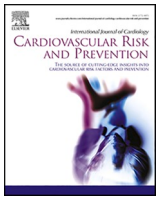
International Journal of Cardiology Cardiovascular Risk and Prevention 18 (2023) 200194

Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention



The association of apolipoprotein in the risk of ST-elevation myocardial infarction in patients with documented coronary artery disease

Astuti Giantini [a,b], Nur Gifarani Pratiwi [a,c,*], Renan Sukmawan [d], Joedo Prihartono [e], Suzanna Immanuel [a], Merci Monica Pasaribu [a], Sri Suryo Adiyanti [a], Yusuf Bahasoan [a]

[a] Clinical Pathology Department, Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo National Public Hospital, Central Jakarta, Indonesia
[b] Universitas Indonesia Hospital, Depok, West Java, Indonesia
[c] Faculty of Medicine and Health, University of Muhammadiyah Jakarta, Jakarta, Indonesia
[d] Cardiology and Vascular Medicine Department, Faculty of Medicine Universitas Indonesia, National Cardiovascular Center Harapan Kita, West Jakarta, Indonesia
[e] Community Medicine Department, Faculty of Medicine Universitas Indonesia, Central Jakarta, Indonesia

ARTICLE INFO

Handling Editor: D Levy

Keywords:
apoB
apoA1
apoB/apoA1 ratio
CAD
STEMI

ABSTRACT

Introduction: Cardiovascular disease (CVD) is the number one cause of death worldwide, in this case, acute coronary syndrome (ACS) or acute myocardial infarction (AMI) that developed from coronary artery disease (CAD). Several risk factors contribute to AMI. Non-modifiable risk factors are age, sex, race, and family history. Modifiable risk factors include dyslipidemia, hypertension, smoking, diabetes mellitus, as well as recent factors that are considered more specific such as homocysteine, lipoprotein a [Lp(a)], high sensitivity C- reactive protein (hs-CRP), and apolipoprotein. This study aimed to determine the role of apolipoprotein as a risk factor for STEMI.
Methods: This study combines three epidemiological designs: a descriptive and cross-sectional correlative study with 62 STEMI patients at the National Cardiovascular Center Harapan Kita and a comparative study of 62 STEMI patients and 20 non-ACS CAD patients at the Universitas Indonesia Hospital.
Results and conclusion: The descriptive study showed the level of apoB 80.71 ± 28.3, apoA1 104.93 ± 27.8, apoB/apoA1 ratio 0.78 ± 0.22, and Lp(a) 6.85 (1.0–48.1). ApoB moderately correlates with LDLc ($p < 0.001$; $r = 0.571$). ApoA1 weakly correlates with HDLc ($p = 0.005$; $r = 0.379$). In comparative study, there were significant differences between the STEMI and non-ACS CAD groups on apoA1 (104.93 ± 27.8 vs. 137.48 ± 26.46), apoB/apoA1 ratio (0.78 ± 0.22 vs. 0.59 ± 0.15), and hs-CRP (2.88 [0.4–215] vs. 0.73 [0.15–8.9]). Multivariate analysis showed that the most significant risk factors for STEMI in this study were hypertension for modifiable factors and apoA1 for apolipoprotein. The apoA1 and apoB/apoA1 ratio examination can be suggested for people who have experienced plaque formation and are at risk for myocardial infarction.

1. Introduction

Cardiovascular disease (CVD) is a global threat and the number one cause of death worldwide. World Health Organization (WHO) stated that 17.9 million people worldwide died from CVD in 2018 [1]. In Indonesia, 652,050 deaths were reported due to CVD, covering 35% of all deaths from non-communicable diseases [1]. Based on Riskesdas 2018, the incidence of CVD is increasing yearly. The prevalence of CVD in Indonesia is 15% or as many as 1,017,290 people [2]. Coronary artery disease (CAD) is the leading cause of death in more than half of patients with CVD. In this case, acute coronary syndrome (ACS) or acute myocardial infarction (AMI) developed from CAD is a global problem [3,4]. In 2013, 116,793 people in the United States suffered from fatal AMI, 57% of men and 43% of women. Approximately 38% of patients who come to the hospital with ACS experience ST-elevation myocardial infarction (STEMI) [5].

Several risk factors contribute to AMI [6]. Modifiable risk factors are age, sex, race, and family history [6,7]. Non-modifiable risk factors include dyslipidemia, hypertension, smoking, impaired glucose tolerance (diabetes mellitus), as well as more recent specific factors, such as homocysteine, Lp(a), and high sensitivity C-reactive protein (hs-CRP) [8]. Identifying the risk of STEMI is very important. Dyslipidemia is a

* Corresponding author. Clinical Pathology Department, Faculty of Medicine Universitas Indonesia, Dr. Cipto Mangunkusumo National Public Hospital, Central Jakarta, Indonesia.
E-mail address: gifarani@gmail.com (N.G. Pratiwi).

https://doi.org/10.1016/j.ijcrp.2023.200194
Received 3 April 2023; Received in revised form 26 June 2023; Accepted 28 June 2023
Available online 29 June 2023

factor that can affect long-term clinical outcomes [9]. Many guidelines for risk assessment and treatment goals, including the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III). LDL cholesterol (LDLc) level is considered the primary target. While for secondary targets, non-HDL cholesterol is proposed [9].

Assessment of CVD risk and complications such as IMA includes total cholesterol (TC), levels of LDLc, HDL-cholesterol (HDLc), and triglycerides (TG) in serum [8]. However, data shows that not all CVD sufferers have high LDLc levels, and not all patients with high LDLc suffer from CVD [10]. Besides TC, LDLc, TG, and HDLc, apolipoproteins such as apolipoprotein B (apoB) and apolipoprotein A1 (apoA1) are biomarkers associated with AMI [11]. Measurement of the functional and structural protein components of lipoproteins, namely apolipoprotein, is considered to have additional value for CAD risk assessment [3,10]. The Prospective Epidemiological Study of Myocardial Infarction (PRIME) and the Apolipoprotein related mortality risk (AMORIS) study confirmed that apolipoprotein is a strong risk factor for the development of CAD. Compared to conventional lipid fraction measurements, apolipoprotein levels are minimally affected by biological variables [4].

