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Prognostic value of non-traditional lipid parameters: Castelli Risk Index I, Castelli Risk Index II, and triglycerides to high-density lipoprotein cholesterol ratio among patients with non-ST-segment elevation myocardial infarction during 1-year follow-up

Aim	Concentrations of classical lipoproteines have a well-established role in non-invasive cardiology. The efficacy of the Castelli Risk Index I (CRI I), Castelli Risk Index II (CRI II), and triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) ratio in clinical practice are currently under evaluation. The study aimed to assess the predictive value of CRI I, CRI II and TG/HDL-C for the incidence of Major Adverse Cardiovascular Events (MACE) and for all-cause mortality during 1-year follow-up of patients with non-ST-segment elevation myocardial infarction (NSTEMI).
Material and Methods	1,301 patients were enrolled in the study. Associations between CRI I, CRI II, TG/HDL-C and occurrence of MACE and 1-year mortality were studied. Moreover correlations between CRI I, CRI II, and TG/HDL-C and the severity of coronary artery disease (CAD) were assessed.
Results	MACE occurred in 10.9% (142) of patients, and 1-year mortality was 13.4% (174). None of the evaluated indices appeared to be an independent predictor of MACE in either the entire population or subpopulations, as divided according to the presence of diabetes or CAD diagnosed prior to admission. Furthermore, no dependence between 1-year mortality and the examined indices was found. Additionally, only a weak correlation between CAD severity and CRI I was observed (R=0.08, p=0.02). No significant correlations for CRI II (p=0.07) and TG/HDL-C (p=0.6) were detected.
Conclusions	CRI I, CRI II and TG/HDL-C should not be used as predictors of MACE or all-cause mortality among patients with NSTEMI. Moreover, these indices do not reflect CAD severity.

Keywords	CRI I; CRI II; TG/HDL-C ratio; MACE; NSTEMI; 1-year mortality
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Introduction

Non-ST-segment elevation myocardial infarction (NSTEMI), usually caused by unstable atherosclerotic plaques, is one of the manifestations of acute coronary syndrome. This condition occurs in more than 50% of patients admitted with acute myocardial infarction (AMI) [1]. Currently, prevention of coronary atherosclerosis is the most important target of non-invasive cardiology. Much effort is put into proper management of the classical risk factors of atherosclerosis, and several novel indicators have been suggested as easily accessible and useful tools to predict coronary artery disease (CAD). Castelli Risk Index I (CRI I), Castelli Risk Index II (CRI II), and the triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-C) are presently being evaluated for their usefulness as novel predictors of cardiovascular events [2–4].

The primary aim of this study was to evaluate the predictive value of CRI I, CRI II, and TG/HDL-C for the occurrence of Major Adverse Cardiovascular Events (MACE) and for all-cause mortality during 1-year follow-up of patients with NSTEMI. Additionally, correlations between those indices with the severity of CAD were assessed.

Material and Methods

A prospective, cohort study was performed among 2,300 patients admitted to our department during 2018–

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2020 with diagnosis of AMI. Patients who met the inclusion criteria were consecutively recruited into the study.

Inclusion criteria were diagnosis of NSTEMI, coronary angiography on admission with presence of haemodynamically relevant atherosclerosis, and full medical documentation. Exclusion criteria were diagnosis of ST-segment elevation myocardial infarction (STEMI) and AMI with non-obstructive CAD (MINOCA).

All patients had undergone emergency coronary angiography followed by percutaneous coronary intervention (PCI) with stent implantation or coronary artery bypass grafting if indicated. Laboratory measurements and echocardiography were performed. CAD severity was assessed by two invasive cardiologists using the Gensini score system [5]. Data concerning MACE and 1-year mortality were obtained from consultations in the outpatient department or by telephone consultations with patients or their families. In some cases, information concerning cause of death remained unknown, so all-cause 1-year mortality was not included in MACE and was assessed separately.

Associations between CRI I, CRI II, TG/HDL-C and occurrence of MACE and 1-year mortality were studied. Furthermore correlations between CRI I, CRI II, and TG/HDL-C and the severity CAD were assessed.

The study protocol was approved by the Jagiellonian University Medical College Ethics Committee (KBET:1072.6120.189.2020). Written informed consent was obtained from all study participants.

