Low Plasma Atherogenic Index Associated with Poor Prognosis in Hospitalized Patients with Acute Myocardial Infarction

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ABSTRAK

Tujuan: *pengaruh nilai indeks aterogenik plasma (IAP) yang dihitung dari rumus logaritme rasio trigliserid:HDL (log10.[TG:HDL]) terhadap kejadian kardiovaskular mayor selama perawatan infark miokard akut (IMA) belum sepenuhnya disepakati. Penelitian ini bertujuan mengetahui peran IAP dalam memprediksi kejadian kardiovaskular mayor selama perawatan IMA.* ***Metode:*** *penelitian ini merupakan studi kohort prospektif. Subjek merupakan pasien IMA yang dirawat di perawatan intensif koroner RSUP Dr. Sardjito, Yogyakarta. Nilai IAP diukur dari darah puasa dalam 24 jam admisi rumah sakit. Kolesterol total, LDL, HDL, dan trigliserida (TG) diukur dan nilai IAP ditentukan dengan rumus log10. [TG:HDL]. Berdasarkan nilai IAP, subjek dialokasikan menjadi IAP rendah (<0,24) dan IAP tinggi (≥0,24). Luaran penelitian ini adalah kejadian kardiovaskular mayor selama perawatan intensif yang berupa kumpulan dari kematian semua sebab, gagal jantung akut, syok kardiogenik, kejadian re-infark, dan VT/VF yang diresusitasi.* ***Hasil:*** *sebanyak 277 subjek direkrut dalam penelitian ini. Grup IAP tinggi terdiri dari 213 subjek (77%) dan grup IAP rendah terdiri dari 64 subjek (33%). Selama perawatan intensif, 66 subjek (24%) mengalami kejadian kardiovaskular mayor dan 20 (7%) subjek meninggal dunia (kematian semua sebab). Insidens kejadian kardiovaskular mayor cenderung lebih besar pada kelompok IAP rendah, meskipun tidak bermakna secara statistik. Insidens kematian semua sebab secara bermakna lebih tinggi pada kelompok IAP rendah (14%) dibandingkan IAP tinggi (5%). Analisis multivariat menunjukkan bahwa IAP rendah memprediksi secara independen kematian semua sebab dengan rasio risiko 3,71 (95% CI 1,26–10,97, nilai p=0,02).* ***Kesimpulan:*** *nilai IAP rendah (<0,24) merupakan prediktor independen kematian semua sebab selama perawatan intensif pada pasien infark miokard akut.*

Kata kunci: *lipid aterogenik, indeks aterogenik plasma, kejadian kardiovaskular mayor, kematian.*

ABSTRACT

Aim: *the impact of atherogenic index of plasma (AIP), calculated as logarithmic of triglyceride:HDL ratio (log10.[TG:HDL]), on major adverse cardiovascular events (MACE) during acute myocardial infarction (AMI) has not been fully accepted. This study aims to investigate the role of AIP in predicting major adverse cardiovascular events following AMI during intensive care in the hospital.* ***Methods:*** *this was a prospective cohort study. We enrolled subjects with AMI hospitalized in intensive coronary care unit at Dr. Sardjito General Hospital, Yogyakarta. The AIP was measured in fasting blood within 24 hours of hospital admission. The total cholesterol, LDL, HDL, and triglyceride (TG), were measured and AIP value was determined as log10. [TG:HDL]). Based on AIP value, subjects were allocated into low AIP (<0.24) and high AIP (≥0.24). The*

outcome of the study was major adverse cardiovascular events during hospitalization, i.e. multipart of all cause mortality, acute heart failure, cardiogenic shock, reinfarction, and rescucitated VT/VF. ***Results:*** *among 277 subjects, the high AIP group comprised 213 subjects (77%) and low AIP group comprised 64 subjects (33%). During intensive hospitalisation, 66 subjects (24%) developed MACE and 20 subjects (7%) developed fatal outcome (all cause mortality). The incidence of MACE tended to be higher in low AIP group, however its difference was not significant. The incidence of all cause mortality was significantly higher in low AIP group (14%) than in high AIP group (5%). Multivariable analysis showed that low AIP predicted all cause mortality independently with a risk ratio 3.71 (95% CI 1.26 – 10.97, p=0.02).* ***Conclusion:*** *low AIP value (<0.24) is an independent predictor for all cause mortality in patients with acute myocardial infarction undergoing intensive hospitalisation.*

