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Insulin resistance is associated with severe coronary artery stenosis in non-diabetic chronic coronary syndrome at Sanglah General Hospital, Bali

Ni Luh Eka Sriayu Wulandari,[1*] I Made Junior Rina Artha,[1] Wira Gotera,[2] I Gde Raka Widiana[2]

[1]Department Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia

*Corresponding author:
Ni Luh Eka Sriayu Wulandari;
Department Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia;
eka.wull@gmail.com

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ABSTRACT

Background: The prevalence of insulin resistance (IR) increases worldwide due to the increasing number of the elderly population, obesity, and physical inactivity. IR modifies insulin's effect on blood vessel walls, with anti-atherogenic effects on insulin-sensitive and pro-atherogenic effects on IR conditions. However, the relationship between IR and the degree of atherosclerosis is still not conclusive. This study will examine the relationship between insulin resistance marker HOMA-IR and the degree of coronary artery stenosis using SYNTAX score measurements in non-diabetic subjects with the chronic coronary syndrome.

Methods: The study was conducted on 68 subjects with non-diabetic chronic coronary syndrome taken by consecutive sampling. The diagnosis of the chronic coronary syndrome (CCS) is defined as subjects with significant ≥50% stenosis findings on coronary angiography. The degree of insulin resistance was measured using HOMA-IR and subjects were divided according to the HOMA-IR quartile. Data were analyzed in bivariate and multivariable modeling by SPSS version 25 for Windows.

Results: The prevalence of severe coronary stenosis was 11.8%, 17.6%, 29.4% and 64.7% in quartiles 1, 2, 3 and 4, respectively. In multivariate analysis, it was found that quartile 4 subjects with cut-off value HOMA-IR ≥12.30 (OR 7.0; 95% CI=1.3-39.0; p=0.025) is an independent predictor of severe coronary stenosis, along with age ≥50 years (OR 13, 8; 95% CI=1.1-174.1; p=0.042), BMI ≥25 kg/m^2 (OR 15.1; 95% CI=2.4-96.7; p=0.004), smoking (OR 18,0; 95% CI=2.0-160.5; p=0.010) Also found that statin therapy ≥2 months (OR 0.11; 95% CI 0.02-0.59; p=0.010) is an independent protective factor against severe coronary stenosis in non-diabetic CCS subjects.

Conclusion: This study shows an independent association between IR and severe coronary stenosis in non-diabetic CCS subjects. This finding further strengthens clinical evidence of the direct pro-atherogenic effect of IR regardless of its glucose control effect and other metabolic syndrome components.

Keywords: Insulin Resistance, Atherosclerosis, Chronic Coronary Syndrome, Non-Diabetic
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INTRODUCTION

The prevalence of insulin resistance (IR) is increasing worldwide due to the increasing number of elderly populations, obesity, and physical inactivity. IR is a significant component of several clinical conditions, such as metabolic syndrome, type 2 diabetes mellitus (T2DM) and early cardiovascular disease (CVD). The underlying pathology for early CVD is atherosclerosis.[1] There is a lot of new clinical evidence that IR increases the risk of coronary artery disease (CAD), even in the absence of hyperglycemia.[2] Multiple epidemiological studies have shown an association between IR and CVD in non-diabetic cohorts that is only partially accounted for by the metabolic syndrome components.[3-8]

Emerging in vitro evidence suggest that IR modifies the effect of insulin on blood vessel walls, with anti-atherogenic effects on insulin-sensitive and pro-atherogenic outcomes on IR conditions.[9,10] Investigators also have reported an independent association between IR, gene polymorphism, and carotid intima medial thickness and coronary artery calcification as indicators of early subclinical atherosclerosis.[9,11-13] Therefore, cardiovascular diseases may be a consequence of insulin resistance rather than being caused by toxic effects of high insulin or glucose concentrations. Apart from the impact of hyperglycemia and hyperinsulinemia, the question remains whether the higher degree of insulin resistance alone plays an important role in developing atherosclerosis. To the best of the author's knowledge, there are no studies in Indonesia that have examined this relationship in non-diabetic special populations.

