

The Association of Carotid Intima-Media Thickness with the Severity of Stenosis Assessed by the Gensini Score in Coronary Artery Disease Patients

Heriadi Heriadi^{a,b*}, Irhas Hasballah^{a,b}, Azhari Gani^{a,b}, Muhammad Diah^{a,b}

*Email: heriadifakhri@gmail.com

^a Department of Internal Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia

^a Department of Internal Medicine, Dr. Zainel Abidin Hospital, Banda Aceh, Indonesia

Abstract

Coronary artery disease (CAD), caused by atherosclerosis, is the leading cause of mortality worldwide. Acehnese people own unique cultures with many traditional events involving various cuisines and possess daily habits that increase the risk of CAD. Measurement of carotid intima-media thickness (CMT) using ultrasonography (USG) has been considered a non-invasive, inexpensive, and safe procedure to assess atherosclerosis in patients. The aim of this study was to evaluate the association between CMT and the severity of stenosis assessed by the Gensini score among Acehnese CAD patients. A cross-sectional study was conducted at Dr. Zainel Abidin Hospital, Banda Aceh from April to June 2022. CMT was measured using ultrasonography and the severity of coronary stenosis was determined through the Gensini scoring system. The cut-off value of CMT was also analyzed using the receiver operating characteristic (ROC) curve. Using SPSS software, the Chi-Square test was employed to evaluate the relationship between the two variables, and a $p < 0.05$ was considered statistically significant. A total of 51 CAD patients were enrolled in the study and most of them were males (84.3%). More than half (58.8%) of the patients had abnormal CMT (≥ 0.9 mm) with an overall CMT mean of 1.02 ± 0.30 mm. Severe stenosis was observed in 41 patients (80.4%) with an average Gensini score of 62.65 ± 51.10 . Chi-Square analysis revealed a significant association between CMT and the severity of coronary stenosis among Acehnese CAD patients ($p = 0.039$). The cut-off value for CMT towards the Gensini score was 0.92 mm with a sensitivity of 60.9% and specificity of 80.0%, suggesting that CMT could accurately predict the severity of stenosis in the CAD patients of the present study.

Keywords: Carotid intima-media thickness, Gensini score, coronary artery disease, Acehnese, ethnicity

1. Introduction

Coronary artery disease (CAD), a type of cardiovascular disease, is the leading cause of death worldwide [1, 2]. It occurs due to the presence of atherosclerosis, characterized by arterial stiffness owing to endothelial dysfunction, inflammation, dyslipidemia, and thrombosis in the vascular wall [3]. In Indonesia, CAD is the main cause of mortality among hospitalized patients according to the Indonesian National Household Health Survey 2012, accounting for approximately 7.13% of death. Further, the National Basic Health Research reported that Aceh province occupied the second rank of the highest CAD cases (0.7%) after Middle Sulawesi (0.8%) in Indonesia [4]. Several factors such as smoking, hypertension, obesity, diabetes mellitus, lack of exercise, anxiety, depression, age, family history of cardiovascular disease, male, and genetic disorders have been associated with the increased risk of atherosclerosis [1, 5, 6]. In terms of race and ethnicity, lifestyle, genetics, and social interactions are among other risk factors for atherosclerosis [1, 7, 8]. Chronic atherosclerosis in the arterial wall has caused stable CAD, whereas unstable CAD has been associated with acute atherosclerosis due to thrombus, hence blood vessel assessment is prominent as an early detection and prevention strategy [9].

Carotid-intima media thickness (CMT) examination is a validated tool for the diagnosis of atherosclerosis [10] and is significantly associated with a risk factor of cardiovascular disease [11]. Indeed, elevated CMT in the carotid segment leads to 0.7%-22% of CAD incidence annually [12]. CMT reflects the early stage of coronary atherosclerosis and can be used as a morphological index to assess early lesions on the arterial wall, as well as to measure the severity and extent of the lesions [13, 14]. It has also been reportedly useful for assessing the progression of cardiovascular risk in clinical trials [15], evaluating atherosclerosis in patients with angina pectoris [16], and detecting the complexity of stenosis in CAD patients [17]. A B Mode Doppler ultrasonography (USG) has been recognized as a non-invasive, safe, and inexpensive procedure for the assessment of CMT [18].