ApoB is a better marker of CVD risk than LDLc and superior to non-HDLc [6,10]. Furthermore, the INTERHEART study also showed that the apoB/apoA1 ratio is a better marker of AMI risk than the TC/HDLc ratio [10]. In addition to apolipoprotein, Lp(a) has become a concerning lipid biomarker because of a causal relationship between high serum levels of Lp(a) and an increased risk of AMI [7]. In Indonesia, the studied lipid parameters associated with AMI were LDL, HDL, triglycerides, and total cholesterol. The association of apolipoprotein components (apoB, apoA1, and apoB/apoA1 ratio) and Lp(a) with CAD is limited and still infrequently studied in Indonesia. In addition, the study only included dyslipidemia patients. This study included AMI patients, especially STEMI, and non-ACS CAD patients, which was determined by the CT-scan calcium scoring. Therefore, this study aims to determine the role of apolipoproteins as a risk factor for STEMI and analyze the apolipoprotein difference between STEMI patients and non-ACS CAD patients.

2. Materials and methods

2.1. Study population

This study was conducted from May to August 2021. This study combined three epidemiological designs: a descriptive study with a cross-sectional design to measure the apoB, apoA1, apoB/apoA1 ratio, and Lp(a); a cross-sectional correlative study to measure the correlation between apoB and LDLc, as well as apoA1 and HDLc; and a comparative study between the STEMI group and non-ACS CAD group for assessing the apolipoprotein difference. Subjects included 62 STEMI patients at National Cardiovascular Center Harapan Kita, and 20 non-ACS CAD patients as control at Universitas Indonesia Hospital. STEMI patients were included from an earlier study by Giantini et al. [12] Controls were selected based on medical record data with CT-scan calcium scoring <100 [13], never had AMI history, and normal ECG results. This study has been approved by the National Cardiovascular Center Harapan Kita, Dr. Cipto Mangunkusumo National Public Hospital, and Universitas Indonesia Hospital Ethics Committee. This study complied with the provisions of the Declaration of Helsinki. The subject's blood was drawn into an EDTA tube. It was excluded if the sample had hemolytic, icteric, or lipemic.

2.2. Apolipoprotein, Lp(a), and hs-CRP test

Examination of apoB, apoA1, Lp(a), and calculation of the apoB/apoA1 ratio was carried out at Permata Cibubur Hospital. The precision tests were divided into two: within-run and between-day tests. Precision tests used two levels of control (low and high) on the TMS 30i machine after calibration. ApoB and apoA1 used a calibrator with Lot number 115RKR, while Lp(a) used a calibrator with Lot number 119RAS. The within-run tests were performed ten times a row on the same day. The between-day was carried out for ten consecutive days. The principle of apoB and apoA1 was turbidimetric immunoassay. The apoB reference value was 69–105 mg/dL, while the apoA1 was 122–161 mg/dL [14,15]. Lp(a) examination used a latex-immunoturbidimetric assay with monoclonal antibodies. The reference value of Lp(a) was ≤30 mg/dL [16]. The hs-CRP examination was conducted at Dr. Cipto Mangunkusumo National Public Hospital.

2.3. Statistical analysis

Data analysis was performed using SPSS ver. 20 and Microsoft Excel. The results of precision tests were presented as mean, standard deviation (SD), and coefficient of variation (CV). The normality test in the control group for each parameter was carried out using the Shapiro-Wilk test, while the STEMI group used the Kolmogorov-Smirnov test. The Pearson test assessed the correlation between the parameters apoB to LDLc and apoA1 to HDLc. A comparative test of the mean difference between the STEMI group and non-ACS CAD group used the *t*-test or Mann-Whitney test. The relationship between various risk factors and STEMI was assessed by multivariate analysis. The first step was bivariate analysis with the Chi-Square or Fisher Exact tests. It obtained the p-value and odds ratio (OR). The multivariate logistic regression analysis included factors with a p-value <0.25 in the first step. Statistical significance was confirmed by a p-value <0.05.

3. Result

3.1. Descriptive and bivariate analysis

Baseline subject characteristics are presented in Table 1. The STEMI group was generally male, aged <60 years, non-obese, hypertension, DM, dyslipidemia, and smoker patients. The non-ACS CAD group was generally male, aged <60 years, non-obese, with no hypertension, no DM, no dyslipidemia, and non-smoker. In bivariate analysis, factors associated with STEMI ($p < 0.05$) were hypertension, DM, dyslipidemia, and smoking. They increased the risk of STEMI.

The within-run test for apoB, apoA1, and Lp(a) on the TMS 30i resulted in the CV of 1.45%, 1.17%, and 1.56% in low control, respectively, and 1.19%, 0.87%, and 1.86% in high control, respectively. The between-day test for apoB, apoA1, and Lp(a) resulted in the CV of 2.30%, 3.02%, and 3.50% in low control, respectively, and 1.95%, 2.48%, and 2.47% in high control, respectively. All of these CVs are still within the limits allowed by the manufacturer. The precision limit by the manufacturer is <5% without distinguishing between within-run and between-day tests.

3.2. Correlation between apoB-LDLc and apoA1-HDLc in STEMI group

Based on the normality test using the Kolmogorov-Smirnov test, apoB, apoA1, and apoB/apoA1 ratio were normally distributed, while Lp(a) was not normally distributed. The Pearson correlation test between apoB–LDLc and apoA1–HDLc is shown in Table 2. ApoB moderately correlated with LDLc ($p < 0.001$; $r = 0.571$), while apoA1 weakly correlated with HDLc ($p = 0.005$; $r = 0.349$). The covariance value between apoB-LDLc and apoA1-HDLc were positive: 541.578 and 87.949, respectively.

Comparative study of apoB, apoA1, apoB/apoA1 ratio, Lp(a), and hs-CRP between STEMI group and non-ACS CAD group.

A comparative study of the mean difference of apoB, apoA1, apoB/apoA1 ratio, Lp(a), and hs-CRP in the STEMI and non-ACS CAD groups is shown in Table 3. There were no significant differences in apoB and Lp(a) between STEMI and non-ACS CAD groups. There were significant differences between the STEMI and non-ACS CAD groups on apoA1 (104.93 ± 27.8 vs. 137.48 ± 26.46), apoB/apoA1 ratio (0.78 ± 0.22 vs.