Keywords: *atherogenic lipids, atherogenic index of plasma, major adverse cardiovascular events, mortality.*

INTRODUCTION

The atherogenic lipid is the main risk factor for coronary artery disease. Atherogenic lipids drive the capability of plasma lipid in mediating atherosclerotic plaque formation in coronary artery. The ability of plasma lipid to migrate into the subintimal layer is an important step to developing atherosclerosis. Lipid and its lipoprotein constituent have been designated as a mediator and a marker of coronary heart disease. Several atherogenic lipids in the blood that have been identified are high level of LDL cholesterol, the high ratio of LDL cholesterol to HDL cholesterol and high level of triglyceride.[1] Atherogenic lipoproteins that have been identified are the high apoliprotein B, low apolipoprotein A1 and the high ratio of apoB: apoA1.[2,3] In addition to lipid and lipoprotein particles, the size of the lipid particles such as small dense LDL also affects the formation and progression of coronary atherosclerosis.[3]

Atherogenic plasma lipid is a reflection of the degrees of plasma atherogenicity. Atherogenic plasma lipid assessment can be used to as a marker that is simple and practical in daily clinical practice. Lipid examination has been widely used in the routine evaluation of patients at risk of cardiovascular disease in general and coronary heart disease in particular.[4] The atherogenic index of plasma (AIP), developed from the 10 logarithmic ratio of triglyceride and HDL cholesterol level, was an indicator of smaller LDL particles and HDL fractional esterification rate that reflects the presence of atherosclerotic disease.[5]

Acute myocardial infarction (AMI) is a clinical spectrum of coronary heart disease that indicates the formation of acute occlusive thrombus in coronary atherosclerotic lesions. In patients with AMI, decreased levels of atherogenic plasma lipids, especially LDL cholesterol and apoB with statins treatment have shown positive results for the secondary prevention after myocardial infarction.[6] In the short term, the impact of atherogenic plasma lipid during hospital care in AMI get less attention than its long term impact before and after the event. Patients with AMI are at risk of MACE that occurred both at admission and during hospital treatment. Our previous data show that about 45% of patients with AMI experienced MACE during hospitalisation.[7,8] The role of AIP value in affecting major adverse cardiovascular events during hospitalisation in AMI is unclear because only few studies have been conducted and they showed conflicting results.

This study aims to investigate whether the AIP value associates with MACE, both fatal or non-fatal events during intensive hospitalization in patients with AMI. This study also investigated whether AIP value acts as a predictor of MACE in patients with AMI.

METHODS

This is a prospective cohort study. We enrolled consecutively, between August 2013 and April 2015, patients with AMI admitted and hospitalized in the intensive coronary care unit (ICCU) at Dr. Sardjito General Hospital, Yogyakarta, Indonesia.

Subjects

We included patients with inclusion criterias: (1) patients with AMI and diagnosed as ST-segment elevation acute myocardial infarction (STEMI) and NSTEMI, based on ACC/AHA and ESC guideline criteria,[9] (2) patients with an identifiable onset of anginal pain ≤24 hours with exception those with NSTEMI, (3) patients with age between 30 and 75 years old, and (4) patients agreed to participate in the study by signing an informed consent. We excluded patients who had exclusion criterias: (1) patients with known chronic heart failure, chronic kidney disease, liver cirrhosis, chronic inflammatory diseases, and malignancy, (2) patients with concomitant severe acute infection and sepsis, (3) patients with concomitant acute stroke, (4) patients taking regular antihyperlipidemic medication before admission, and (5) patients already revascularized (fibrinolysis) before admission.