In assessing the complexity of stenosis, the Gensini scoring system has been used. It determines the severity of stenosis based on the severity and anatomical location of the lesions using an angiographic procedure. It can assess not only the number of vessels with stenosis but also the burden and location of the stenosis by burdening each of coronary artery segment, thus providing more representative results [19]. Determination and scoring of stenosis complexity can predict the prognosis of CAD during long-term follow-up of up to 8 years [20]. The severity of arterial stenosis is directly related to CIMT since elevated CIMT leads to coronary stenosis [11, 13, 14].

Many studies regarding CIMT have been conducted and revealed different CIMT among various ethnicities or races, leading to a different incidence of CAD between races. Black African-Caribbean have a higher CIMT compared to that of white European races, while South Asian and other Asian have similar CIMT scores as white European races. In all races, CIMT was positively correlated with age, systolic, and diastolic blood pressure, but inversely related to the combination of skinfold thickness and serum triglycerides [21]. These differences in CIMT among races have been associated with different genetics, culture, and diet associated-lifestyle [1, 7, 8, 22]. Aceh province, Indonesia whose population consists of 8 ethnic groups with different cultures (Acehnese, Aneuk Jamee, Tamiang, Gayo, Kluet, Singkil, Alas, Simeulu tribes) [23] possess many traditional events involving various traditional cuisines rich in fatty acids [24-31]. Studies in Banda Aceh suggested that Acehnese community have a large consumption of saturated fatty acids and sodium, significantly related with the incidence of CAD in Aceh [32, 33]. In addition, the existence of a large number of coffee shops in Aceh has contributed to another unhealthy habit such smoking among Acehnese males [34]. Considering the presence of potential risk factors for CAD owing to unhealthy lifestyle and diets among Acehnese population which leads to a higher incidence of CAD, this study aimed to assess the relationship between CIMT with the severity of coronary stenosis based on the Gensini score among Acehnese CAD patients.

2. Methods

A cross-sectional study was carried out among CAD patients at Dr. Zainoel Abidin Hospital, Banda Aceh from April to June 2022. The inclusion criteria were the patients over 18 years of age with stable condition, diagnosed with CAD through cor angiography examination, the third generation of Acehnese residents, and willing to provide consent to participate after receiving a brief explanation of the research flow. On the other hand, the patients with poor coronary artery visualization, had previously underwent revascularization procedure or coronary artery bypass surgery, and those refusing to provide consent to participate were excluded from the study. Ethical Approval were obtained from the Institutional Review Board of Faculty of Medicine, Universitas Syiah Kuala (068/EA/FK-RSUDZA/2022) and Dr. Zainoel Abidin Hospital Banda Aceh (664/Litbang).

Two variables were included in the study: independent (CIMT) and dependent (the severity of coronary stenosis based on the Gensini score). CIMT was assessed using B Mode Doppler ultrasonography (USG) (frequency of 12 Hz) on the patients' neck at the right and left common carotid artery (RCCA and LCCA). The measurements were performed manually by assessing three sites in RCCA and LCCA. The average CIMT values from each site were calculated and recorded as the average of the RCCA and LCCA in millimeters (mm). CIMT of <0.9 mm was considered normal; >0.9 mm (thickened); and >1.2 mm (atherosclerosis plaque) [35, 36]. The severity of stenosis was measured using the Gensini score based on coronary angiography findings. The Gensini score of <20 was considered mild, while a score of ≥ 20 was considered severe [19]. Several demographic and clinical characteristics of the patients, including age, gender, risk factors, Acehnese race lineage, evaluation of vital signs, weight, height, body mass index (BMI), laboratory findings, and ECG were also recorded.