However, the current risk stratification

model does not yet include IR that might improve the prediction of CVD events in non-diabetic individuals. There is a great need to identify practical surrogate markers of IR, which could be useful for coronary risk stratification in patients at risk for CAD. HOMA-IR is a validated marker of insulin resistance and is often used for clinical purposes. This study assesses the association between HOMA-IR with the severity of coronary artery stenosis using SYNTAX score measurement among non-diabetic CCS.

METHODS

This cross-sectional study was performed from November 2019 to April 2020. The inclusion criteria were: non-diabetic patients with significant ≥50% stenosis findings on coronary angiography performed in the catheterization laboratory of Sanglah General Hospital, Bali, Indonesia. Their medical history was obtained and recorded from all of the subjects. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2) and blood samples were taken for the laboratory to be studied.

Patients with a history of prior coronary revascularization, heart failure NYHA III-IV, impaired renal function (eGFR <30 ml/min), COPD, steroid treatment, history of myocardial infarction within 30 days were excluded from the study. Factors that influence the degree of coronary artery stenosis include age, sex, hypertension, dyslipidemia, smoking, and dyslipidemia treatment controlled by multivariate analysis.

After minimally 8-hour fasting, blood samples were taken from the patients, including fasting glucose, fasting insulin concentration, CBC, liver function tests, lipid profile, BUN, and creatinine. All parameters were evaluated in the hospital laboratory. We estimated insulin resistance using the homeostatic model assessment index of IR (HOMA-IR) developed by Mathew with the following formula: HOMA-IR = baseline insulin concentration (mU/L)×baseline glucose concentration (mg/dL)/405.[14]

Coronary angiography was performed using the Axiom Artis Siemens equipment (Germany) or Phillips in all patients. Angiographic measurements using SYNTAX score calculation were made by one experienced interventional cardiologists who were blinded to insulin resistance status and other clinical variables. According to the SYNTAX score, patients were divided into two groups with mild and severe coronary artery disease with a cut-off for severe stenosis was >22. Only patients with at least 50% coronary stenosis on coronary angiography were included in the study.

Chi-square test was used for comparing categorical data and correlation between them. These data are presented as numbers (percentages). We applied a student's T-test to compare the continuous variables and were expressed as mean±SD. Differences between more than two groups were tested with one-way ANOVA. We also used multivariate logistic regression to control the confounding factors that affected IR and CAD relationships. Finally, we analyzed the data using SPSS version 25.0 for Windows and a p-value less than 0.05 was considered statistically significant.

RESULTS

The subjects of this study were 68 people consisting of 89.7% men (n = 61) and 10.3% women (n = 7). The mean age of subjects was 56.9 ± 8.7 years, with an age range of 34 to 77 years. The mean HOMA-IR value was 9.6 ± 7.0, with a range of 1.68-27.35 (Table 1). Baseline subjects' characteristics are divided according to the HOMA-IR quartile (larger quartile values indicate a higher HOMA-IR value) and are presented in tables 1 and 2. Quartile 1: ≤3.66; quartile 2: 3,67-8,56; quartile 3: 8,57-12,29; quartile 4: ≥12,30. Patients with higher HOMA-IR were found to have higher age, BMI, waist circumference (WC), and SYNTAX scores and tended to have a history of dyslipidemia (Table 1). There were no significant differences in proportions between quartiles for risk factors such as hypertension, smoking, family history, and history of previous acute coronary syndromes (ACS) (p>0.05) (Table 1). ACE-I/ARB therapy was found to be the lowest percentage (76.5%) in