Table 1
Subject characteristics. The STEMI group was generally male, aged <60 years, non-obese, hypertension, DM, dyslipidemia, and smoker patients. The non-ACS CAD group was generally men, aged <60 years, non-obese, with no hypertension, no DM, no dyslipidemia, and non-smoker. In bivariate analysis, factors associated with STEMI ($p < 0.05$) were hypertension, DM, dyslipidemia, and smoking. They increased the risk of STEMI.

Characteristics	Groups		p-value	OR	95% CI	
	STEMI n = 62 (%)	non-ACS CAD n = 20 (%)			Low	High
Sex						
Male	47 (75.80)	16 (80.00)	1.000	0.783	0.227	2.708
Female	15 (24.19)	4 (20.00)				
Age, y						
60–77 y	27 (43.55)	4 (20.00)	**0.059**	3.09	0.93	10.30
24–59 y	35 (56.45)	16 (80.00)				
Mean ± SD age	59.0 ± 8.2	53.1 ± 8.8				
Nutritional status						
Obese	28 (45.16)	8 (40.00)	0.884	1.235	0.443	3.443
Non-obese	34 (54.84)	12 (60.00)				
Hypertension						
Yes	50 (80.65)	4 (20.00)	**<0.001**	16.67	4.71	58.99
No	12 (19.35)	16 (80.00)				
Diabetes mellitus						
Yes	36 (58.06)	1 (5.00)	**0.002**	13.72	1.73	109.1
No	26 (41.93)	19 (95.00)				
Dyslipidemia						
Yes	56 (90.32)	7 (35.00)	**<0.001**	17.33	4.99	60.27
No	6 (9.67)	13 (65.00)				
Smoking						
Yes	51 (82.26)	1 (5.00)	**<0.001**	88.09	10.64	729.4
No	11 (17.74)	19 (95.00)				

ACS: acute coronary syndrome; CAD: coronary artery disease; STEMI: ST-elevation myocardial infarction.

Table 2
Pearson correlation test of apoB–LDLc and apoA1–HDLc. ApoB moderately correlates with LDLc, while apoA1 weakly correlates with HDLc.

Independent variables	Dependent variables	p-value	r	Covariance
apoB	LDLc	**< 0.001**	0.571	541.578
apoA1	HDLc	**0.005**	0.349	87.949

HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol.

0.59 ± 0.15), and hs-CRP (2.88 [0.4–215] vs. 0.73 [0.15–8.9]).

ROC curve analysis was performed on the significant parameters (apoA1, apoB/apoA1 ratio, and hs-CRP), calculating the area under the curve (AUC) and determining the optimal cut-off point, sensitivity, and specificity to differentiate STEMI and non-ACS CAD groups. Obtained AUC for apoA1, apoB/apoA1 ratio, and hs-CRP were 82.6%, 77.2%, and 78.1%, respectively (Fig. 1). The curves in Fig. 2 show the apoA1, apoB/apoA1 ratio, and hs-CRP cut-offs were 120.55 mg/dL (sensitivity 75.8% and specificity 85%), 0.6589 (sensitivity 71.0% and specificity 65.0%), and 0.98 mg/L (sensitivity 79.0% and specificity 70.0%), respectively.

Table 3
The mean difference between laboratory examination in STEMI group and non-ACS CAD group. There were no significant differences in apoB and Lp(a) between STEMI group with non-ACS CAD group. There were significant differences between the STEMI and non-ACS CAD groups on apoA1, apoB/apoA1 ratio, and hs-CRP.

Parameters	Groups				p-value
	STEMI (n = 62)		non-ACS CAD (n = 20)		
	Mean/ Med	SD/ Range	Mean/ Med	SD/ Range	
apoB	80.71	±28.3	83.45	±22.79	0.695
apoA1	104.93	±27.8	137.48	±26.46	**<0.001**
apoB/apoA1 ratio	0.78	±0.22	0.59	±0.15	**<0.001**
Lp(a)[a])	6.85	0.7–48.1	10.25	1.0–84.2	0.394
hs-CRP[a])	2.88	0.4–215.0	0.73	0.15–8.9	**<0.001**

ACS: acute coronary syndrome; CAD: coronary artery disease; hs-CRP: high-sensitive C-reactive protein; Med: median; SD: standard deviation; STEMI: ST-elevation myocardial infarction.
[a]) Mann-Whitney rank test.

Furthermore, the cut-off point was used to divide the category of each group apoA1, apoB/apoA1 ratio, and hs-CRP.

3.3. Multivariate analysis of various factors contributing to STEMI

The association between various risk factors and the incidence of STEMI was assessed by multivariate logistic regression analysis. The first step was bivariate analysis with the Chi-Square or Fisher Exact test. The factors with p-value<0.25 in Table 1 and Table 4 were continued to logistic regression multivariate analysis. The results of the multivariate analysis are shown in Table 5. Hypertension, apoA1, and apoB/apoA1 ratio were predictor factors associated with STEMI. Hypertension was associated with an increased risk of STEMI ($p = 0.001$; OR = 16.27 [95% CI 3–88.31]). Low apoA1 levels were associated with an increased risk of STEMI ($p = 005$; OR = 11.82 [95% CI 2.14–65.26]). A high apoB/apoA1 ratio was associated with a reduced risk of STEMI ($p = 0.031$; OR = 0.13 [95% CI 0.02–0.83]).

4. Discussion

4.1. Characteristics of STEMI group

The proportion of males was more than females. These results are in line with the studies of Linawaty et al. [17], Prashanth et al. [4], Nurulita et al. [7], Benn et al. [13], and Alhassan et al. [14] which found that the male patients with ACS were greater than females because male sex is a risk factor for CAD. Most of the subjects were <60 years old. Riskesdas 2018 shows that the highest prevalence of CAD is in the age group >75 years [2]. This difference may be associated with the influence of other CAD risk factors. In this study, the majority of subjects were non-obese. A study by Jensen et al. [15] obtained different results that ACS patients with BMI ≥25 were more found. An increase in BMI is directly related to an increased risk of AMI [6].