Variables

We collected and recorded the sociodemographic, risk factors, and clinical presentation data. Diabetes mellitus was determined as subjects with previously known diabetic or those taking antidiabetic medication on admission. Hypertension was determined as subjects with previously known hypertension or those taking antihypertensive medications or those with systolic blood pressure ≥150 mmHg and diastolic blood pressure ≥90 mmHg. Smoking was determined as having been smoking cigar and/or cigarettes within previous month until current event. Chronic heart failure, chronic kidney disease, hepatic cirrhosis and malignancy were determined by history taking. Chronic inflammatory diseases, i.e. rheumatoid arthritis, inflammatory bowel disease or psoriasis, was also unravelled through history taking. Severe acute infection was determined as fever and known focal infection. Sepsis was determined based on standard criterias and confirmed by an internist in consultation. Acute stroke was determined as an infarct or hemorrhage stroke, confirmed by a neurologist. The diagnosis of STEMI and NSTEMI was in accordance with the criteria of ACCF/AHA and ESC.[9]

For laboratory examination, we collected the venous blood from the antecubital veins in supine position in every subject. Blood collection was performed on admission, before revascularisation, and anticoagulant therapy started, and after fasting in early morning. Routine blood cell counts, renal function and random glucose were measured using on admission sample with an automated blood cell counter and chemistry analyzer in the hospital laboratory. Blood samples for atherogenic plasma lipid measurement was taken using fasting blood sample (within 24 hours from admission). The lipid profiles were total cholesterol, low density liporotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride (TG). They were measured with a chemistry analyzer in the hospital laboratory. The AIP was determined by calculation based on formula =10 logarithmic of [TG:HDL].[5] Based on previous classification of AIP value[10], we divided the subjects into two categories, which are low AIP (<0.24) and high AIP (≥0.24).

We monitored the clinical progression and treatment strategy of the subjects during intensive hospitalisation in ICCU. The outcome of the study is the incidence of major adverse cardiovascular events (MACE), which determined as multipart of all cause mortality, acute heart failure, cardiogenic shock, re-infarction, and rescucitated VT/VF. Fatal event was all cause mortality which was determined as death from all etiologies during intensive hospitalisation. Acute heart failure was defined as the presence of symptom of breathlesness and fatique with the signs of congestion and subsequent use of intravenous diuretics. Cardiogenic shock was termed as systolic blood pressure <90 mmHg and the signs of low perfusion with subsequent use of vasopressor (dopamine and norepinephrine). Reinfarction was defined as recurrent chest pain, recurrent ST-segment elevation, and a recurrent elevation of creatine kinase-MB after subjects subsided clinically. Rescucitated VT/VF was defined as an episode of defibrillation and cardiopulmonary rescucitation due to VT or VF. The confirmation of each item of MACE was finalized by attending cardiologists. All treatment of the subjects and related to the events were in the discretion of attending cardiologists. Uneventful discharge of subjects from ICCU

was determined as the end of observation. All subjects or familiy were participated voluntarily and confirmed an informed consent. The study had been approved by The Medical and Health Research Ethics Committee Faculty of Medicine Universitas Gadjah Mada and Dr. Sardjito General Hospital, Yogyakarta.

Statistic Analysis

The subjects were allocated into two groups, which are low AIP and high AIP. The incidence of MACE were compared between two groups. Univariate and multivariable analysis were performed to explore the relationship between AIP value and MACE. $p<0.05$ was determined as statistical significancy.

RESULTS

The study enrolled 277 subjects consecutively. The mean AIP value was 0.43, median value was 0.43 with minimum value -0.34 and maximum value 1.31. The high AIP group comprised 213 subjects (77% of all subjects) and the low AIP group consisted of 64 (33% of all subjects). **Table 1** showed the comparison of each characteristic between subjects with high AIP and low AIP.

The AIP value has weak inversely correlation with age ($r = -0.30$, $p<0.01$), moderate inversely correlation with HDL cholesterol ($r=-0.63$, $p<0.01$), and strong correlation with triglyceride ($r=0.79$, $p<0.01$). **Table 2** showed the correlation between AIP value with other continuous variables.