Laboratory tests

Lipid profile was obtained from fasting blood samples collected within 24 hr of admission and measured by the direct enzymatic colorimetric method, using commercial in vitro diagnostic devices (cobas c, Roche, Switzerland). CRI I, II, and TG/HDL-C were calculated manually using the following formulas: CRI I = total cholesterol (TC)/HDL-C and CRI II = low-density lipoprotein cholesterol (LDL-C)/HDL-C [6]; TG/HDL-C = triglycerides (TG)/HDL-C [7].

Definitions

AMI was defined according to the European Society of Cardiology guidelines [8]. MACE was defined as the composite of myocardial infarction (MI), in-stent restenosis, unstable angina (UA), stroke or transient ischaemic attack, and hospitalisation due to heart failure. Hypertension was defined as the use of antihypertensive drugs or a blood pressure of 140/90 mmHg or higher on at least two separate measurements. Diabetes was defined according to guidelines valid on the day of hospital admission [9].

Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were expressed as medians with the first and third quartiles. Normality was assessed by the Shapiro–Wilk test. Nonnormally distributed continuous variables were evaluated with Mann–Whitney and Kruskal–Wallis tests. Categorical variables were compared by the Fisher exact test for 2×2 tables or by the Pearson's χ^2 test for other tables. The Spearman's Rank correlation coefficient was used to determine dependence between the Gensini score and the examined indices. Stepwise logistic regression analysis was performed for determining the independent predictors of MACE and all-cause mortality. The final multivariable model included variables that were significant univariate predictors. A two-sided p-value <0.05 was considered to be statistically significant. All calculations were made using the STATISTICA 13.3 software package (TIBCO Software Inc., Palo Alto, CA, USA).

Results

Patients

Of the initial group of 2,300 patients, 852 were excluded due to diagnosis of STEMI, 142 were diagnosed with MINOCA, and 5 did not agree to participate in the study. The final analysis included 1,301 patients who met the inclusion criteria. The age of these participants was 70 (62-79) yrs, and most were male (67%). The occurrence of hypertension and diabetes was 90.4% (1,176) and 42.1% (548), respectively; moreover 47.5% (618) of the patients had been previously diagnosed with CAD.

Evaluation of MACE

At the end of 1-year follow-up, MACE had occurred in 142 (10.9%) of the participants. There were 72 cases of MI, 45 cases of UA, 29 cases of in-stent restenosis, 17 hospitalisations due to heart failure, and 8 cases of stroke or transient ischaemic attack. In addition, among those cases, 27 patients developed at least two incidents of MACE during the 1-year follow-up. These included 17 cases of MI with in-stent restenosis, 7 cases of UA and in-stent restenosis, 1 case of MI and hospitalisation due to heart failure, and 1 case of UA and stroke or transient ischaemic attack. In addition, 1 patient developed MI with in-stent restenosis and was hospitalised due to heart failure.

Detailed characteristics of the patients is showed in Supplementary. Comparison of the groups of patients with and without incidence of MACE revealed no significant differences in median body mass index (BMI), left ventricular ejection fraction (LVEF), Gensini score, eGFR, HDL-C, TG, TG/HDL-C ratio, use of lipid-lowering therapy prior to admission, all-cause mortality, or the percentage of males,

Table 1. Predictors of MACE (univariate regression analysis)

Predictors of MACE during 1-year follow up	OR	95% CI	p-value
Age	1.02	1–1.03	<0.01
CAD diagnosed prior to admission	2.14	1.49–3.07	<0.01
Diabetes	1.84	1.3–2.62	<0.01
CRI II	0.83	0.7–0.97	0.02

CAD, coronary artery diseasve; CRI, Castelli Risk Index; OR, odds ratio; CI, confidence interval.

and individuals diagnosed with hypertension. Patients with incidence of MACE were older, with higher incidence of diabetes and CAD diagnosed before the current admission. In addition, there were differences in median LDL-C, non-HDL-C, and TC; however these median values were lower than in patients with no incidence of MACE. Finally, there were significant differences in median CRI I and II, but those values appeared to be higher in patients with no occurrence of MACE.

CAD severity

Spearman's rank correlation coefficient analysis revealed weak positive correlation between CAD severity determined by the Gensini system score and CRI I (R=0.08, p=0.02). No correlation was found between CAD severity and CRI II (p=0.07) or between CAD severity and TG/HDL-C (p=0.6).

Predictors of MACE

Univariate regression analysis revealed that age, CAD diagnosed prior to admission, diabetes, and CRI II were significant predictors of MACE. In the multivariable model, CAD diagnosed prior to admission along with diabetes remained independent predictors of these events with odds ratio (OR) =1.98 (95% confidence interval (CI): 1.36–2.85, p<0.01) and OR=1.7 (95% CI:1.2–2.4, p<0.01), respectively. CRI II was an insignificant predictor in the multivariable model (p=0.2); moreover, in the univariate analysis, this indicator was a negative predictor (OR=0.83, 95% CI:0.7–0.97, p=0.02). Statistically significant predictors of MACE are listed in Table 1.