Based on the risk factors for ACS, most STEMI subjects had hypertension. This result corresponded with Alhassan et al. [14], who found that the proportion of ACS patients with hypertension was 83.13%. Hypertension is a major risk factor for atherosclerosis in coronary arteries, accelerating atheroma formation, increasing shear stress in plaques, interfering with the functional effects of coronary flow, and impairing endothelial function and sympathetic tone control [6,18]. Most STEMI subjects have smoking habits. This result corresponded to a study by Sandi et al. [19] which found that the proportion of smokers was 84.72%. Smoking is associated with atherogenesis, increased LDLc levels and triglycerides, and decreased HDLc levels. Smoking triggers free radical damage to LDL and causes accumulation of oxidized LDLc in

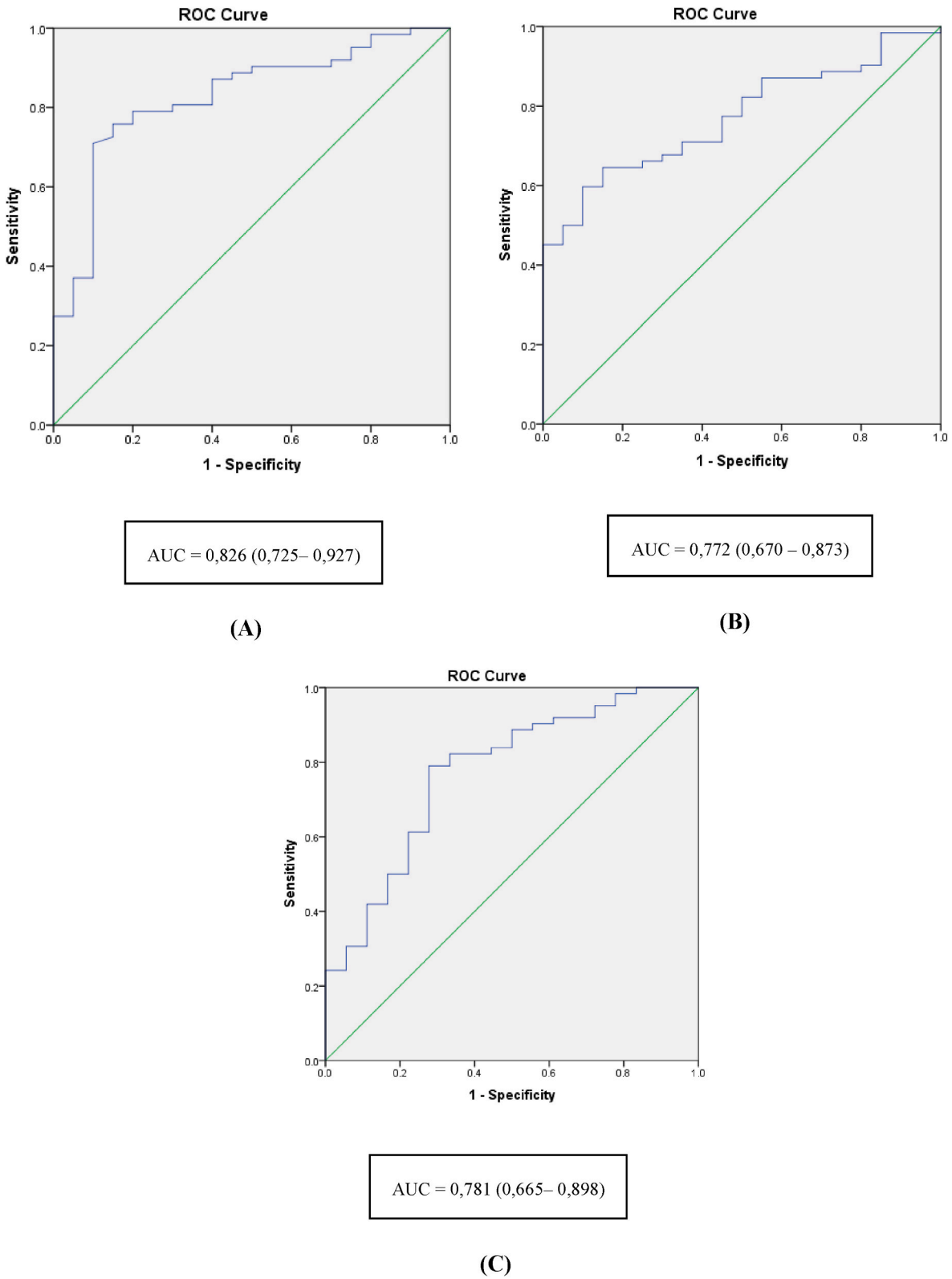
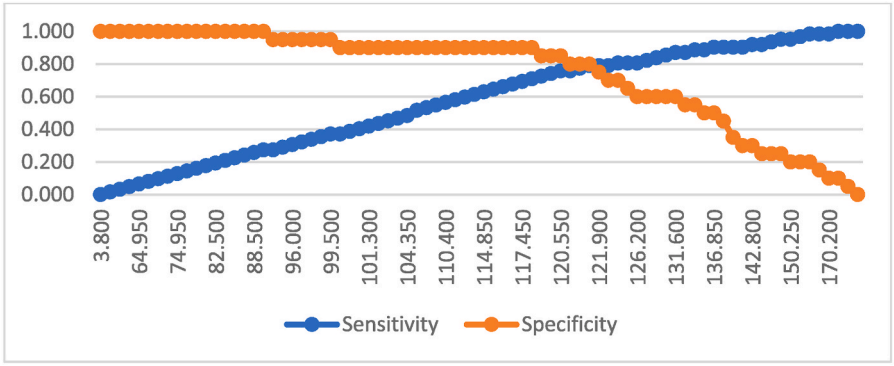


