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CLINICAL STUDY

Prognostic significance of atherogenic index of plasma, atherogenic coefficient and lipoprotein combined index among elderly patients with non-ST-segment elevation myocardial infarction in 1-year follow-up

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ABSTRACT
OBJECTIVES: Coronary artery disease (CAD) remains a leading cause of death in elderly patients. Recently, novel lipoproteins- Atherogenic Index of Plasma (AIP), Atherogenic Coefficient (AC) and Lipoprotein Combine Index (LCI) have been suggested as CAD risk factors; their clinical usefulness, however, remains unknown. The aim of the study was to assess the predictive value of AIP, AC and LCI concerning incidence of major adverse cardiovascular events (MACE) and all-cause mortality in 1-year follow-up.
METHODS: For the study, 1,083 patients, aged 60 or older, with NSTEMI were enrolled and divided into two groups: young-old and old-old.
RESULTS: MACE occurred in 11.8 % of the patients; LCI showed a borderline significance, but only in univariate analysis. Analysis in groups revealed ambiguous results. None of the examined indices was a predictor of MACE in the young-old group whereas all three of them were significant, but negative predictors in the old-old group. Finally, all-cause mortality at follow-up was 14.9 %. AC predicted 1-year mortality in the whole study population (OR = 1.1 (95% CI: 1–1.2; p = 0.02), but was insignificant in the multivariable model. Additionally, it was an independent predictor in the old-old group, but with borderline significance (OR = 1.14 (95% CI: 1–1.3, p = 0.036).
CONCLUSIONS: AIP, AC and LCI should not be used as predictors of MACE and 1-year mortality among elderly patients with NSTEMI *(Tab. 5, Ref. 23)*. Text in PDF *www.elis.sk*
KEY WORDS: AIP, AC, LCI, NSTEMI, MACE, all-cause mortality.

Introduction

Population aging is a global phenomenon that affects healthcare systems throughout the world. According to Eurostat data, in 2017, the percentage of people aged 60 years and older was 25.6 % of the European Union population and 23.5 % for Poland (1). Moreover, this percentage is continuously increasing (1).

Cardiovascular disease remains the leading cause of death, especially among older individuals. Prevention of acute myocardial infarction (AMI), including NSTEMI, is one of the main goals of modern cardiology. Therefore, much effort is put into eliminating cardiovascular risk factors, both in primary and secondary prevention.

In recent years, several novel indicators have been proposed as non- traditional cardiovascular risk factors, however their significance and usefulness remains unknown (2–5).

The aim of this study was to evaluate the prognostic significance of the Atherogenic Index of Plasma (AIP), Atherogenic Coefficient (AC) and Lipoprotein Combine Index (LCI) among patients aged 60 years and older, who were admitted to our department due to NSTEMI. We assessed the prognostic value of these indices for the occurrence of Major Adverse Cardiovascular Events (MACE) and all-cause mortality in 1-year follow-up.

Methods

A retrospective, cross-sectional and observational study was conducted among 1,100 patients admitted to our department between 2018 and 2020 with NSTEMI. The patients, who met the inclusion criteria were consecutively recruited for the study.

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Inclusion criteria were diagnosis of NSTEMI, coronary angiography performed on admission with the presence of hemodynamically relevant atherosclerosis and age of at least 60 years on the day of admission.

In turn, the study exclusion criteria were diagnosis of STEMI, unstable angina (UA), AMI with non-obstructive coronary artery disease (CAD) (i.e. with MINOCA), cardiogenic shock on admission, the necessity of hemodialysis before or during hospitalization and age under 60 years on the day of admission.

After coronary angiography, PCI with stent implantation or coronary artery bypass grafting was performed if there were indications for these procedures. The severity of CAD in each patient was assessed by two experienced invasive cardiologists using the Gensini score system (6). In addition, laboratory tests and echocardiography were undertaken. Finally, data on MACE and all-cause mortality were obtained from hospital records and through interviews (telephone consultations or visits to our outpatient clinic) with the patients or their families one year after NSTEMI.