Data analysis was performed using SPSS software, involving univariate and bivariate analyses. Univariate analysis was carried out to provide the distribution of frequency of each tested variable. Categorical variables were expressed as numbers and percentages (%), while quantitative variables were presented as mean \pm SD (standard deviation). Bivariate analysis using the Chi-Square test was performed to identify the association between CIMT and the severity of stenosis based on the Gensini score at $\alpha=0.05$. The receiver-operating characteristic (ROC) curve analysis was employed to determine the cut-off point for CIMT as a marker of stenosis severity. The area under curve (AUC) is used to assess the diagnostic accuracy of an examination. The closer the value to 1, the better the accuracy of the examination being tested [37].

3. Result

A total of 51 CAD patients were enrolled in the study and most of them (84.3%) were males and residents of Banda Aceh (33.3%). The demographic and clinical characteristics of the patients are presented in Table 1. More than half of the patients (70.6%) were smokers and had no family history of CAD (72.5%). The average age was 56.51 years possessing at least one comorbidity. The most common comorbidity was hypertension (74.5%),

followed by dyslipidemia, diabetes mellitus, stroke, obesity, and chronic kidney disease. The average value of systolic (123.53 mmHg) and diastolic (77.94 mmHg) were within normal limit. Stable angina pectoris was the most dominant diagnosis prior to coronary angiography (56.9%), whereas CAD2VD and CAD3VD were mostly observed after the angiography procedure (41.2% each).

Table 1. Baseline characteristics of the patients

Characteristics	Statistic
Gender, n (%)	
Male	43 (84.3)
Female	8 (15.7)
Address, n (%)	
Aceh Besar	9 (17.6)
Banda Aceh	17 (33.3)
Pidie	6 (11.8)
Aceh Tengah	2 (3.9)
Aceh Utara	2 (3.9)
Lhokseumawe	4 (7.8)
Aceh Jaya	2 (3.9)
Bireun	2 (3.9)
Others (Nagan Raya, Pidie Jaya, Bener Meriah, East Aceh, Langsa, South Aceh, Seumeulu)	7 (13.7)
Age (year), mean \pm SD	56.51 \pm 9.17
Systolic, mean \pm SD	123.53 \pm 18.53
Diastolic, mean \pm SD	77.94 \pm 12.30
Comorbidities, n (%)	
Diabetes Mellitus	16 (31.4)
Hypertension	38 (74.5)
Dyslipidemia	25 (49.0)
Stroke	9 (17.6)
Obesity	4 (7.8)
Chronic Kidney Disease (CKD)	1 (2.0)
Smoking history	
Yes	36 (70.6)
No	15 (29.4)
Family history of CAD, n (%)	
Yes	14 (27.5)
No	37 (72.5)
Diagnoses pre-coronary angiography, n (%)	
SAP	29 (56.9)
UAP	9 (17.6)
NSTEMI	6 (11.8)
STEMI	7 (13.7)
Diagnoses post-coronary angiography, n (%)	
CAD1VD	9 (17.6)
CAD2VD	21 (41.2)
CAD3VD	21 (41.2)

Abbreviation: CAD: Coronary artery disease; CKD: Chronic kidney disease; NSTEMI: Non-ST Elevation Myocardial Infarction; STEMI: ST Elevation Myocardial Infarction; SAP: Stable Angina Pectoris; UAP: Unstable Angina Pectoris, VD: Vessel disease

The results of CIMT measurement are presented in table 2. The mean value of the left CCA was higher (1.05 ± 0.38 mm) compared to that of the right CCA (0.99 ± 0.31 mm), with the average CIMT of 1.02 ± 0.30 mm, suggesting abnormal CIMT among Acehnese CAD patients in general. More than half of the patients (58.8%) were found with CIMT of higher than 0.9 mm. In terms of the severity of coronary stenosis, the vast majority of the patients (80.4%) had severe stenosis, indicated by the Gensini score of ≥ 20 . The average Gensini score of the patients was 62.65 ± 51.10 (Table 3).

