age (hazard ratio [HR]: 1.09, 95% confidence interval [CI]: 1.02–1.16, P=.005), presence of advanced Killip class (HR: 2.08, 95% CI: 1.35–3.21, P<.001), peak troponin I (HR: 1.72, 95% CI: 1.08–2.75, P=.023), hs-CRP (HR: 1.40, 95% CI: 1.03–1.92, P=.038) and serum YKL-40 level (HR: 1.65, 95% CI: 1.14–2.39, P=.008) were found to be independent predictors of MACE (Table 4).

4. Discussion

Studies about YKL-40 and cardiovascular disease have accelerated in recent years; however, data concerning the prognostic value of this glycoprotein in STEMI are still lacking. In this work, we found that admission serum YKL-40 level was significantly associated with some clinical features in STEMI patients referred to primary PCI, including age, history of type 2 diabetes, smoking habits, Killip class, number of diseased vessels, intra-aortic balloon pump treatment and levels of admission glucose, triglyceride, HDL-C, and hs-CRP. More importantly, serum YKL-40 could offer important prognostic information and might be a useful predictor of MACE in patients with STEMI.

To the best of our knowledge, this is the first study investigating the association of YKL-40 with long-term outcomes after PCI in STEMI patients. Previous reports have also documented the predictive value of YKL-40 for adverse cardiovascular events. For example, Kastrup et al[13] studied the follow-up data from 4298 patients with stable coronary heart disease, and found that serum YKL-40 was independently related to all-cause mortality and cardiovascular mortality, but not to MI, after adjustment of cardiovascular risk factors. Likewise, serum YKL-40 level was elevated in patients with chronic HF, which could facilitate the detection of high-risk individuals for future cardiac events.[14] In a recent study of 80 STEMI patients, serum YKL-40 level could predict myocardial reperfusion and in-hospital MACE after primary PCI.[15]

In line with the existing literature in cardiovascular disease,[6,15,16] we found that STEMI patients with higher serum YKL-40 levels tended to have older age, type 2 diabetes, smoking habits, advanced Killip class, more obstructed vessels and abnormal circulating biomarkers. All of these features point toward an unfavorable clinical profile in patients with elevated YKL-40 level, which may influence the long-term outcomes of

STEMI.[17] After adjustment of these clinical factors, however, the association between YKL-40 and MACE maintained significant, implying that YKL-40 could provide independent predictive power for the prognosis of STEMI.

The reasons for the observed correlation between YKL-40 and MACE are unclear. The possible mechanisms may include the potential effects of YKL-40 on inflammation and myocardial remodeling, which function importantly in the pathological process of MI.[18,19] YKL-40 has been suggested as a new inflammatory marker; and, elevated circulating YKL-40 levels were observed in conditions featured by inflammation, tissue remodeling and ongoing fibrosis, such as rheumatoid arthritis, liver fibrosis, asthma, chronic obstructive pulmonary disease, and cardiovascular diseases.[8,20–22] Also, our study showed that serum YKL-40 was positively related to an established inflammatory maker, hs-CRP. But in contrast to CRP that is secreted by hepatocytes in response to systemic inflammation, YKL-40 is synthesized by macrophages and neutrophils in local inflamed tissues and by differentiated macrophages and activated neutrophils.[13] YKL-40 is also produced by VSMCs and in turn promotes the dedifferentiation, adhesion and migration of VSMCs,[23] potentially contributing to development of neointima formation and vascular restenosis. In addition, YKL-40 may protect cardiac myocytes from ischemia-induced apoptosis, since its expression is up-regulated in carcinoma cells exposed to hypoxia.[24] Therefore, it is plausible that YKL-40 plays a role in the acute inflammatory process eliciting or responding to protect against the plaque instability and in the recovery and remodeling process after acute STEMI.[25] In line with this speculation, Hedegaard et al[26] demonstrated that higher serum YKL-40 level may predict a lower left ventricular ejection fraction recovery after STEMI.[26]

There are several limitations that need to be acknowledged. Firstly, this study was conducted in a single center with small sample size. Therefore, the probability of selection bias cannot be excluded. Secondly, some confounders were not measured such as the inflammatory markers beside YKL-40 and hs-CRP (e.g., growth differentiation factor 15), which may have interfered with our results. Thirdly, we cannot evaluate the changes in YKL-40 level after STEMI due to the lack of sequential measurements.

In conclusion, our study suggests that YKL-40 is a predictor of long-term MACE in STEMI patients receiving primary PCI, independently of traditional cardiovascular risk factors. Thus, early measurement of serum YKL-40 level may provide valuable information for the risk stratification of STEMI patients.

Author contributions

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Writing – review & editing: Jinhui Tan, Shouzhi Fu.

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