Table 1. Baseline Characteristics of Subject Stratified by HOMA-IR Quartiles

Variables	Baseline Insulin Resistance (HOMA-IR)				Total (n=68)
	Quartile 1 (n=17)	Quartile 2 (n=17)	Quartile 3 (n=17)	Quartile 4 (n=17)	
Age (year) (mean±SD)	53.5±5.0	59.0±7.9	55,2±10,9	59.8±9.1	56.9±8.7
Sex, n (%)					
Male	15 (88.2)	14 (82.4)	17 (100.0)	15 (88.2)	61 (89.7)
Female	2 (11.8)	3 (17.6)	0 (0.0)	2 (11.8)	7 (10.3)
BMI (kg/m^2) (mean±SD)	23.2±2.2	23.3±2.7	25.3±2.6	26.1±2.9	24.5±2.8
Waist circumference (cm) (mean±SD)	90.7±4.8	88.1±4.9	91.8±6.7	94.2±8.7	91.2±6.7
Dyslipidemia, n (%)	3 (17.6)	1 (5.9)	8 (47.1)	10 (58.8)	22 (32.4)
Hypertension, n (%)	12 (70.6)	8 (47.1)	9 (52.9)	12 (70.6)	41 (60.3)
Smoking, n (%)	10 (58.8)	9 (52.9)	12 (70.6)	11 (64.7)	42 (61.8)
Family history, n (%)	1 (5.9)	3 (17.6)	1 (5.9)	1 (5.9)	6 (8.8)
Prior to ACS, n (%)	9 (52.9)	9 (52.9)	9 (52.9)	8 (47.1)	35 (51.5)
ACE-I/ARB treatment, n (%)	17 (100.0)	17 (100.0)	14 (82.4)	13 (76.5)	61 (89.7)
β-blocker treatment, n (%)	17 (100.0)	17 (100.0)	16 (94.1)	17 (100.0)	67 (98.5)
Dyslipidemia treatment ≥2 months, n (%)	10 (58.8)	14 (82.4)	9 (52.9)	9 (52.9)	42 (61.8)
Ejection fraction (%) (mean±SD)	56.2±13.9	59.2±13.8	56.1±11.6	51.8±15.1	56.3±14.2

Table 2. Subject Baseline Metabolic Profile Stratified by HOMA-IR Quartiles

Variables	Baseline Insulin Resistance (HOMA-IR)				Total (n=68)
	Quartile 1 (n=17)	Quartile 1 (n=17)	Quartile 1 (n=17)	Quartile 1 (n=17)	
Fasting glucose (mg/dL)	90,2±14,0	92,5±14,3	91,4±10,5	102,9±18,1	94,3±15,1
Fasting insulin (mIU/L)	11,9±2,6	23,4±7,3	47,1±7,0	88,3±25,2	42,7±32,4
HbA1c	5,5±0,6	5,2±0,4	5,2±0,5	5,1±0,5	5,3±0,5
SC (mg/dL)	1,2±0,37	1,1±0,2	1,2±0,2	1,3±0,5	1,2±0,4
Total cholesterol (mg/dL)	151,2±38,2	157,6±40,7	161,7±37,0	171,6±44,4	160,5±40,0
LDL cholesterol (mg/dL)	95,6±22,8	105,0±30,5	113,8±43,5	123,5±44,3	108,0±36,0
HDL cholesterol (mg/dL)	39,2±7,9	40,2±6,4	38,5±7,2	38,6±11,0	39,1±8,2
Triglyceride (mg/dL)	115,6±22,4	153,7±67,0	157,0±85,8	176,4±95,5	150,7±75,0

Table 3. Table of Correlation Between HOMA-IR Quartiles and SYNTAX Scores Obtained by Chi-square Procedure.

Variables		SYNTAX Score				p	PR (95% CI)
		>22		≤22			
		N=21	%	N=47	%		
HOMA-IR	Quartile 1	2	11.8	15	88.2	-	*References*
	Quartile 2	3	17.6	14	82.4	0.628	1.5 (0,3-7,9)
	Quartile 3	5	29.4	12	70.6	0.396	2.5 (0,5-19,0)
	Quartile 4	11	64.7	6	35.3	0.005*	5.5 (2.3-81.5)*

PR: Prevalence Ratio; CI: Confidence Interval; *Statistically significant if p-value less than 0.05

Table 4. Chi-Square Test Results of Relationships Between Several Confounding Variables and SYNTAX Scores

Variable	p	PR	95% CI	
			Lower limit	Upper limit
Age ≥50 year	0.129	4.3	0.6	28.9
Male sex	0.568	2.3	0.4	14.6
BMI ≥25 kg/m^2	0.001*	3.7	1.7	7.8
Hypertension	0.324	1.6	0.7	3.7
Smoking	0.057	2.6	1.0	7.0
Dyslipidemia	0.038*	2.3	1.2	4.6
Dyslipidemia treatment ≥2 months	0.016*	0.4	0.2	0.8

*Statistically significant if p-value less than 0.05

quartiles 4. Statin therapy proportion did not show significant differences in interquartile (Table 1).

