RESEARCH LETTER

YKL-40 as a predictor of mortality after acute coronary syndrome

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Introduction The role of biomarkers in cardiovascular disease has not been fully elucidated so far. Although biomarkers proved to be useful in specific situations in patients with malignancy, their utility has been questioned in guidelines developed by cardiac societies.[1] As cardiovascular mortality remains high worldwide, with an annual mortality rate due to myocardial infarction (MI) of nearly 20% in Poland alone (12.3% in patients undergoing invasive treatment),[2] it seems necessary to identify a biomarker that could be used in risk stratification and prognosis in patients with MI.

Considering that inflammation is involved in the pathogenesis of atherosclerosis, YKL-40 is one of the potentially interesting biomarkers in cardiovascular disease. However, it remains unclear whether increased expression of YKL-40 triggers inflammation or its secretion is secondary to ongoing inflammation.[3]

The aim of this study was to assess plasma concentrations of YKL-40 in patients with acute coronary syndrome (ACS) and to investigate the potential role of this parameter as a predictor of mortality.

Patients and methods The present research was a subanalysis of a previous study on patients with ischemic heart disease (not only those with MI).[4] We enrolled patients with ST-segment elevation MI (STEMI) and non-STEMI on admission, who underwent urgent coronary angiography and were either referred for urgent percutaneous coronary intervention (PCI) or a cardiac consultation. Patients with a history of PCI or surgical revascularization, stage 4 or 5 chronic kidney disease, cancer, active inflammation, or shock were excluded from the study.

Prior to coronary angiography, a 5-ml sample of venous blood was obtained from a peripheral vein in each patient. Plasma YKL-40 levels were determined once with the immunoenzymatic assay MicroVue YKL-40 (Quidel, San Diego, California, United States) and quantified with the automatic scintillation gamma counter Wizard 2470 (PerkinElmer, Waltham, Massachusetts, United States).

Data on mortality of all patients were collected from the Polish National Health Fund (Polish: Narodowy Fundusz Zdrowia [NFZ]) during 4-year follow-up.

The study protocol was approved by the local bioethics committee at Wroclaw Medical University, Wrocław, Poland. All patients provided written consent to participate in the study.

Statistical analysis Normality of data distribution was verified with the Lilliefors test. The significance of intergroup differences in normally and nonnormally distributed variables was assessed with the *t* test for independent variables and the Mann–Whitney test, respectively. Depending on the study group size, distributions of dichotomous variables were compared with the χ^2 test (with or without the Yates correction) or the Fisher exact test.

Based on the receiver operating characteristic analysis, the study population was divided into 2 groups according to the YKL-40 level cutoff value with the highest specificity and sensitivity to predict the outcome. The Youden index was used to identify the cut point of YKL-40 levels. Then, a survival analysis was performed for several time intervals (30 days; 3, 6, 12, 24, 36, and 48 months) using the Kaplan–Meier method to compare the study groups, and the Cox regression analysis was used to test the association of clinical variables with the hazard ratio for mortality.

A *P* value less than 0.05 was considered significant.

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TABLE 1 Cox proportional hazards regression analysis of the association between clinical variables and the hazard ratio for mortality

Variable	Mortality, HR	Lower 95% CI	Upper 95% CI	*P* value
YKL-40 ≥360 ng/ml	10.3	2.01	53.5	0.005
SYNTAX score	1	0.96	1.01	0.98
LVEF	0.95	0.89	1.02	0.18
Diabetes	0.93	0.17	5.08	0.93

Abbreviations: HR, hazard ratio; LVEF, left ventricular ejection fraction

Results We recruited 67 consecutive patients after acute MI (44 men and 23 women; median [range] age, 67 [24–97] years) in a prospective study with a median (range) follow-up of 1460 (1–1460; mean, 1306) days. The study groups did not differ in the length of follow-up. No significant differences were found in YKL-40 concentrations between patients with STEMI (n = 47) and NSTEMI (n = 20): median (interquartile range), 270.4 (176.8–363.7) ng/ml versus 199.1 (165.2–366.1) ng/ml.

In the receiver operating characteristic curve analysis, the YKL-40 value of 360 ng/ml or higher on admission (area under the curve, 0.93; 95% CI, 0.86–0.98; *P* = 0.001) predicted mortality at up to 4 years after ACS, with a sensitivity and specificity of 80% (*P* = 0.001 for both tests). There were no differences between the study groups (YKL-40 levels ≥360 ng/ml; n = 17 vs YKL-40 levels <360 ng/ml; n=50) in terms of sex, age, hypertension, type 2 diabetes, atrial fibrillation, heart failure, valvular heart disease, obesity, and history of smoking. No differences were also observed for complete blood count and lipid profile. Of note, there was also no difference in peak troponin I levels, left ventricular ejection fraction, and severity of coronary atherosclerosis assessed by the SYNTAX score. However, the study groups differed in terms of statin use before admission (17% of patients with YKL-40 levels ≥360 ng/ml vs 40% of patients with YKL-40 levels <360 ng/ml). No other differences in pharmacotherapy were reported between the compared groups on admission.