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

Laboratory measurements

Fasting blood samples were collected within 24-hours of admission. Concentrations of lipoproteins: TC, HDL-C, LDL-C and TG were measured by the direct enzymatic colorimetric method, using commercial in vitro diagnostic devices (cobas c, Roche, Switzerland) whereas non-HDL-C was calculated manually (Non-HDL-C= TC-HDL-C). AIP, AC and LCI were also calculated manually using the following formulas: $AIP=Log_{10}(TG/HDL\text{-}C)$; AC= Non-HDL-C/HDL-C; LCI= TC*TG*LDL-C/HDL-C (3, 7).

Definitions

Old age was defined in accordance with the World Health Organization (WHO) definition (8). MACE was a composite of AMI, in-stent restenosis, UA, stroke or transient ischemic attack and hospitalization due to heart failure. AMI was defined in accordance with the European Society of Cardiology guidelines - the Fourth Universal Definition of Myocardial Infarction (9). CAD diagnosed prior to admission was a documented coronary artery stenosis revealed by coronary angiography or coronary computed tomography angiography performed at any time before this particular hospitalization. Blood pressure of 140/90 mmHg or higher, on at least two separate measurements, or use of antihypertensive drugs were defined as hypertension. Finally, use of hypoglycemic drugs or diabetes diagnosed prior to admission were classified as diabetes (10).

Statistical analysis

All the calculations were made using the STATISTICA 13.3 software package (TIBCO Software Inc., Palo Alto, CA, USA). A two-sided p-value <0.05 was considered to be statistically significant. Categorical variables were expressed as numbers and percentages and compared by the Fisher exact test for 2x2 tables or by Pearson's χ^2 test for other tables. Continuous variables were expressed as medians with the first and third quartiles. Normality was assessed by the Shapiro-Wilk test. Non-normally distributed continuous variables were evaluated with the Mann-Whitney and Kruskal-Wallis tests. 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 predictors in univariate analysis. Due to the retrospective and observational character of the study, power analysis to estimate the required sample size was not performed.

Results

Patients

For the initial analysis, we enrolled 1,100 patients aged 60 years and older admitted with NSTEMI. A total of seven patients were excluded because of long term hemodialysis treatment. Four patients were excluded due to cardiogenic shock on admission and six people did not agree to participate in the study.

The final study group consisted of 1,083 patients with the median age of 73 years, of whom 63.6 % (n = 689) were male. The median body mass index (BMI) was 27 kg/m^2. The majority of the patients (92.2 %) suffered from hypertension while 48.5 % (n

Tab. 1. Characteristics of the study population.

Variables	Young-old (n=585)	Old-old (n=498)	p
Male gender, n (%)	416 (71.1)	273 (54.8)	<0.01
BMI, kg/m2*	27.7 (25.2–30.8)	26 (23.4–29)	<0.01
CAD diagnosed prior to admission, n (%)	278 (47.5)	247 (49.6)	0.5
LVEF, %*	55 (45–60)	45 (39–55)	0.03
Hypertension, n (%)	539 (92.1)	460 (92.4)	0.9
Diabetes, n (%)	244 (41.7)	242 (48.6)	0.02
Gensini score	56 (26–96)	64 (32–108)	0.06
eGFR, ml/min/1.73 m^2*	56.3 (46.2–65.8)	50.3 (39.4–60.6)	<0.01
AIP*	0.08 (–0.08 – 0.25)	–0.02 (–0.17 – 0.1)	<0.01
AC*	2.73 (1.95–3.67)	2.3 (1.6–3)	<0.01
LCI*	13.9 (7.3–24.5)	8.7 (4.6–15)	<0.01
LDL-C, mmol/l*	2.66 (2–3.5)	2.3 (1.7–3)	<0.01
HDL-C, mmol/l*	1.15 (0.96–1.4)	1.2 (1–1.45)	<0.01
Non-HDL-C, mmol/l*	3 (2.4–3.96)	2.7 (2.1–3.5)	<0.01
TC, mmol/l*	4.3 (3.6–5.15)	4 (3.3–4.7)	<0.01
TG, mmol/l*	1.34 (1–1.85)	1.12 (0.87–1.44)	<0.01
Lipid- lowering therapy prior to admission, n (%)	515 (88)	404 (81)	<0.01
Incidence of MACE, n (%)	61 (10.4)	67 (13.4)	0.12
1-year mortality, n (%)	45 (7.7)	117 (23.5)	<0.01
In- hospital mortality, n (%)	5 (2.4)	10 (5.3)	0.12