Table 1. Characteristics between subjects with high AIP and low AIP

Variables	Low AIP (n=64)	High AIP (n=213)
Demographic characteristics		
- Age (years), mean (SD)	61.9 (9.1)	56.6 (8.8)
- Male sex, n (%)	50 (78)	171(80)
- Body mass index, mean (SD)	23.4 (3.0)	23.9 (3.3)
Risk factors		
- Diabetes mellitus, n (%)	11 (17)	66 (31)
- Hypertension, n (%)	39 (61)	134 (63)
- Current smoking, n (%)	29 (45)	104 (49)
Clinical presentations		
- Systolic b.p (mmHg), mean (SD)	132.7 (22.0)	125.9 (26.1)
- Heart rate (bpm), mean (SD)	73.5 (15.1)	80.0 (19.2)
- Killip II-IV, n (%)	6 (9)	36 (17)
Laboratory, mean (SD)		
- Haemoglobin (g/dL)	13.5 (1.8)	13.7 (1.9)
- Leucocytes (10^3/mm^3)	12.1 (4.1)	12.5 (4.2)
- Platelets (10^3/mm^3)	243.9 (71.6)	259.7 (84.4)
- Blood urea nitrogen (mg/dL)	17.1 (8.3)	16.1 (7.8)
- Creatinine (mg/dL)	1.2 (0.4)	1.2 (0.6)
- Glucose (mg/dL)	177.6 (105.3)	188.9 (103.8)
- Troponin I (ng/dL)*	8.8 (9.7)	6.5 (9.3)
- Total cholesterol (mg/dL)	180.8 (48.2)	186.9 (44.7)
- LDL cholesterol (mg/dL)	110.0 (30.9)	126.9 (39.6)
- HDL cholesterol (mg/dL)	60.5 (22.9)	40.0 (10.7)
- Triglyceride (mg/dL)	69.9 (21.9)	144.4 (69.3)
Diagnosis		
- STEMI, n (%)	49 (77)	160 (75)
- NSTEMI, n (%)	15(23)	53 (25)
Admission treatment		
- Primary PCI, n (%)	14 (22)	60 (28)
- Fibrinolysis, n (%)	20 (31)	50 (24)
- Heparinisation, n (%)	31 (48)	104 (49)
Coronary angiography**		
- 1 vessel disease	4 (6)	15 (7)
- 2 vessel disease	6 (9)	20 (9)
- 3 vessel disease	8 (13)	21 (10)

SD, standard deviation; AIP, atherogenic index of plasma;b.p, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; STEMI, ST elevation myocardial infarction; NSTEMI, Non ST elevation myocardial infarction; PCI, percutaneous coronary intervention.
* measured in 135 subjects, ** performed in 74 subjects (primary PCI)

During intensive hospitalisation, 66 subjects (24%) developed MACE. Among those, 18 (28%) were subjects with low AIP and 48 (23%) were subjects with high AIP. No significant

Table 2. Correlation between AIP value with continuous variables from subjects characteristics on admission

Variables	Coefficient correlation	P value
Age	- 0.30	<0.01
Body mass index	0.09	0.13
Systolic blood pressure	0.02	0.86
Heart rate	0.10	0.19
Haemoglobin (g/dL)	0.14	0.02
Leucocytes (103/mm3)	-0.03	0.65
Platelets (103/mm3)	0.01	0.97
Blood urea nitrogen (mg/dL)	- 0.07	0.27
Creatinine (mg/dL)	0.03	0.58
Glucose (mg/dL)	0.06	0.32
Troponin I (ng/dL)	- 0.05	0.41
Total cholesterol (mg/dL)	0.03	0.59
LDL cholesterol (mg/dL)	0.17	<0.01
HDL cholesterol (mg/dL)	- 0.63	<0.01
Triglyceride	0.79	<0.01

difference was detected on the incidence of MACE between two groups. A subgroup analysis, based on diagnosis of STEMI and NSTEMI, the incidence of MACE did not differ significantly, only a tendency toward higher incidence in the low AIP group between two spectra of diseases, especially in NSTEMI (**Figure 1**).

Subsequent analysis showed that the incidence of fatal events (7%), i.e. all cause mortality, was significantly higher in subjects with low AIP (9 out of 64 or 14%) than in those with high AIP (11 out of 213 or 5%) (**Figure 2**). Whereas the incidence of non fatal cardiovascular events was not significantly different (14% and 17%, respectively). Since the statistically significant difference was observed in the incidence of all cause mortality between groups, we further explore the association between covariables with all cause mortality.