In the Kaplan–Meier analysis, the mortality rate differed between patients with YKL-40 levels of 360 ng/ml and higher and those with YKL--40 levels below 360 ng/ml at 30-day follow-up (17.6% vs 0; *P* = 0.02), with the most significant difference observed at 12 months (35.3% vs 2%; *P* = 0.001). The difference was still present at 4-year follow-up (35.3% vs 6%; *P* = 0.01) (Supplementary material, *Figure S1*).

The Cox proportional hazards regression analysis including YKL-40 levels, the SYNTAX score, left ventricular ejection fraction, and presence of diabetes showed an independent effect of elevated YKL-40 levels on hazard ratio for mortality (TABLE 1).

Discussion YKL-40 was previously studied by other authors. Its blood levels were shown to be associated with higher mortality in patients admitted to hospital due to various causes, including stable coronary artery disease or heart failure.[5-8] In a study on unselected patients admitted due to various causes, Mygind et al[5] reported that individuals with elevated YKL-40 levels (with the 95th percentile used as a cutoff value) had higher mortality, irrespective of the cause, at 11-year follow-up. The most significant differences were reported in patients with the lowest and the highest quartiles of YKL-40 concentrations and in the first year of follow-up.[5]

Kastrup et al[6] and Harutyunyan et al[7] showed a linear relationship between YKL-40 levels and both short- and long-term all-cause mortality in patients with stable coronary artery disease. In a study on patients with heart failure with reduced ejection fraction, an increase in serum YKL-40 levels, when divided into quartiles, was associated with higher all-cause mortality at 7-year follow-up. When serum YKL-40 levels were regarded as a continuous variable, they proved to be only a weak predictor of all-cause mortality.[7] Bilim et al,[8] in a study with 2-year follow-up, including patients with heart failure, showed that high YKL-40 levels were associated with the highest rates of cardiac events, including death, when the study group was divided according to YKL-40 quartiles. It was also demonstrated that YKL-40 levels in patients with peripheral arterial disease were significantly associated with cardiovascular and all-cause mortality at 7-year follow-up when the study group was divided according to YKL-40 tertiles.[9]

Recently, 2 studies have been published that were carried out on populations including patients with MI, as in our study. They revealed that patients with MI have increased YKL-40 levels.[4] Yang et al[10] hypothesized that YKL-40 may be a useful biomarker for predicting long-term outcomes in patients with STEMI undergoing PCI. After dividing patients into 2 groups (below and above the median YKL-40 levels), the incidence of major adverse cardiac events (MACEs) was higher in patients with high YKL-40 levels than in those with low YKL-40 levels at 24-month follow-up (28.4% vs 11.1%; *P* <0.001). The Kaplan–Meier curve showed that elevated YKL-40 levels were associated with lower MACE-free survival rates. A multivariable Cox regression analysis revealed that high serum YKL-40 levels were an independent predictor of MACEs. In a study on patients with STEMI and NSTEMI, Pala et al[11] reported that death at 8-year follow-up occurred in those with plasma YKL-40 levels on admission above the median value more often than in those with the levels below it.[11] In a prospective study with 6-month follow-up, including 358 patients with STEMI, patients were divided into 2 groups according to the median value of YKL-40 levels. Patients above the median YKL-40 level more often experienced MACEs, including cardiac death, rehospitalization, recurrence of angina, and arrhythmia. The difference was particularly notable

for cardiac death (16.8% vs 1.1%). The overall survival was longer in patients with YKL-40 levels below the median value.[12]

Based on our study with a mean follow-up of 1306 days, it seems that a cutoff value for blood YKL-40 levels may be established and used for risk stratification in patients admitted due to MI to identify those at high mortality risk and to introduce more intensive, targeted therapy. To our knowledge, this is the first study reporting the possibility of establishing such a threshold value.

A small study group was the most important limitation of this study. Moreover, information on all-cause mortality at 4-year follow-up was obtained from the Polish mortality registry, which lacks data on the exact causes of reported deaths. However, despite the low number of patients, we could show a significant difference in long-term mortality for the chosen cutoff value of baseline YKL-40 levels.

In conclusion, the YKL-40 level of 360 ng/ml or higher on admission in patients with MI is associated with a higher mortality rate at up to 4 years after ACS.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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