*Data are shown as median (interquartile range) unless otherwise indicated. p < 0.05 was considered significant. AC – Atherogenic Coefficient; AIP – Atherogenic Index of Plasma; BMI – body mass index; CAD – coronary artery disease; eGFR – estimated glomerular filtration rate; HDL-C – high-density lipoprotein cholesterol; LCI – Lipoprotein Combine Index; LDL-C – low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; MACE – Major Adverse Cardiovascular Events; non-HDL-C – non-high-density lipoprotein cholesterol; TC – total cholesterol; TG – triacylglycerol

Tab. 2. Demographic and clinical characteristics of patients with and with no incidence of MACE in 1-year follow-up.

Variables	Patients with incidence of MACE in 1-year follow – up n=128	Patients with no incidence of MACE in 1-year follow – up n=955	p
Male gender, n (%)	86 (67.2)	603 (63.2)	0.4
Age, years*	75 (66.5–81)	73 (67–80)	0.4
BMI, kg/m2*	26.5 (24–29.9)	27.2 (24.2–30)	0.4
CAD diagnosed prior to admission, n (%)	80 (62.5)	445 (46.6)	<0.01
LVEF, %*	50 (40–55)	50 (38–60)	0.8
Hypertension, n (%)	119 (93)	880 (92.2)	0.7
Diabetes, n (%)	72 (56.2)	414 (43.3)	<0.01
Gensini score	64 (27–119,5)	56 (28–100)	0.18
eGFR, ml/min/1.73 m2*	51.8 (40–63.7)	53.8 (42.9–64.4)	0.4
AIP*	–0.02 (–0.16 –0.23)	0.03 (–0.13 –0.19)	0.4
AC*	2.27 (1.63–3.16)	2.57 (1.8–3.42)	0.02
LCI*	8.32 (4–17)	11.4 (6–20.3)	<0.01
LDL-C, mmol/l*	2.14 (1.56–3)	2.51 (1.94–3.31)	<0.01
HDL-C, mmol/l*	1.14 (0.88–1.46)	1.17 (0.98–1.4)	0.5
Non-HDL-C, mmol/l*	2.5 (2–3.56)	2.93 (2.3–3.8)	<0.01
TC, mmol/l*	3.83 (3–4.76)	4.17 (3.51–5)	<0.01
TG, mmol/l*	1.17 (0.93–1.53)	1.25 (0.97–1.64)	0.09
Lipid- lowering therapy prior to admission, n (%)	103 (80.5)	816 (85.4)	0.14

* Data are shown as median (interquartile range) unless otherwise indicated. P <0.05 was considered significant. Abbreviations see Tab. 1.

Tab. 3. Predictors of MACE in 1-year follow-up (univariate regression analysis).

Predictors of MACE in 1-year follow up	OR	95% CI	p
LCI	0.98	0.97–0.99	0.03
Diabetes	1.68	1.16–2.44	<0.01
CAD diagnosed prior to admission	1.9	1.3–2.8	<0.01

OR – odds ratio; others, see Table 1

Tab. 4. Predictors of all-cause mortality in 1-year follow-up (univariate regression analysis).

Predictors of all-cause mortality in 1-year follow up	OR	95% CI	p
AC	1.1	1–1.2	0.02
GFR	0.97	0.96–0.99	<0.01
LVEF ≤ 30 %	6.28	1.8–21.8	<0.01
BMI	0.91	0.87–0.95	<0.01
Age	1.1	1.07–1.12	<0.01

Abbreviations see Tab. 1.