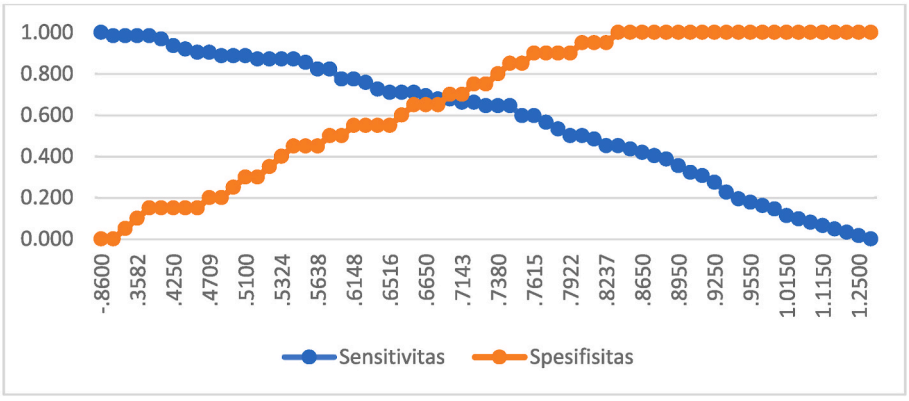
Fig. 1. ROC curve to differentiate STEMI and non-ACS CAD groups. (A) ApoA1 (AUC = 82.6%). (B) ApoB/apoA1 ratio (AUC = 77.2%). (C) hs-CRP (AUC = 78.1%).

the artery walls. Smoking also contributes to the inflammation of blood vessels as a sign of atherosclerosis [6]. Almost all STEMI patients had dyslipidemia. A study by Alhassan et al. [14] and Sandi et al. [19] obtained lower results: 59% and 68.05%, respectively. The Framingham Study establishes a link between dyslipidemia and CAD. High levels of total and LDLc and low levels of HDLc increase the formation of atherosclerotic plaques in the pathogenesis of CAD [6]. DM subjects did not differ from the study by Alhassan et al. [14], which obtained 59%. A study by Sandi et al. [19] found higher results: 81.94%. Diabetes can accelerate plaque development and affect the lipid profile forming atherosclerotic plaques [6].

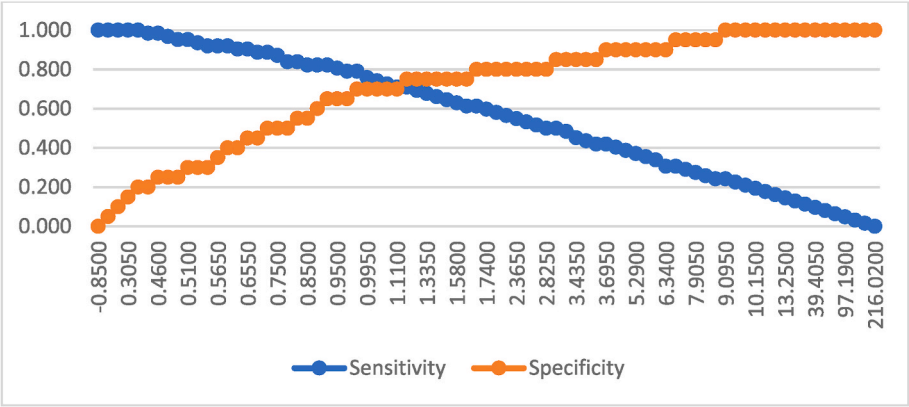
CAD could be determined based on cardiac catheterization



(A)



(B)



(C)

Fig. 2. Cut off curves of sensitivity and specificity to differentiate STEMI and non-ACS CAD groups. (A) ApoA1 (cut off = 120.55 mg/dL; sensitivity 75.8%; specificity 85). (B) ApoB/apoA1 ratio (cut off = 0.6589; sensitivity 71.0%; specificity 65.0%). (C) hs-CRP (cut-off = 0.98 mg/L; sensitivity 79.0%; specificity 70.0%).

examinations and angiograms, echocardiograms, electrocardiograms, cardiac CT scans, and exercise stress tests. The non-AMI CAD group selected as control had never experienced AMI and had cardiac CT-scan for the Coronary Artery Calcium (CAC) score assessment. CAC has high sensitivity but low specificity for CAD. Several clinical trials have found the CAC score more significant than the Framingham risk score when used in asymptomatic patients. Patients with elevated CAC are ±10 times more likely to develop heart disease over the next 3–5 years. CAC is considered superior to factors such as hs-CRP and carotid intima-media thickness (CIMT) as predictors of cardiovascular events [16].

4.2. ApoB, apoA1, apoB/apoA1 ratio, and Lp(a) in the STEMI group

The mean of apoB in the STEMI group was 80.1 ± 28.3 mg/dL. This result was still within the reference value. In contrast, Yaseen et al. [20] showed an increase in apoB, especially in the STEMI and NSTEMI groups. Prasanth et al. [4] also obtained the mean of apoB were 55.19 ± 20.37 in the STEMI group and 90.62 ± 15.8 in the control group. Statins most effectively reduce LDLc in both primary and secondary prevention of AMI [21]. The different apoB results from previous studies may be due to LDL levels in subjects within the reference value. In line with Walldius et al. [22], who stated that apoB did not contribute to predicting ACS in the low LDLc group. In addition, it was possibly the response to dyslipidemia that statins also have anti-inflammatory effects, including

Table 4
The association between apoA1, apoB/apoA1 ratio, and hs-CRP to STEMI. These laboratory parameters were associated with STEMI.

Factors	Groups		p-value	OR	95% CI	
	STEMI n = 62 (%)	non-ACS CAD n = 20 (%)			Low	High
ApoA1						
< 120.55	47 (75.80)	4 (20.00)	**<0.001**	9.40	2.93	30.20
≥ 120.55	15 (24.20)	16 (80.00)				
ApoB/apoA1 ratio						
≥ 0.6589	18 (29.03)	13 (0.65)	**0.004**	0.22	0.08	0.64
< 0.6589	44 (70.94)	7 (0.35)				
hs-CRP						
≥ 0.98	49 (79.03)	7 (0.35)	**<0.001**	7.00	2.32	21.11
< 0.98	13 (20.97)	13 (0.65)				

ACS: acute coronary syndrome; CAD: coronary artery disease; CI: confidence interval; hs-CRP: high-sensitive C-reactive protein; Med: median; OR: odss ratio; STEMI: ST-elevation myocardial infarction.