The association between CIMT and the severity of stenosis based on the Gensini score is shown in Table 4. Most of the CAD patients (70.0%) with mild level of stenosis had normal CIMT, whereas those with severe stenosis (69.9%) showed abnormal CIMT. Pearson Chi Square analysis suggested a significant association between CIMT and the severity of stenosis based on the Gensini score ($p=0.039$) among Acehnese CAD patients in this study.

To determine the cut-off, point of CIMT for detecting stenosis severity, diagnostic analysis using receiver operating characteristic (ROC) curved was performed. The cut-off value obtained for CIMT was 0.92 mm, with a sensitivity of 60.9% and a specificity of 80.0%. The area under the ROC curve was 71.2% and was statistically significant ($p \geq 0.05$), suggesting that CIMT can be used to accurately predict the severity of stenosis based on the Gensini score.

Table 2. The characteristics of carotid intima-media thickness of the patients

Characteristics	Statistic
CIMT, mean \pm SD (mm)	
Right CCA	0.99 ± 0.31
Left CCA	1.05 ± 0.38
Average	1.02 ± 0.30
CIMT category, n (%)	
Normal (< 0.9 mm)	21 (41.2)
Abnormal (≥ 0.9 mm)	30 (58.8)

CCA: Common carotid artery

Table 3. The severity of coronary stenosis of the patients based on the Gensini score

Characteristics	Statistic
The Gensini score, mean \pm SD	62.65 ± 51.10
The Gensini score category, n (%)	
Mild (< 20)	10 (19.6)
Severe (≥ 20)	41 (80.4)

Table 4. The association between CIMT and the severity of stenosis based on the Gensini score

	CIMT		Pearson Chi-square	p-value
	Normal (< 0.9 mm)	Abnormal (≥ 0.9 mm)		
The Gensini score				
Mild (< 20)	7 (70.0%)	3 (30.0%)	4.267	0.039
Severe (≥ 20)	14 (34.1%)	27 (65.9%)		

4. Discussion

We conducted a cross-sectional study among Acehnese CAD patients at Dr. Zainoel Abidin Hospital, Banda Aceh. Of the total 51 respondents, more than half (84.3%) were males, indicating that Acehnese males had a higher prevalence of CAD compared to females. Previous investigations reported that CIMT were approximately 0.1-0.2 mm higher in males compared to females [38, 39]. In addition to gender, age also affects CIMT. In the present study, the average age of the patients was 56.51 years with an average CIMT of 1.02 mm. Another study showed that the highest CIMT was observed in patients of above 60 years, while the lowest was detected in those below 30 years [38]. CIMT has also been reportedly increased by about 0.01-0.02 mm along with a one-year increase in age [40]. Furthermore, all patients in the current study possessed at least one comorbidity accompanying CAD, with hypertension (74.5%), dyslipidemia (49.0%), and diabetes mellitus (31.4%) as the most common ones. In addition, the majority of the patients were also smokers (70.6%) (Table 1). These findings were in accordance with that

reported in a previous investigation, indicating that men, smokers, as well as patients with hypertension, dyslipidemia, and diabetes mellitus (DM) had a higher mean of CIMT [39]. A study in South Korea suggested that elevated CIMT was associated with old age, male, high body mass index (BMI), high cholesterol levels, and a history of diabetes mellitus [41]. CIMT measurement is critical in patients diagnosed with hypertension and CAD since CIMT is a strong and independent predictor for various cardiovascular complications [42]. Stroke, hypertension, DM, and obesity have been associated with a 3.5, 1.6, 1.2, and 1.2 times higher risk of CAD, respectively [43].