Metabolic characteristics of subjects are described in Table 2. The value of fasting blood glucose, fasting insulin, total cholesterol, LDL-cholesterol, triglycerides is higher concordant with the HOMA-IR quartile. But only the fasting blood glucose and fasting insulin values showed significant differences between quartiles. HbA1c, serum creatinine, and HDL cholesterol did not show significant differences between quartiles (p>0.05) (Table 2).

Bivariate analysis in this study aims to determine the relationship between HOMA-IR insulin resistance markers and SYNTAX score. The comparative test is done by Chi-square test, and the association size used is Prevalence Ratio (PR). When compared to the group of subjects in quartile 1, subjects in quartile 4 were found with a higher SYNTAX score (PR 5.5; 95% CI=2.3-81.5; p=0.005), as well as subjects in quartile 3 (PR 2.5; 95% CI=0.5-19.0; p=0.396) and quartile 2 (PR 1,5; 95% CI 0.3-7.9; p=0.628) (Table 3). The group with a larger HOMA-IR was associated with a higher SYNTAX score, with a statistically significant relationship showed in quartile 4 (p<0.05) (Table 3).

Bivariate analysis of some confounding variables with SYNTAX scores is described in Table 4. A significant relationship was obtained from a high SYNTAX score with a BMI ≥25 kg/m^2, dyslipidemia, and statin treatment ≥2 months (Table 4).

Multivariate analysis in this study used logistic regression analysis with the backward LR method to control other variables that affect the SYNTAX score's value (Table 5). These variables include age ≥50 years, sex, BMI ≥25 kg/m^2, smoking, hypertension, dyslipidemia, and dyslipidemia treatment ≥2 months. The results of the multivariate analysis are summarized in Table 5. For multivariate analysis, the HOMA-IR cut-off value used was ≥12.3 representing the HOMA-IR value at the 75th percentile.

In the final results of the logistic regression analysis, we found 5 variables that were independently related to the SYNTAX score> 22, including HOMA-IR (≥12,30), age ≥50 years, BMI ≥25 kg/m^2, smoking and dyslipidemia treatment ≥2 months with protective effect (Table 5).

DISCUSSION

In this study, we found a significant association between IR represented by HOMA-IR above p75 and the presence of severe coronary artery stenosis in non-diabetic CCS patients referred for coronary angiography. Although much literature and theory show the role of resistance insulin in atherosclerosis and coronary heart disease, several studies assessing the relationship between insulin resistance and the extent of coronary lesions show variable results.[15-26] The results of the preliminary research are described in Table 6 (Appendix).

Table 5. Results of Multivariate Analysis of Variables Relating to the Degree of Coronary Artery Stenosis - SYNTAX score in CCS Patients

Variable	Coefficient	SE.	Wald	df	p	OR	95% CI	
							Lower limit	Upper limit
HOMA-IR ≥p75	1.951	0.873	4.997	1	0.025	7.0	1.3	39.0
Age ≥ 50 years	2.625	1.293	4.118	1	0.042	13.8	1.1	174.1
BMI ≥25 kg/m^2	2.717	0.946	8.242	1	0.004	15.1	2.4	96.7
Smoking	2.890	1.116	6.702	1	0.010	18.0	2.0	160.5
Dyslipidemia treatment ≥2 months	2.204	0.854	6.666	1	0.010	0.11	0.02	0.59

Table 6. Preliminary Studies of The Relationship Between Insulin Resistance and The Degree Of Coronary Stenosis