= 525) of the study participants had previously diagnosed CAD and 44.9 % (n = 486) had diabetes.

Initially, we aimed to divide the patients into three groups according to the age categories defined by WHO (8): young-old (age 60–74 years), old-old (age 75–89 years) and oldest-old (age 90 years and older). However, in the oldest-old group there was only one participant with incidence of MACE, thus statistical analysis of the predictors of these events was not possible for that group. Finally, the patients were divided into two groups according to age. The first group consisted of patients aged 60–74 years, referred to as young-old, and the second included patients aged 75 years and older, referred to as old-old. The characteristics of these groups are shown in Table 1.

Analysis of MACE and 1-year mortality

MACE occurred in 11.8 % (n = 128) of the patients; in-hospital mortality rate was 1.4 % (n = 15), whereas 1-year mortality was 14.9 % (n = 162).

The following MACE occurred: 46 cases of AMI, 32 of UA, 14 of hospitalization due to heart failure, seven of stroke or transient ischemic attack and four of in-stent restenosis. Moreover, there were 24 patients, who developed two incidences of MACE in 1-year follow-up (16 cases of AMI and in-stent restenosis, six of UA and in-stent restenosis, one of UA and AMI and one of hospitalization due to heart failure and AMI). In addition, one patient was hospitalized due to heart failure, AMI and in-stent restenosis. Detailed characteristics of the patients with and without MACE are presented in Table 2.

Predictors of MACE

Univariate regression analysis revealed that LCI, diabetes and CAD diagnosed prior to admission were significant predictors of MACE, however LCI showed borderline significance. AIP and AC were insignificant in univariate analysis (p = 0.3, p = 0.08 respectively). Furthermore, only diabetes and CAD diagnosed before admission remained independent predictors in the multivariable model (OR = 1.64 (95% CI: 1.1–2.4, p < 0.01), OR = 1.75 (95% CI: 1.2–2.6, p < 0.01) respectively). LCI was insignificant (p = 0.1). The predictors of MACE are presented in Table 3.

Predictors of 1-year mortality

Predictors of 1-year mortality are shown in Table 4. LCI and AIP did not prove to be significant predictors of such mortality (p = 0.2 and p = 0.9, respectively). AC was a predictor of all-cause mortality but with borderline significance. Neither of the lipid indices assessed in the study was significant in the multivariable model. Only LVEF ≤ 30 % remained an independent predictor of 1-year mortality (OR = 6.5 (95% CI: 1.5–28, p = 0.01)).

Predictors of MACE and 1-year mortality in subpopulations

None of the examined indices showed a statistical significance as a predictor of MACE in the young-old patient group. Only CAD diagnosed prior to hospital admission was a predictor of those events, moreover it remained an independent predictor in the multivariable model (OR = 2.2 (95% CI: 1.3–3.9, p < 0.01).

Surprisingly, all lipid indices assessed in the study appeared to be significant, but negative predictors of MACE in the old-old subpopulation, however they were not significant as independent predictors. Only diabetes was an independent indicator with OR=1.75 (95% CI: 1.01–3.02, p = 0.04).

AC, AIP and eGFR were predictors of all-cause mortality in the young-old population, however none of them remained an in-

Tab. 5. Predictors of MACE and all-cause mortality in 1-year follow-up in subgroups of patients (univariate regression analysis).

Young-Old Patients			
Predictors of MACE in 1-year follow-up	OR	95% CI	p
CAD diagnosed prior to admission	2.28	1.3–3.9	<0.01
Predictors of 1–year morality	OR	95% CI	p
AC	1.2	1–1.4	0.04
AIP	3.2	1.1–10.3	0.04
eGFR	0.97	0.95–0.99	<0.01
Old-Old patients			
Predictors of MACE in 1-year follow-up	OR	95% CI	p
AIP	0.32	0.1–0.9	0.04
AC	0.65	0.5–0.85	0.01
LCI	0.94	0.91–0.98	0.03
Diabetes	1.8	1.1–3	0.02
Predictors of 1-year mortality	OR	95% CI	p
AC	1.1	1–1.3	0.04
eGFR	0.98	0.97–0.99	0.02
BMI	0.93	0.87–0.97	<0.01