Table 5
Logistic regression multivariate analysis between various risk factors and STEMI. Hypertension, apoA1, and apoB/apoA1 ratio was the predictor factors for STEMI.

Factors	beta	p-value	OR	95% CI	
				Low	High
Age	1.99	0.062	7.33	0.91	59.21
Hypertension	2.79	0.001	16.27	3.00	88.31
Diabetes mellitus	1.95	0.129	7.04	0.57	87.30
ApoA1	2.47	0.005	11.82	2.14	65.26
ApoB/apoA1 ratio	−2.06	0.031	0.13	0.02	0.83
Constant	−1.34				

CI: confidence interval; OR: odds ratio.

reducing CRP. LDLc, which can affect the inflammatory process, is lowered due to the effect of statins, so low LDLc affects low apoB levels [23].

The mean of apoA1 in the STEMI group was 104.93 ± 27.8 mg/dL, indicating a decrease in levels based on the reference value. Saez et al. [24] found that apoA1 was a predictor factor for ACS. Prasanth et al. [4] also found decreased apoA1 levels in the AMI group (93.32 ± 10.19). ApoA1 is the main structural protein of HDL. HDL can increase the inflammatory response in individuals with chronic diseases characterized by systemic oxidative stress and inflammation. If the nature of HDL changes, apoA1 levels will be found to decrease [25]. ApoA1 influences the return of cholesterol flow in homeostasis. In addition, apoA1 levels are also low in patients with genetic dyslipidemia, especially familial hyperlipidemia [21].

This study's apoB/apoA1 ratio mean was 0.78 ± 0.22. Setiawan et al. [26] obtained the apoB/apoA1 ratio mean of 0.92. The ratio was classified as high risk. In a study by Saputri et al. [27], the group with an apoB/apoA1 ratio >0.9 was at high risk for AMI. Walldius et al. [20] suggested a cut-off point for the apoB/apoA1 ratio was 0.8. A high ratio could represent an increased risk of CAD [20]. A study by Bodde et al. [9] found that the apoB/apoA1 ratio was strongly associated with AMI. The apoB/apoA1 ratio is a better marker of CVD than lipid, lipoprotein, or other ratios. Therefore, several studies have shown that the apoB/apoA1 ratio can differentiate between patients with CAD and those without, even when CAD patients have normal lipid levels. The cut-off values for the apoB/apoA1 ratio determining high CVD risk are proposed to be 0.9 for men and 0.8 for women [28].

The median value of Lp(a) was 6.85 (1.0–48.1) mg/dL. In this study, low Lp(a) levels were found, in contrast to other studies, which found increased Lp(a) in STEMI. According to Fruchart et al. [8], no clinical trials showed that low Lp(a) levels would reduce the risk of CAD. It is supported by Kamstrup et al. [20], who stated that increased Lp(a) was associated with AMI but not in all studies. One retrospective study found a strong association between high Lp(a) and the risk of CVD, but other prospective studies stated that Lp(a) was not an independent risk factor for CVD, so the possibility of measuring the apolipoprotein(a) isoform was considered not standardized [8]. The Lp(a) isoform commonly measured is kringle IV type 2 (KIV2). Different examination methods, including ELISA, mass spectrometry, and turbidimetry, use monoclonal antibodies and are considered to have a positive association between high Lp(a) levels and CAD [29]. In addition, it is known that Lp(a) levels differ in each race. African have the highest levels of Lp(a) (about 60–70% have levels of Lp(a) > 25 mg/dL), followed by South Asian, Caucasian, Hispanic, and East Asian [30].

4.3. Correlation between apoB-LDLc and apoA1-HDLc in the STEMI group

There is a significant correlation between apoB and LDLc with moderate strength. It corresponded with Nurulita et al. [7], which stated that apoB could predict LDLc with moderate correlation strength ($p < 0.006$; $r = 0.408$). Khan et al. [31] showed similar results with $r = 0.308$. Several things caused this moderate correlation. One of the factors is insulin resistance and DM. These conditions will increase apoB significantly as a form of atherogenic apolipoprotein, and in this study, almost all STEMI patients had DM. A study by Suh et al. [32] supported this theory. It was found that DM patients had smaller mean LDL particle size and a higher proportion of small dense LDL. Smaller LDL particle size indicates higher apoB, although the LDL remains constant. On the other hand, Benn et al. [13] showed a strong correlation ($r = 0.70$ in women) and a very strong correlation ($r = 0.78$ in men) between LDLc and apoB, so apoB was considered to be able to predict AMI better than LDL. ApoB levels reflect LDLc levels because apoB is the main structural protein of LDL [20].

There is a significant correlation between apoA1 and HDLc with weak strength. This finding also corresponded with Khan et al. [31]' which showed a weak correlation between apoA1 and HDLc ($r = 0.203$). In DM patients, HDL particle size is increased, corresponding with a study by Ahmed et al. [33] Change in HDL size can affect the HDLc without the increase of apoA1. Li et al. [34] also found that AMI patients with CETP mutation can affect HDLc but not the apoA1. In contrast to a study by Saez et al. [24], with a total sample of 897 subjects, a strong correlation was found between HDLc and apoA1 ($r = 0.760$). In this study, the number of samples may differ greatly from that of Saezz et al. However, there are several other possibilities where the results of low HDLc and apoA1 measurements indicate that the protective properties of HDLc turn into pro-inflammatory. In addition, low HDLc and low apoA1 levels can be influenced by genetic disorders, although this is very rare [24].

4.4. The analysis of various risk factors associated with STEMI

There are eight risk factors both non-modifiable (age), modifiable (hypertension, DM, dyslipidemia, smoking), and laboratory (apoA1, apoB/apoA1 ratio, hs-CRP), which are considered to be related to the risk of STEMI. Based on the bivariate analysis of the Chi-Square test, it was found that each risk factor had a relatively high OR of STEMI. Prior to multivariate analysis, a collinearity test was carried out to see whether there was a relationship between the independent variables. The risk factors analyzed in multivariate analysis were age, hypertension, DM, apoA1 level, and apoB/apoA1 ratio. The most strongly associated independent variables have the greatest Beta (absolute) and OR values. Therefore, hypertension and apoA1 levels are the variables most strongly associated with STEMI. The group with hypertension had a risk of experiencing STEMI events of 16.27 (95% CI; 3.00–88.31) times higher than the non-hypertensive group, and the group with low apoA1 levels had a risk of experiencing STEMI events of 11.82 (95% CI; 2 0.14–65.26) times higher than the group with high apoA1 levels.