Study, year	Subject/Population	Assessment	HOMA-IR value	Results	Refference
Bressler et al., 1996	CAD and susp. CAD, USA	*Euglyvemic insulin clamp* vs *vessel score*	-	Significant correlation	[15]
Takezako et al., 1999	CAD and susp. CAD, male, non-DM, Japan	HOMA-IR vs Gensini score	2,9	Significant correlation	[16]
Wlodarczyk et al., 2008	CCS, non-DM, Poland	HOMA-IR vs *vessel score*	1,73	No significant correlation	[17]
Isailovic et al., 2010	Susp. CAD, Czech	HOMA-IR vs *vessel score*	-	No significant correlation	[18]
Srinivasan et al., 2013	CAD and susp. CAD, DM, India	HOMA-IR vs Gensini score	3,37	Significant correlation	[19]
Karrowni et al., 2013	IMA, non-DM, USA	HOMA-IR vs *vessel score*	Female: 3,63 Male: 3,99	Independent predictor to multivessel disease	[8]
Kruszelnicka et al., 2013	Stable angina pectoris, male, non-DM, Switzerland	HOMA-IR vs *vessel score*	-	No significant correlation	[20]
Kurniadhi et al., 2014	CAD and susp. CAD, Indonesia	HOMA-IR vs Gensini score	4,63	Significant correlation	[21]
Srinivasan et al., 2014	CAD and susp. CAD, T2DM >5 years, India	HOMA-IR vs SYNTAX score	Mean: 3.40±1.62	Significant correlation, independent predictor	[22]
Mossmann et al., 2015	Susp. CAD, non-DM, non-obese, Brazil	HOMA-IR vs *anatomic burden score*	4,21	Significant correlation	[23]
Vafaimanesh et al., 2018	CAD and susp. CAD, non-DM, Iran	HOMA-IR vs visual stenosis evaluation (*cut-off* stenosis 50%)	2,5	No significant correlation	[6]
Cho et al., 2019	CAD and susp. CAD, South Korea	IR marker: HOMA-IR, Triglyceride-glucose (TyG) index, TG/HDL ratio, HbA1c vs visual stenosis evaluation (*cut-off* stenosis 50%)	-	HOMA-IR: no significant correlation; TyG indeks: significant correlation in non-DM; HbA1C: significant correlation in DM subject	[24]
Uppunda et al., 2019	Stable angina pectoris, obese, India	HOMA-IR vs SYNTAX score	Mean: 9,42±4,76	Significant correlation in subject with metabolic obesity; No significant correlation in phenotipically obese subject (IMT >25 kg/m^2)	[25]
Mao et al., 2019	ACS NSTEMI, China	IR marker *Triglyceride-Glucose Index* vs SYNTAX score	-	Independent predictor for CAD severity and major adverse cardiac event	[26]

The results in this study are in accordance with most preliminary studies of non-diabetic patients, including the study by Karrowni W et al., 2013, which found an independent relationship between HOMA-IR and multivessel CAD in non-diabetic post-IMA patients.[8] Similar results were also stated in the study of Mossmann M et al., 2015, who found an independent association of HOMA-IR with significant coronary stenosis (at least 1 lesion with stenosis ≥50%) in non-diabetic and non-obese subjects.[5] Likewise, a preliminary study by Takezako T et al., 1998 found a significant correlation between HOMA-IR and Gensini scores in non-diabetic male subjects in Japan.[16]

Evidence and data from studies with large populations show that insulin resistance is associated with increased cardiovascular events (even after adjusting for metabolic syndrome components). This indicates insulin resistance is likely to be the main root of metabolic syndrome and a mediator of associated cardiovascular risk. This is also supported by the latest biological findings of evidence that supports the direct pro-atherogenic effect of insulin resistance against arterial blood vessels. In the state of insulin resistance, there is downregulation of the phosphatidylinositol-3-kinase (PI3K) pathway, which plays an essential role in producing nitric oxide (NO) by endothelial cells, which have anti-inflammatory and anti-atherogenic effects. This is accompanied by upregulation of the mitogen-activated protein kinase (MAPK) pathway in endothelial cells and vascular smooth muscle, which has multiple pro-atherogenic effects through endothelin-1 (ET-1). Changes in insulin receptors also occur in monocytes and circulating macrophages that trigger a series of critical cellular events in atherosclerotic plaque progression. In insulin resistance, activation of the stress-apoptotic pathway in the macrophage endoplasmic reticulum triggers apoptosis of macrophages in atherosclerotic lesions. This condition is exacerbated by defects in the efferocytosis system (phagocytic processes that normally function to cleanse apoptotic bodies to prevent inflammation and post-apoptotic cellular necrosis in insulin resistance conditions. The combination of macrophage apoptosis combined with defects in the efferocytosis system will trigger plaque necrosis and accelerate atherosclerotic plaque rupture.[10]