The bivariate analysis to identify predictors of all cause mortality in all subjects resulted in several variables as potential predictors. Other than low AIP, these variables were age, diabetes mellitus, heart rate, Killip class II-IV, haemoglobin level, urea nitrogen level, creatinine level, and glucose level. **Table 3** showed the bivariate analysis of potential predictors of fatal event.

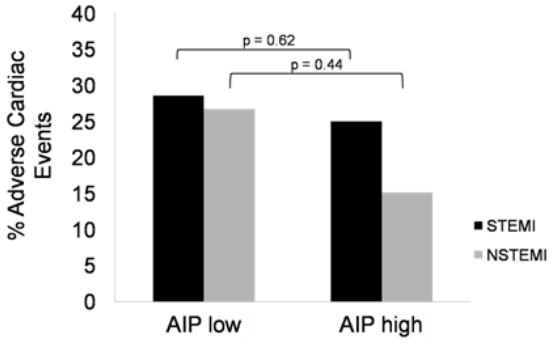

Figure 1. The incidence of MACE was comparable between low AIP and high AIP groups with a tendency toward higher incidence in subject with low AIP both in STEMI (29% vs 25%) and NSTEMI (27% vs 15%).

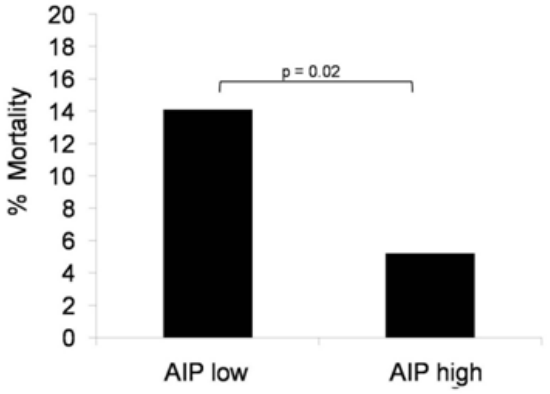

Figure 2. The incidence of fatal event, i.e. all cause mortality, was significantly higher in subjects with low AIP as compared to those with high AIP (14% v.s. 5%, p=0.02)

Using logistic regression analysis, the multivariable analysis was constructed to identify the independent predictors of all cause mortality. The result showed that low AIP was an independent predictor for all cause mortality in patients with AMI. The risk ratio of all cause mortality during hospitalisation in subjects with low AIP was 3.71 (95% CI 1.26 – 10.97, p value = 0.02). **Table 4** showed the logistic regression analysis for independent predictors of all cause mortality.

DISCUSSION

The result of our study indicates that the value of AIP influences the clinical prognosis in the hospitalized patients with AMI. The patients with lower value of AIP, with cut-off value 0.24, had a trend toward higher risk to develop MACE

Table 3. Bivariate analysis of potential predictors for all cause mortality

Variables	Risk Ratio (95% CI)	P value
Age	1.05 (0.99 – 1.10)	0.10
Diabetes mellitus	2.84 (1.13 – 7.11)	0.03
Heart rate	1.03 (0.99 – 1.05)	0.11
Killip II-IV	3.42 (1.28 – 9.15)	0.01
Haemoglobin	0.86 (0.68 – 1.08)	0.19
Blood urea nitrogen	1.07 (1.03 – 1.12)	0.01
Creatinine	1.48 (0.86 – 2.54)	0.16
Glucose	1.01 (1.00 – 1.02)	0.01
Low AIP	3.01 (1.19 – 7.62)	0.02

Table 4. Multivariable analysis for independent predictors of all cause mortality

Variables	Adjusted Risk Ratio (95% CI)	P value
Age	1.04 (0.98 – 1.10)	0.23
Diabetes mellitus	1.98 (0.63 – 6.17)	0.24
Heart rate	1.02 (0.99 – 1.05)	0.26
Killip II-IV	2.27 (0.72 – 7.14)	0.16
Haemoglobin	0.96 (0.74 – 1.25)	0.78
Blood urea nitrogen	1.06 (0.99 – 1.13)	0.09
Creatinine	0.89 (0.36 – 2.19)	0.81
Glucose	1.00 (0.99 – 1.01)	0.12
Low AIP	3.71 (1.26 – 10.97)	0.02

and significant increased in fatal event, i.e. all cause mortality, as compared to those with higher value of AIP. The risk of death during intensive hospitalisation was almost 4-fold higher in patients with low AIP. This was the first time evidence to report the impact of low AIP value on in-hospital mortality in patients with AMI.