A study on apolipoprotein as a risk factor for STEMI, including apoB, apoA1, apoB/apoA1 ratio, and Lp(a), has not been widely carried out in Indonesia, even in the world. Apolipoprotein is known and considered a new risk factor that may influence the incidence of ACS. However, clinicians have not yet included these tests routinely. This study shows that patients with normal lipid profiles are still at risk of experiencing infarction based on a decrease in apoA1 levels with a cut-off point of 120.55 mg/dL and apoB/apoA1 ratio with a cut-off point of 0.6589. In addition, the control group was not normal, but they were people with AMI risk factors assessed based on cardiac CT-scan calcium scoring. The limitation of this study was finding controls who met the criteria during the pandemic. The sample comparison between STEMI and control groups did not reach a ratio of 1:1 but 3:1, which is still allowed. The distribution of risk factor data was abnormal, resulting in very high ORs because significant differences between the two groups influence them. Before the subject recruitment, lipid profiles (LDLc and HDLc) were examined earlier in STEMI patients. In this study, the correlation test of LDLc-apoB and HDLc-apoA was carried out in the STEMI group, so the control (non-ACS CAD group) was not examined for LDLc and HDLc.

5. Conclusion

ApoA1 and apoB/apoA1 ratios in this study showed significant differences in the STEMI and non-ACS CAD groups. ApoA1 was a risk factor for STEMI, and the cut-off value was 120.55 mg/dL. The apoB/apoA1 ratio was obtained as a risk factor for STEMI with a lower cut-off value than other studies (0.6589). In this study, apoB and Lp(a) did not show a significant difference between the STEMI and non-ACS CAD groups. There is a correlation between apoB and LDLc levels in the STEMI group with moderate strength. There is a correlation between apoA1 and HDLc levels in the STEMI group with weak strength. There are eight risk factors: both non-modifiable (age), modifiable (hypertension, DM, dyslipidemia, and smoking), and laboratory (apoA1, apoB/apoA1 ratio, and hs-CRP), which are considered to be related to STEMI. In multivariate analysis, the most significant risk factors were hypertension for modifiable risk factors and low apoA1 levels for risk for laboratory parameters.

The apoA1 and apoB/apoA1 ratio examination can be suggested to clinicians for people who have experienced plaque formation (assessed by cardiac CT-scan calcium scoring) and are at risk for plaque rupture and infarction in the future. Further research with more specific ACS classification can be conducted to assess the further function of apoB, apoA1, apoB/apoA1 ratio, and Lp(a) in clinical terms to predict AMI. The use of bigger samples in both ACS and control groups is suggested. Including ACS patients with a normal lipid profile is expected to provide clinical significance for apolipoprotein assay.

Credit author Statement

Astuti Giantini: Conceptualization, Investigation, Resources, Data Curation, Writing – Review & Editing. Nur Gifarani Pratiwi: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review & Editing. Renan Sukmawan: Supervision, Resources, Validation. Joedo Prihartono: Methodology, Formal Analysis. Suzanna Immanuel: Supervision, Validation. Merci Monica Pasaribu: Supervision, Validation. Sri Suryo Adiyanti: Supervision, Validation. Yusuf Bahasoan: Supervision, Validation.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that the research was carried out in the absence of any commercial relationships that could be a potential conflict of interest.

Acknowledgments

A sincere gratitude is given to the Cardiology and Vascular Medicine Department, Faculty of Medicine, National Cardiovascular Center Harapan Kita; the Clinical Pathology Department, Faculty of Medicine, Dr. Cipto Mangunkusumo National Public Hospital; and Universitas Indonesia Hospital, that had facilitated our study. The authors are also grateful to all health workers who participated in this study, who interacted with patients, and did laboratory procedures. The authors give their respect and gratitude to all patients that participated as the subjects.