Predictors of MACE in subpopulations

To examine the predictive value of CRI I, II and TG/HDL-C in more homogenous cohorts, we performed several separate analyses. Predictors of MACE were analysed for patients with and without diabetes, with CAD diagnosed prior to admission, and for those with first manifestation of CAD.

In patients with diabetes, only CAD diagnosed prior to admission was a significant predictor of MACE. Moreover, it remained an independent predictor with OR=1.73 (95% CI:1.06–2.83, p=0.03). In patients without diabetes, CRI I, II, and CAD diagnosed prior to admission were significant predictors. However, CRI I and II appeared to be negative indicators, and only previously diagnosed CAD was an independent predictor (OR=2.16, 95% CI:1.24–3.75, p<0.01). Analysis revealed no significant predictor of MACE in the group of patients previously diagnosed with CAD. Thus, among patients with first manifestation of CAD, age along with diabetes were predictors of MACE. Furthermore, both parameters remained independent predictors with OR=1.03 (95% CI:1–1.06, p=0.03) and OR=2.05 (95% CI:1.14–3.67, p=0.01) respectively. Predictors of MACE in the subpopulations are showed in Table 2.

Predictors of 1-year mortality

The 1-year mortality rate was 13.4% (n=174), whereas in-hospital mortality was 1.2% (n=16). No difference was found in 1-year mortality between patients with and without occurrence of MACE. In univariate regression analysis, age, BMI, LVEF≤35% and eGFR were significant pre-

Table 2. Predictors of MACE in subgroups of patients according to univariate regression analysis

Predictors of MACE during 1-year follow-up	OR	95% CI	p-value
Patients with diabetes mellitus			
CAD diagnosed prior to admission	1.73	1.06–2.83	0.02
Patients without diabetes mellitus			
CAD diagnosed prior to admission	2.52	1.47–4.33	<0.01
CRI I	0.73	0.58–0.92	<0.01
CRI II	0.65	0.49–0.86	<0.01
Patients with first manifestation of CAD			
Age	1.03	1–1.06	0.01
Diabetes mellitus	2.23	1.25–3.96	<0.01

Abbreviations: see Table 1

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Table 3. Predictors of all-cause mortality during 1-year follow-up as shown by univariate regression analysis

Predictors of all-cause mortality during 1-year follow up	OR	95% CI	p-value
Age	1.08	1.06–1.1	<0.01
BMI	0.92	0.88–0.95	<0.01
LVEF ≤ 35%	6.2	1.8–21.1	<0.01
eGFR	0.97	0.96–0.98	<0.01

BMI, body mass index; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

dictors of all-cause mortality, however only LVEF≤35% remained a strong independent predictor (OR=6, 95% CI:1.7–22, p<0.01). CRI I, II and TG/HDL-C were insignificant predictors. Predictors of 1-year mortality are showed in Table 3.

Discussion

Elevated LDL-C and TG concentrations, as well as low HDL-C concentrations, have a relatively well-established role in the development of coronary atherosclerosis [10–12]. All of the lipoproteins containing apoB, especially those containing TG, may cross the endothelial boundary and form atherosclerotic plaques [13, 14]. It remains unknown whether a calculated ratio of those lipoproteins may reflect the proatherogenic capacity of lipoprotein complexes and predict cardiological outcomes among patients with AMI. To our knowledge, this study is the first to explore the predictive value of CRI I, II and TG/HDL-C when determined on hospital admission among patients with NSTEMI.

CRI I and II were initially introduced by Castelli et al. [6] as strong predictors of CAD. TG/HDL-C was introduced as a predictor of MI among patients with no prior history of CAD [7]. Since then, several studies regarding the potential use of those indices have been conducted worldwide. CRI I proved to be a predictor of AMI in middle-aged women [15], whereas CRI II was associated with the incidence of sudden cardiac death [16]. Both Castelli indices showed statistical significance for predicting peripheral arterial disease [17], intracranial atherosclerotic stenosis [18], and cardiovascular risk in men [19]. TG/HDL-C was correlated with increased risk of MACE [4], and it was also a predictor of long-term all-cause mortality in patients with high clinical likelihood of CAD [20]. As far as we are aware, the available literature describes no studies concerning predictive value of CRI I among patients with MI.