The result of our study is rather surprising in which the low AIP value, rather than high AIP, independently predicts in-hospital mortality in AMI, both for STEMI and NSTEMI. It signifies the role of AIP in the pathogenesis of acute myocardial infarction. Hypertriglyceridemia and low HDL level increased the risk of coronary heart disease and its subsequent complication, such as acute coronary syndrome. Patients with hypertriglyceridemia and low HDL associate with other components of metabolic syndrome, i.e. increased body mass index, hypertension and elevated glucose level.[11] However, our study indicates no correlation between those parameters with AIP in patients with AMI. Coronary angiography, measuring the severity of coronary atherosclerosis and thrombosis, were comparable between low AIP subjects and those with high AIP.

The higher ratio of TG:LDL is an independent predictor of cardiovascular mortality from acute episode until 35 months follow-up patients with in acute coronary syndrome.[12] Increased AIP value was a significant predictor of mortality events independent of age, gender, smoking, and diabetes. It remains predictive after adding coronary artery disease severity score.[12] In contrast to a previous study, here we show that lower AIP, other than high AIP value, significantly and independently predict in-hospital mortality in AMI. The previous study enrolled acute coronary syndrome undergoing revascularisation, whereas in our current study not all subject undergo coronary revascularisation. Furthermore, all cause mortality was assessed in the long term (more than 30 months) in the previous study, which extent its finding that higher AIP predicts long term mortality after acute coronary syndrome.[12] Our study assessed mortality and major adverse cardiovascular events only during hospitalisation, which was a critical period of time within acute cardiac care.

The level of plasma TG and HDL cholesterol have been used to predict coronary vascular disease risk in healthy population and worse prognosis after acute coronary syndrome. The logarithmic ratio of TG:HDL conveys more precise prediction as compared to single measurement of TG or HDL or the ratio of TG:HDL.[5] Research indicates that 10 logarithmic of ratio TG:HDL closely correlates with LDL particle size and esterification rate in apoB-lipoprotein-depleted plasma (FERHDL).[5] The FERHDL is an indirect calculation of lipoprotein particle size, i.e. HDL and LDL particle size which are deemed strong atherogenic lipoprotein. The fastest FERHDL is found in the smallest HDL particles, whereas the slowest is found in larger HDL particles.[13] Furthermore, high FERHDL and AIP value is higher in individual suffering from myocardial infarction.[14,15] The AIP reflects a balance between plasma TG and HDL cholesterol level in actual value which determine

the course of cholesterol transport in circulation.[5]

Our study showed that AIP value negatively correlated with years of age. It means the older the patients, the lower the AIP value. This finding corroborated other studies which revealed similar observation.[16,17] The correlation markedly significant especially in male individuals.[16] Age is a significant predictor for morbidity and mortality following acute intensive care in patients with acute myocardial infarction. However, multivariable analysis showed that age do not predict the incidence of in-hospital mortality. In our cohort of patients, low AIP group comprised older age as compared to high AIP group, whereas the gender was comparable of male predominance. The explanation as to why low AIP increased the risk of mortality remains elusive. The role of dietary intake is a promising explanation, since our subjects mostly came from suburban area with low fat and high fiber diet which may affect the trygliceride and HDL level. This speculative hypothesis needs to be corroborated.

Some limitations of this study were as follow: (1) the number of subjects with fatal events (i.e. all cause mortality) was small, therefore the precision of the result was low, (2) the lack of mechanism as to why AIP influenced acute coronary events should be explored, and (3) the data of previous medication that may influence plasma lipid were not available.

CONCLUSION

A low AIP value (<0.24) is an independent predictor for mortality in patients with AMI undergoing intensive hospitalisation. A low AIP value had a tendency toward higher incidence of major adverse cardiovascular events (MACE), but no statistical significance was found. Further study is encouraged to corroborate this finding and investigate the clinical mechanism.

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