References

[1] A. Damasceno, Non-communicable Disease. Heart of Africa: Clinical Profile of an Evolving Burden of Heart Disease in Africa, 2016, pp. 155–157.
[2] R.I. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan, Laporan Nasional Riskesdas 2018, Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan, Jakarta, 2019, p. 146.
[3] World Health Organization, The top 10 causes of death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death, 2020.
[4] K. Prashanth, I. Khan, Apolipoproteins and serum lipid profile in acute myocardial infarction, Scholars J. Appl. Med. Sci. 3 (2D) (2015) 816–820.
[5] B.J. Ansell, K.E. Watson, A.M. Fogelman, M. Navab, G.C. Fonarow, High-density lipoprotein function: recent advances, J. Am. Coll. Cardiol. 46 (10) (2005) 1792–1798.
[6] V. Rathore, Risk factors of acute myocardial infarction: a review, Eurasian J Med Investig 2 (1) (2018) 1–7.
[7] A. Nurulita, U. Bahrun, M. Arif, Perbandingan kadar apolipoprotein B dan fraksi lipid sebagai faktor resiko sindrom koroner akut, JST Kesehat 1 (1) (2011) 94–100.
[8] J.C. Fruchart, M.C. Nierman, E.S.G. Stroes, J.J.P. Kastelein, P. Duriez, New risk factors for atherosclerosis and patient risk assessment, Circulation 109 (23 SUPPL) (2004) 15–19.
[9] M.C. Bodde, M.P.J. Hermans, J.W. Jukema, M.J. Schalij, W.M. Lijfering, F. R. Rosendaal, et al., Apolipoproteins A1, B, and apoB/apoA1 ratio are associated with first ST-segment elevation myocardial infarction but not with recurrent events during long-term follow-up, Clin. Res. Cardiol. 108 (5) (2019) 520–538.
[10] S. Tsimikas, A Test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies, J. Am. Coll. Cardiol. 69 (6) (2017) 692–711.
[11] E.H.F.R. Brunori, C.T. Lopes, A.M.R.Z. Cavalcante, V.B. Santos, J. de L. Lopes, A.L. B.L. de Barros, Association of cardiovascular risk factors with the different presentations of acute coronary syndrome, Rev Lat Am Enfermagem 22 (4) (2014) 538–546.
[12] A. Giantini, I.S. Timan, R. Dharma, R. Sukmawan, R. Setiabudy, I. Alwi, et al., The role of clopidogrel resistance-related genetic and epigenetic factors in major adverse cardiovascular events among patients with acute coronary syndrome after percutaneous coronary intervention, Front Cardiovasc Med 9 (2023), 1027892.
[13] M. Benn, B.G. Nordestgaard, G.B. Jensen, A. Tybjærg-Hansen, Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B: the Copenhagen City Heart Study, Arterioscler. Thromb. Vasc. Biol. 27 (3) (2007) 661–670.
[14] S.M. Alhassan, H.G. Ahmed, Risk factors associated with acute coronary syndrome in Northern Saudi Arabia, J Cardiol Curr Res 8 (3) (2017), 00281.
[15] M.K. Jensen, S.E. Chiuve, E.B. Rimm, C. Dethlefsen, A. Tjønneland, A.M. Joensen, et al., Obesity , Behavioral Lifestyle Factors , and Risk of Acute Coronary Events, 2008, pp. 3062–3069.
[16] M.J. Budoff, K.M. Gul, Expert review on coronary calcium, Vasc. Health Risk Manag. 4 (2) (2008) 315–324.
[17] S. Linawaty, J.B. Suparyatmo, T. Tahono, Angka banding apoB/apoA-I pada gejala koroner akut (apoB/apoA-I ratio in acute coronary syndrome), Indones J Clin Pathol Med Lab 20 (2013) 29–33.
[18] S. Biswas, P.K. Ghoshal, S.C. Mandal, N. Mandal, Association of low-density lipoprotein particle size and ratio of different lipoproteins and apolipoproteins with coronary heart disease, J. Cardiol. 52 (2) (2008) 118–126.
[19] M.R. Sandi, S. Martini, K.D. Artanti, S. Widati, The description of modifiable risk factors in coronary heart disease at dr. soetomo regional public hospital, J Berk Epidemiol 7 (2) (2019) 85.
[20] R.I. Yaseen, M.H. El-Leboudy, H.M. El-Deeb, The relation between apoB/apoA-1 ratio and the severity of coronary artery disease in patients with acute coronary syndrome, Egypt Hear J 73 (1) (2021) 24.
[21] G. Walldius, I. Jungner, Is there a better marker of cardiovascular risk than LDL cholesterol? Apolipoproteins B and A-I–new risk factors and targets for therapy, Nutr. Metabol. Cardiovasc. Dis. 17 (8) (2007) 565–571.

[22] G. Walldius, The apoB/apoA-I Ratio Is a Strong Predictor of Cardiovascular Risk, 2012, https://doi.org/10.5772/47869.
[23] S.W. Kim, H.J. Kang, M. Jhon, J.W. Kim, J.Y. Lee, A.J. Walker, et al., Statins and inflammation: new therapeutic opportunities in psychiatry, Front. Psychiatr. 10 (103) (2019) 1–16.
[24] M. Vacas, M. Santos, D. Lafuente, J.D. Sagastagoitia, E. Molinero, J.A. Iriarte, Relation of high-density lipoprotein cholesterol and apoproteinA1 levels with presence and severity of coronary obstruction, ISRN Vascular Medicine 2012 (2012) 1–6.
[25] G.H. Bindu, V.S. Rao, V.V. Kakkar, Friend turns foe: transformation of anti-inflammatory hdl to pro-inflammatory HDL during acute-phase response, Cholesterol 2011 (2011), 274629.
[26] W.E. Setiawan, A.B. Hartopo, R. Rozqie, Correlation between apolipoprotein B/apolipoprotein A-I ratio with atherogenic index of plasma among acute myocardial infarction patients, Indones Biomed J 10 (2) (2018) 179–183.
[27] D. Saputri, H. Hariawan, B. Irawan, High apoB/apoA-1 serum ratio as a predictor of in-hospital major adverse cardiovascular events in acute coronary syndrome patients, J Acta Cardiol Indones 1 (2) (2017).
[28] A.M. Kaneva, N.N. Potolitsyna, E.R. Bojko, Odland Jø, The apolipoproteinB/apolipoprotein A-I ratio as a potential marker of plasma atherogenicity, Dis. Markers 2015 (2015), 591454.
[29] J. Cegla, M. France, S.M. Marcovina, R.D.G. Neely, Lp(a): when and how to measure it, Ann. Clin. Biochem. 58 (1) (2021) 16–21.
[30] S. Tsimikas, J.L. Hall, Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies, J. Am. Coll. Cardiol. 60 (8) (2012) 716–721.
[31] S.H. Khan, A.H. Afzel, R. Shahid, R. Manzoor, Relationship between apolipoproteins, lipoprotein (a) and conventional cholesterol and lipids with insulin resistance, Prof. Med. J. 29 (6) (2022) 745–751.
[32] S. Suh, H.-D. Park, S.W. Kim, J.C. Bae, A.H.-K. Tan, H.S. Chung, et al., Smaller mean LDL particle size and higher proportion of small dense LDL in Korean type 2 diabetic patients, Diabetes Metab. J 35 (2011) 536–542.
[33] M.O. Ahmed, R.E. Byrne, A. Pazderska, R. Segurado, W. Guo, A. Gunness, et al., HDL particle size is increased and HDL-cholesterol efflux is enhanced in type 1 diabetes: a cross-sectional study, Diabetologia 64 (2021) 656–667.
[34] W. Li, X. Liu, C. Huang, L. Liu, X. Tan, X. Wang, The loss-of-function mutation of CETP affects HDLc levels but not ApoA1 in patients with acute myocardial infarction, Nutr. Metabol. Cardiovasc. Dis. S0939–4753 (20) (2020), 30458.