Srinivasan et al., 2014 stated insulin resistance appeared to be the most important risk factor for developing CAD in subjects with T2DM. However, due to the reduction in insulin resistance conditions is not significant in the majority of T2DM patients, this may explain the residual risk even after controlling for traditional risk factors for T2DM.[22] Insulin resistance is the only component of the metabolic syndrome that is relatively constant in DMT2 subjects. Other risk factors, such as blood biochemistry and anthropometric measurements, are dynamic over time.[27] Even the United Kingdom Prospective Diabetes study that evaluated conventional DMT2 therapy for 6 years revealed insulin sensitivity, reciprocal insulin resistance, appearing constant with 62, 60, and 62% at 0,1 and 6 years, respectively. The unique evolution of insulin resistance and its significant correlation with CAD can help identify individuals at high risk early in the disease.[28]

A study by Srinivasan et al., 2014 also found that T2DM with a duration of more than 5 years had more severe vascular disease quantitatively and qualitatively compared to a duration of less than 5 years.[22] The peak effects of insulin resistance and hyperinsulinemia may occur during the 4-5 years T2DM period and the possibility of significant vascular disease can occur after 5 years duration of T2DM. In their study, it was found that subjects with T2DM more than 5 years were characterized by severe coronary lesions, long segments, and multivessel disease when compared to T2DM less than 5 years.[22]

Aggressive glycemic control for T2DM with a longer duration does not appear to benefit the macrovascular system—chronic hyperinsulinemia results in functional or structural changes in blood vessels. NO mediates functional changes due to resistance at the level of insulin receptors. Structural changes occur due to pro-atherogenic responses mediated by the MAP kinase pathway. These changes appear to be progressive in the first 5 years of T2DM and aggressive glycemic therapy given over the past 5 years seems unable to reverse all these changes. Because of the strong correlation of insulin resistance, therapeutic modalities that target insulin resistance in the first 5-year period are crucial. Therefore, the opportunity for the prevention of cardiovascular complications is very limited in the 0-5 year period of T2DM. Over a period of 5 years, there have been severe and irreversible complications. So, their study concluded that patients with high insulin resistance tended to experience more severe CAD after 5 years duration of T2DM. Given the status of insulin resistance has remained relatively constant from the start, patients at high risk for severe CAD can be easily identified in the early phases of the disease. For clinicians, this will allow early risk stratification and identification of high-risk diabetic patients to initiate a very aggressive risk reduction strategy from the start. Patients with high insulin resistance must be managed aggressively.

Based on the data above, our study results, which show a significant correlation of HOMA-IR even in non-diabetic populations with a normal glucose response, further strengthen the role of insulin resistance in the progression and severity of CAD. Identifying the condition of insulin resistance in non-diabetic populations with CAD will significantly assist in the risk stratification and identification of patients at high risk, for guidance in the administration of aggressive management both with pharmacological and lifestyle management. This will further have implications for preventing long-term microvascular and other macrovascular complications, bearing in mind that the golden period for preventing these complications is less than 5 years from T2DM. And will be even more effective if these efforts are made at an earlier phase of the disease course.

From the multivariate analysis, besides HOMA-IR, the independent predictors of severe stenosis were age ≥50, BMI ≥25 kg/m^2, smoking, and without statin therapy. All of these factors are traditional PKV risk factors that are well known for their role in the course of CAD.

This study proves that insulin resistance with hyperinsulinemia compensation is associated with CAD progression and a more severe degree of coronary stenosis,

even in the absence of hyperglycemia. These findings also confirm the preceding study regarding HOMA-IR's critical role as a risk predictor of cardiovascular disease in non-diabetic populations. New therapeutic modalities that target insulin resistance can contribute to reducing cardiovascular disease and atherosclerotic plaque formation.

CONCLUSIONS

There is a relationship between HOMA-IR of insulin resistance markers and SYNTAX scores. High HOMA-IR is independently related to severe coronary stenosis in non-diabetic CCS subjects. Other independent predictors include age ≥ 50 years, BMI ≥25 kg/m^2 smoking, and independent protective factors are statin treatment ≥2 months.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper

ETHICS APPROVAL

All individuals signed informed consent prior to their enrollment in the study. This research was conducted after obtaining approval from the Faculty of Medicine, Universitas Udayana, Sanglah General Hospital Denpasar, Bali, with a letter of Ethical Clearance from the Director of Human Resources (HR) and Education of Sanglah Hospital Denpasar, Bali.

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AUTHOR CONTRIBUTION

All authors contribute to the study from the conceptual framework, data gathering, and data analysis until reporting the study results through publication.

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