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Short title:
YKL-40 – biomarker of mortality

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**Introduction**

The role of biomarkers in cardiovascular disease has not been fully elucidated. While biomarkers have been confirmed 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 worldwide remains high, with an annual mortality due to myocardial infarction (MI) of nearly 20% in Poland alone (12.3% in patients on invasive treatment) [2], it seems necessary to identify a biomarker that could be used in risk stratification and prognosis of patients with MI.

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

The aim of the 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 current 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 myocardial infarction (STEMI) and non-STEMI (NSTEMI) on admission, who underwent urgent coronary angiography and were either referred for urgent percutaneous coronary intervention or a heart team consultation. Patients with a history of percutaneous coronary intervention 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 of each patient. Plasma YKL-40 levels were determined once with an immunoenzymatic assay, MicroVue YKL-40 (Quidel, San Diego, California, United States). Plasma
YKL-40 levels were quantified with an automatic scintillation gamma counter, Wizard 2470 (PerkinElmer, Waltham, Massachusetts, United States).

Data on mortality of all the patients were collected from the National Health Fund in Poland during a 4-year follow-up.

The study protocol was approved by the local bioethics committee at Wroclaw Medical University, Wroclaw, Poland.

**Statistical analysis**

Normality of the data distribution was verified with Lilliefors test. The significance of intergroup differences in normally and non-normally distributed variables was verified with the Student t test for independent variables and the Mann-Whitney U test, respectively. Depending on the group size, distributions of dichotomous variables were compared with chi-squared test (with or without Yates’ correction) or Fisher exact test.

On the basis of the ROC analysis the whole group was divided in two groups according to the YKL-40 level cut-off with highest specificity and sensitivity to predict outcome. Youden index was used for identification of the cut-point of YKL-40. Than a survival analysis was performed for different time spans (30-days; 3-, 6-, 12-, 24-, 36-, 48-months) using the Kaplan-Meier method for comparison of groups and the Cox regression analysis was used to test the association of clinical variables with death hazard.

The threshold of statistical significance was p<0.05.

**Results**

We recruited 67 consecutive patients after acute MI (44 men and 23 women; median age, 67 years [range, 24-97 years]) in a prospective study with a median follow-up of 1460 days (range, 1-1460 days, mean 1306 days). The groups did not differ in the length of the follow-up. No significant differences were found in YKL-40 concentrations between patients with STEMI (n = 47) and NSTEMI (n = 20): median (IQ), 270.4 (176.8-363.7) ng/ml vs 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 death up to 4 years after ACS, with a sensitivity and specificity of 80% (\( P = 0.001 \) for both tests). There were no differences between groups (YKL-40 \( \geq 360 \) ng/ml; \( n = 17 \) vs. YKL-40 <360 ng/ml; \( n = 50 \)) in terms of sex, age, presence of hypertension, type 2 diabetes mellitus, 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 were also no differences in peak troponin I levels, left ventricular ejection fraction, and severity of coronary atherosclerosis assessed by the SYNTAX score. However, the groups differed in terms of statin use before admission (17% of patients with YKL-40 levels of 360 ng/ml or higher vs 40% of patients with YKL-40 levels lower than 360 ng/ml), there was no other differences in pharmacotherapy on admission between the compared groups.

In the K-M analysis the mortality rate differed between patients with YKL-40 levels above and below 360 ng/ml for 30 days of follow-up (17.6% vs 0; \( P = 0.02 \)), with the most significant difference observed for 12 months (35.3% vs 2%; \( P = 0.001 \)). The difference was still present at 4-year follow-up (35.3% vs 6%; \( P = 0.01 \)) (Figure 1).

The Cox proportional hazard regression analysis including YKL-40, SYNTAX Score, LVEF and presence of diabetes showed independent effect of elevated YKL-40 level on death hazard (Table 1).

**Discussion**

YKL-40 has been previously studied by other authors. Its blood levels were shown to be associated with higher mortality in patients admitted due to various causes, including stable coronary artery disease or heart failure [5-8]. In a study on unselected patients admitted for 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 in an 11-year
follow-up. The most significant differences were reported for 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 in a 7-year follow-up. When the serum YKL-40 level was used as a continuous variable, it was only a weak predictor of all-cause mortality [7]. Bilim et al [8], in a study with a 2-year follow-up including patients with heart failure, revealed 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 shown that in patients with peripheral arterial disease, YKL-40 levels were significantly associated with cardiovascular and all-cause mortality in a 7-year follow-up, when the study group was divided according to YKL-40 tertiles [9].

Recently, 2 studies have also been published in 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 percutaneous coronary intervention. After dividing patients into 2 groups (below and above the median level), the incidence of major adverse cardiac events (MACEs) was higher in patients with high than in those with low YKL-40 levels during a 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 reduced MACE-free survival rates. A multivariable Cox regression analysis revealed that the high serum YKL-40 level was an independent predictor of MACEs. In a study on patients with STEMI and NSTEM, Pala et al [11] reported that death occurred more often in those with plasma YKL-40 levels above the median than in those with the levels below the median on admission in an 8-year follow-up [11]. In a prospective study with a 6-month follow-up including 358 patients with STEMI, patients were divided into 2 groups according to the median value of
YKL-40. Patients above the median level more often experienced MACEs, including cardiac death, rehospitalization, recurrence of angina, and arrythmia. The difference was particularly notable for cardiac death (16.8% vs 1.1%). The overall survival was longer in patients with the YKL-40 levels below the median [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 that could be used in risk stratification of patients admitted due to MI with the aim to identify those at high risk of death and to introduce a more intensive, targeted therapy. To our knowledge, this is the first study reporting the possibility of establishing such a threshold value.

The most important limitation of this study was a small study group. Moreover, information on all-cause mortality during the 4-year follow-up was obtained from a death registry, and data on the exact cause of death are lacking. However, despite the low number of patients, we were able to show a significant difference in long-term mortality for the chosen cutoff value of baseline YKL-40 levels.

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


9. Höbaus C, Tscharre M, Herz C, et al. YKL-40 levels increase with declining ankle-brachial index
and are associated with long-term cardiovascular mortality in peripheral arterial disease patients. Atherosclerosis. 2018; 274: 152-156.


Table 1. Cox Proportional Hazards Regression Analysis with death hazard as an independent variable, including YKL-40, SYNTAX score, left ventricular ejection fraction and diabetes as depended variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death hazard ratio</th>
<th>lower 95% CI</th>
<th>upper 95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>YKL-40 ≥ 360 ng/ml</td>
<td>10.3</td>
<td>2.01</td>
<td>53.5</td>
<td>0.005</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>1.00</td>
<td>0.96</td>
<td>1.01</td>
<td>0.98</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.95</td>
<td>0.89</td>
<td>1.02</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.93</td>
<td>0.17</td>
<td>5.08</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Abbrreviation: LVEF, left ventricular ejection fraction