Jung et al. [21], studied patients who underwent PCI and achieved a target level of LDL-C (<1.8 mmol/l) during a follow-up period of 1–3 yrs, and assessed whether CRI I or a decrease in CRI I predicted MACE. They found no significant difference in MACE survival rates between the tertiles of CRI I or tertiles of decreases in CRI I. Moreover, the highest tertile of CRI I showed no prognostic value for the incidence of MACE.

A study, by Tian et al. [22] of patients with coronary heart disease with >50% stenosis in at least one of the major coronary segments and who had undergone PCI also revealed poor clinical value of CRI I. There were no significant associations between quartiles of CRI I and MACE, with and without adjustment for confounders (age, sex, BMI, diabetes, hypertension, smoking, alcohol consumption). Compared to the current study, patients in that study did not have AMI and, moreover, the study population was younger, with fewer individuals diagnosed with diabetes, hypertension, and CAD prior to admission. Those findings did, however, correspond with our results.

In addition, a study by Yu et al. [23] regarding the predictive value of CRI I among patients with type 2 diabetes showed that a CRI I value above 2.8 was a predictor of hospitalization and re-hospitalization due to cardiovascular disease. In contrast, in our study population, median value of CRI I was above 2.8 in both groups of patients (with and without incidence of MACE). We should emphasize that value proposed by Yu et al. is very low since other studies suggest that the target value of CRI I for patients with diabetes should be below 4.0 [24].

The predictive value of CRI II has been evaluated more extensively than has CRI I. Zhong et al. [25] assessed the predictive value of CRI II in patients with AMI after PCI during 1-year follow-up. Patients enrolled in the study were divided into two groups according to the median value of CRI II. MACE was defined as a composite of cardiovascular death, nonfatal MI, target lesion revascularisation, and stent thrombosis. Zhong et al. showed no statistical difference in CRI II for 1-year cardiovascular death and MI, whereas patients in the high CRI II group were more likely to have target lesion revascularisation, stent thrombosis, or MACE. Furthermore, age, diabetes and CRI II were independent predictors of MACE during the 1-year follow-up. In contrast, our study found a difference in median CRI II among patients with and without incidence of MACE, however patients with MACE had lower values. Moreover, CRI II was a negative predictor of MACE, but only in univariate regression analysis for the whole study population and for patients without diabetes. CRI II did not show significance as an independent predictor of MACE in any analysis. In our study, only CAD diagnosed prior to admission, along with diabetes, were independent

predictors of those events. Furthermore, we demonstrated no prognostic value of CRI II for all-cause 1-year mortality. Zhong et al. [25] provided a table with the number of patients with 1, 2 and 3 – vessel disease in the groups with low and high CRI II. Data in their table showed no statistical difference between those groups in the number of atherosclerotic vessels. However, in that study, no correlation analysis was provided, so we can assume that, if correlation analysis had been performed, it would have demonstrated no statistically significant correlation.

A study by Li et al. [26] of young male patients admitted with AMI, found that CRI II was a strong predictor of MACE. Moreover, patients with more severe, multivessel CAD had higher values of CRI II. Our study results are opposite to those of Li et al. However, a simple comparison is not possible, since patients in that study were younger, and the exclusion criteria were a history of prior MI, a history of PCI, and lipid-lowering drug therapy. The cut-off value for a high level of CRI II was 3.36 which, in our opinion, is relatively high.

Endo et al. [27] also examined the predictive value of CRI II, but their study was performed among patients with a previous history of PCI, and who had developed CAD after a stabilisation period of 6–12 mos. That research found that CRI II was an independent contributor to late target lesion revascularisation and new lesion revascularisation, particularly in patients with an LDL-C concentration >2.59 mmol/l. In our study, we did not perform a separate analysis for each component of MACE, however the majority of those events were MI, UA, and in-stent restenosis. We demonstrated no predictive value of CRI II among patients previously diagnosed with CAD.

TG/HDL-C has been often assessed as a marker of insulin resistance, however few studies among patients with AMI have been performed. Wan et al. [28] assessed the predictive value of TG/HDL-C among patients with STEMI who underwent PCI in 30-month follow-up. That study revealed that TG/HDL-C was an independent predictor of MACE in female patients but not in males. Moreover, in a study by Chen et al. [29], also performed among patients with STEMI, individuals with higher values of TG/HDL-C had superior 30-day and 1-year clinical outcomes than patients with low values. In that study, poor outcomes were associated with incidence of diabetes but not with a high value of TG/HDL-C. Chen et al. determined that TG/HDL-C greater than 3.5 in men and 2.5 in women was high. Our results, even though performed among patients with NSTEMI, partially correspond with those of Chen et al. In our analysis, TG/HDL-C did not show significance; however, the presence of diabetes was an independent predictor of MACE in the general population and in patients with the first manifestation of CAD.