Abbreviations see Tab. 1.

dependent indicator. In the old-old group, the AC, eGFR and BMI were predictors of all-cause mortality. Furthermore, all of them appeared to be independent indicators in multivariable analysis, with OR = 1.14 (95% CI: 1–1.3, p = 0.036) for AC, OR = 0.98 (95% CI: 0.97–0.99, p < 0.01) for eGFR and OR = 0.94 (95% CI: 0.89–0.99, p = 0.026) for BMI, respectively.

Predictors of MACE and 1-year mortality in subgroups are shown in Table 5.

Discussion

A proper concentration of basic lipoproteins has a well-established position in both primary and secondary prevention of cardiovascular disease; however the genesis of atherosclerosis is complex and not yet fully examined. In everyday clinical practice, only basic blood plasma lipoproteins are routinely measured, therefore some new, calculated lipid indices have attracted the attention of researchers and have been proposed as potential novel predictors of CAD. It is thought that those indices might represent lipoproteins that are not routinely assessed because of cost and complexity of measurement.

In blood plasma, there are many lipoproteins that reflect atherogenic and antiatherogenic potential of the serum. Non-HDL-C is a surrogate marker of atherogenic apolipoprotein B, which reflects a serum concentration of cholesterol contained in atherogenic lipoproteins, whereas apolipoprotein AI, a major component HDL-C, reflects the antiatherogenic potential of the plasma (11). Therefore AC, a ratio of Non-HDL-C to HDL-C, was introduced as a risk factor for development of cardiovascular disease in various populations (3, 4, 12).

A wide analysis of the available literature revealed no studies concerning the predictive value of AC among the patients with AMI as well as in the patients with chronic coronary syndrome. As we mentioned before, this index was only used as a predictor for the development of atherosclerosis, so our study, performed among the patients with hemodynamically relevant atherosclerosis, is unique in that field.

AIP was initially introduced by Dobiasova et al (7) as a surrogate marker for an atherogenic lipoprotein: small dense low-density lipoprotein cholesterol. Dobiasova proved that a simple logarithmic transformation of the routinely examined serum lipid concentrations determines lipoprotein particle size, moreover AIP was inversely related to LDL-C diameter (13). This lipid parameter was previously assessed as a strong marker for predicting the risk of CAD (14–16), however none of those studies were performed among elderly patients with NSTEMI.

Ma et al (17), in their study, assessed the predictive value of AIP concerning incidence of MACE among 798 patients with AMI, undergoing PCI and diagnosed with type 2 diabetes mellitus. In contrast to our study, Ma et al. research was performed among a younger population (mean age 61 years versus median age of 73 years in our study), moreover, the mean age of the individuals in the highest quartile of the AIP group was only 58 years, so a simple comparison of those studies is not accurate. Furthermore, the study group was more heterogeneous than ours (included STEMI, NSTEMI and UA) and, additionally, the patients with LVEF < 30 % and with prior coronary artery bypass grafting were excluded.

The primary endpoint of the Ma et al. study was a composite of all-cause death, non-fatal AMI, non-fatal ischemic stroke and unplanned repeat revascularization, whereas the secondary endpoint was a composite of cardiovascular death, non-fatal AMI, and non-fatal ischemic stroke. The study showed that the patients with the highest values of AIP had a higher incidence of primary endpoint, however such dependence was insignificant for the secondary endpoint. Moreover, incidence of all-cause death, cardiovascular death, non-fatal ischemic stroke and non-fatal MI did not differ among the AIP quartiles at follow-up. Ma et al performed another analysis – Cox proportional hazards analyses – where they showed that AIP in the highest quartile was a strong and independent predictor of both primary and secondary endpoint at follow-up. In contrast, we revealed no difference in median value of AIP between the patients with and with no incidence of MACE. Furthermore, AIP was an insignificant predictor of MACE for the whole study population, but it showed statistical significance as a predictor of MACE in the old-old group. It was, however, a negative predictor.