CIMT has been considered a potential marker of atherosclerosis development and a useful predictor for evaluating the severity of CAD [11]. A 1.15-mm increase in CIMT can lead to a 94% chance of developing CAD [14]. CIMT is a morphological index assessing early lesions on the arterial wall and is the leading cause of systemic vascular atherosclerosis [13]. It reflects the degree, extent, and severity of atherosclerotic lesions. Furthermore, CIMT has been reportedly correlated with the severity of coronary artery stenosis, which is recognized as a narrowing of a coronary artery due to atherosclerosis plaque building, resulting in reduced blood flow [44]. Once the atherosclerotic plaque is formed on the arterial wall, it will result in luminal stenosis. This volume of plaque in the arteries can then reflect the degree of stenosis [45].

To measure the severity of stenosis in CAD patients who had undergone angiography procedures, the Gensini scoring system was employed [46-49]. This system has been developed to characterize the complexity of CAD by considering 3 main parameters for each lesion, including the severity score, region multiplier factor, and collateral adjustment factor [19, 50]. Using Chi-Square analysis, our data suggested a significant association between CIMT and the Gensini score among Acehnese CAD patients (p value= 0.039) (Table 4). The patients with abnormal CIMT (≥ 0.9 mm) tended to have the Gensini score of ≥ 20 , suggesting severe stenosis, and vice versa. This finding was in line with those of previous studies, suggesting that CIMT increased along with the increased number of blocked arteries [13]. Patients with coronary artery disease involving 3 vessels (CAD3VD) had higher CIMT compared to those with CAD1VD, CAD2VD, and control [38, 39]. CIMT was also observably higher in angiographic-confirmed CAD patients compared to those with normal coronary arteries [39]. Simply put, CIMT measurement by ultrasonography plays a role in stratifying CAD risk and is strongly correlated with coronary computed tomography angiography [51], suggesting a linear correlation between CIMT and the severity of CAD, as well as revealing a strong correlation between carotid artery atherosclerosis and coronary artery atherosclerosis [39].

A number of studies regarding CIMT showed several differences in the completeness of CIMT measurement, including the cut-off point used for CIMT in determining the severity of stenosis. Our diagnostic analysis using ROC curve obtained the cut-off value of 0.92 mm, with area under the curve (AUC) of 71.2%, sensitivity of 60.9%, and specificity of 80.0%. A study in Japan which compared the flow-mediated vasodilation (FMD) in the brachial artery with CIMT to assess the severity of CAD showed the CIMT cut-off value of 0.88 mm, with 88% sensitivity, 90% specificity, and 92% AUC [52]. Another investigation regarding the use of CIMT as a prediction marker to assess lower leg artery lesions in diabetic patient feet obtained the CIMT cut-off point of 0.71 mm, with a sensitivity of 79.6%, specificity of 61.1%, and AUC of 74.7% [53]. However, a meta-analysis assessing 22 eligible studies found that the common sensitivity and specificity of CIMT for the diagnosis of CAD were 68% and 70%, respectively. This meta-analysis divided the cut-off values based on subgroups, where a cut-off value of 0.8 mm gave a sensitivity and specificity of 66%; a cut-off value of 0.8-1 mm gave a sensitivity of 71% and a specificity of 67%, and a cut-off point of >1 mm gave a sensitivity of 66% and a specificity of 79%. A cut-off value of 1 mm had been proven to be more accurate for evaluating the severity of CAD [54].

Many investigations regarding the relationship between ethnicity and CAD have been conducted around the world [55-57]. The results suggested that different ethnicities had different incidences of CAD affected by genetic and cultural factors [56]. Culture can influence the risk of CAD, particularly owing to diet-associated lifestyle. Individuals consuming foods containing high saturated fatty acids will be more likely to suffer from CAD [22, 57]. Aceh is one of the provinces in Indonesia with numerous traditional events involving a variety of cuisines containing a large amount of fatty acid and sodium, which had been significantly associated with a high incidence of CAD among the Acehnese population. Excessive sodium and fatty acid consumption can respectively lead to hypertension and fat accumulation in the blood vessels, which are related to the pathophysiology of CAD [32]. Cholesterol and triglyceride levels have been reportedly the most influential factors in CAD [33]. However, culture and tradition are difficult to change and are considered a form of respect for ancestors. Hence, controlling unhealthy food consumption is critical to lower the risk of CAD [22]. In addition, other aspects of the cardiovascular diseases also need to be explored in the future.