The correlation between CRI I, II, and TG/HDL-C and CAD severity has not been widely investigated. Yang et al. [30] showed significance for the correlation between CAD severity and the values of CRI I and II. On the other hand, Song et al. [31] found no significant difference in mean CRI I and TG/HDL-C among patients divided into tertiles according to the Gensini score. There was, however, a difference in mean CRI II. Additionally, CRI I and II were significant predictors of the highest tertile of the Gensini score, but, after adjustments for confounders, both indices were statistically insignificant in multivariable models. Also, TG/HDL-C was insignificant in univariate analysis. Those authors suggested that another parameter assessed in the study, apoB100/apoAI, might be used as a predictor of the severity of CAD, but no recommendation for the use of CRI I and II was given. Our study found no correlation for CAD severity with CRI II or TG/HDL-C. There was, however, a correlation between CAD and CRI I, but it was very weak with borderline significance.

Study limitations

This study has several limitations:

1) a relatively short follow-up period;
2) insufficient information concerning patient compliance with prescribed therapy;
3) shortage of information concerning cause of death.

Finally, no values of the analysed lipid parameters were obtained during the follow-up period.

Conclusions

Even though this study showed some statistically significant dependences between CRI I, CRI II, and the incidence of MACE in different subgroups of patients, we believe that CRI I and CRI II should not be used in everyday clinical practice, since their predictive value appears to be both weak and negative, and none proved to be an independent predictor of MACE. Moreover, correlation between CRI I and CRI II and severity of CAD was either insignificant or very weak. In addition, our study showed that TG/HDL-C should not be considered in patients with NSTEMI. Furthermore, neither CRI I, CRI II or TG/HDL-C was a predictor of all-cause mortality. We believe that our findings do not justify the use of these indices. However, additional, larger studies should be performed to further evaluate these parameters.

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No conflict of interest is reported.

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Application: Supplementary Tables

Application 1. Demographic and clinical characteristics of patients with and without incidence of MACE during 1-year follow-up

Variables	Patients with incidence of MACE during 1-year follow-up (n=142)	Patients with no incidence of MACE during 1-year follow-up (n=1159)	p-value
Male gender	98 (69)	774 (66.8)	0.59
Age, years*	73 (64-80)	70 (62-79)	0.02
BMI, kg/m^2*	26.5 (24–30.1)	27.3 (24.4–30.1)	0.3
CAD diagnosed prior to admission	91 (64)	527 (45.5)	<0.01
LVEF, %*	50 (40–55)	48 (35–60)	0.58
Hypertension	131 (92.2)	1045 (90.1)	0.4
Diabetes	79 (55.6)	469 (40.5)	<0.01
Gensini score	62 (27-113)	54 (27-96)	0.18
eGFR, ml/min/1.73 m^2*	52.5 (40.3–64)	55.6 (45–65.9)	0.07
CRI I	3.42 (2.68–4.23)	3.68 (2.9–4.61)	0.02
CRI II	1.97 (1.4–2.75)	2.32 (1.6–3.12)	<0.01
TG/HDL-C ratio	1.06 (0.7–1.74)	1.11 (0.76–1.66)	0.3
LDL-C, mmol/l*	2.29 (1.62–3.17)	2.61 (1.98–3.5)	<0.01
HDL-C, mmol/l*	1.12 (0.88–1.42)	1.16 (0.97–1.4)	0.45
Non-HDL-C, mmol/l*	2.6 (2–3.62)	3 (2.35–3.94)	<0.01
TC, mmol/l*	3.98 (3.15–4.9)	4.23 (3.55–5.15)	<0.01
TG, mmol/l*	1.18 (0.93–1.65)	1.28 (0.98–1.72)	0.06
Lipid-lowering therapy prior to admission	114 (80.3)	998 (86.1)	0.06
All-cause mortality	12 (8.5)	162 (14)	0.07

Data are number (percentage) or median (interquartile range). p<0.05 was considered significant. BMI, body mass index; CAD, coronary artery disease; CRI, Castelli Risk Index; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, Major Adverse Cardiovascular Events; non-HDL-C, non-high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

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