The Bendzala et at (18) study involved a similar age group to that which we researched – the patients older than 60 years – where they assessed the predictive value of AIP concerning 10-year all-cause death. AIP was a strong independent positive predictor of all-cause death, however only in women and no dependence was found for men. In our study, AIP was a predictor of all-cause death only in the young-old group; moreover, it was insignificant in multivariable analysis.

Another study concerning the occurrence MACE and AIP values was performed by Zhu et al (19). That research assessed the incidence of a single MACE (in-stent restenosis) in 6–18 months of follow-up after PCI performed because of AMI. In-stent restenosis occurred in 15.1 % (n = 199) of the study group and AIP value was higher among the patients with in-stent restenosis. Moreover, this index was an independent positive predictor of these events.

In our study, in-stent restenosis occurred in 27 (1.6 %) of the patients; we did not assess dependence for each MACE separately. Furthermore, in our study there was no difference in median AIP among the patients with and without incidence of MACE.

According to Dobiasova (20), AIP values of –0.3 to 0.1 are associated with low cardiovascular risk, 0.1 to 0.24 with medium and those above 0.24 with high risk. In our study, median AIP was below 0.1 in all the subgroups, despite the fact that all the patients had AMI, indicating that their cardiovascular risk should be high at the baseline. Moreover, in old-old patients, this index was a negative predictor of MACE, therefore individuals with lower values of AIP were more likely to suffer these events. We found one study that partially corresponds with our findings. Hartopo et al (21), in their study, assessed the incidence of MACE during hospitalization because of AMI and showed that a low AIP value (< 0.24) was an independent predictor of in-hospital all-cause mortality. In our study, we did not assess MACE during hospitalization, but at 1-year follow-up. However, these findings showed that the use of AIP in clinical practice remains controversial.

There are few studies assessing LCI. This index has proved to be a predictor of the development of CAD (3), moreover, a positive correlation between LCI and CAD was found among kidney transplant recipients (22). LCI was never evaluated among elderly patients with NSTEMI.

We found only one study concerning values of LCI among the patients with AMI. Si et al (23) compared the patients with AMI to those with no hemodynamically relevant stenosis in coronary arteries (no stenosis or stenosis less than 50 % of the vessel) and discovered that the patients with AMI were more likely to have higher values of LCI. Moreover, a cut-off point of 16 was proposed as an optimal diagnostic value. Additionally, in that study, LCI > 16 was an independent predictor of AMI. In contrast, in our study, the median LCI value was lower than 16 in both young-old and old-old groups and all the patients had AMI. We believe that the LCI value that predicts AMI proposed by Si et al might be too high.

Study limitations

This study has several limitations. Firstly, a relatively short follow-up period. Secondly, no analysis of the values of AIP, AC, LCI and their potential changes during follow-up period was conducted. Furthermore, we evaluated those parameters in a homogeneous group of patients with NSTEMI. Additionally, a thorough analysis, involving the patients with STEMI and UA, should be performed in the future. Finally, this was a single-center study, therefore a multi-regional and multi-ethnic study is needed.

Conclusions

Although our study showed that LCI is a predictor of MACE and AC predicts all-cause 1-year mortality among elderly patients with NSTEMI, we believe that those indices should not be used in everyday clinical practice. Both showed a borderline significance and, moreover, they were not independent predictors. Analysis in subgroups, divided according to participants age, brought even more ambiguous results. On the one hand, all of the examined indices proved to be negative, but not independent predictors of MACE in the old-old group, but on the other hand AC and AIP appeared to be positive predictors of 1-year mortality in the young-old group. AC was even an independent predictor of 1-year mortality in the old-old group. To conclude, we believe that AC, AIP and LCI should not be used in predicting poor clinical outcomes in the elderly patients with NSTEMI and further, larger studies should be performed to prove the potential clinical usefulness of these indices.

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