This study possessed several limitations such as the involvement of a small number of subjects (51 individuals). We also employed a cross-sectional study design that collected data only on one occasion, hence the data obtained

might be limited. In addition, CITM measurement was performed and calculated manually, which might result in less data accuracy.

5. Conclusion

In total, 51 Acehnese CAD patients were enrolled in the study and most of them were male (84.3%) and aged 56.51 ± 9.17 years on average. Each patient possessed at least one comorbidity accompanying CAD. The most common comorbidity was hypertension (74.5%), followed by dyslipidemia, diabetes mellitus, stroke, obesity, and chronic kidney disease. The mean value of the patients' CINT was 1.02 ± 0.30 mm. More than half of the patients (58.8%) were found with CINT of higher than 0.9 mm, suggesting abnormal CINT among Acehnese CAD patients. The majority of the patients (80.4%) had severe stenosis, indicated by the Gensini score of ≥ 20 . The result of the Chi-Square analysis suggested a significant association between CINT and the severity of coronary artery stenosis measured using the Gensini score ($p < 0.039$). Further investigation or a prospective cohort study regarding the correlation between CINT and the severity of stenosis involving a larger number of samples should be conducted to obtain a more definitive conclusion. In addition, further studies evaluating plausible factors influencing the thickening of CIM and the severity of stenosis among the Acehnese population should also be performed to prevent a greater incidence of CAD among the Acehnese ethnics.

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References

1. Zaromitidou M, Siasos G, Papageorgiou N, Oikonomou E, Tousoulis D. Atherosclerosis and coronary artery disease: From basics to genetics. *Cardiovascular Diseases*: Elsevier; 2016. p. 3-24.
2. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Annals of translational medicine*. 2016; 4(13).
3. Adi P. Pencegahan dan penatalaksanaan arterosklerosis. *Buku Ajar Ilmu Penyakit Dalam*. IV ed. Jakarta 2016. p. 1425–35.
4. Kemenkes RI. Riset Kesehatan Dasar (RISKESDAS) 2013. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI Tahun 2013; 2013.
5. Hunziker PR, Imsand C, Keller D, Hess N, Barbosa V, Nietlispach F et al. Buser P. Bedside quantification of atherosclerosis severity for cardiovascular risk stratification: a prospective cohort study. *Journal of the American College of Cardiology*. 2002; 39(4): 702-9.
6. Hajar R. Risk factors for coronary artery disease: historical perspectives. *Heart views: the official journal of the Gulf Heart Association*. 2017; 18(3): 109.
7. Kuller LH. Ethnic differences in atherosclerosis, cardiovascular disease and lipid metabolism. *Current opinion in lipidology*. 2004; 15(2): 109-13.
8. Spring B, Moller AC, Colangelo LA, Siddique J, Roehrig M, Daviglius M et al. Liu K. Healthy lifestyle change and subclinical atherosclerosis in young adults: Coronary Artery Risk Development in Young Adults (CARDIA) study. *Circulation*. 2014; 130(1): 10-7.
9. He J, Chen P, Luo Y, Chen L, Li S, Pan Y, Fu S. Relationship between the maximum carotid plaque area and the severity of coronary atherosclerosis. *International Angiology: a Journal of the International Union of Angiology*. 2018; 37(4): 300-9.
10. Naik V, Gamad R, Bansod P. Carotid artery segmentation in ultrasound images and measurement of intima-media thickness. *BioMed research international*. 2013; 2013.
11. Kotsis VT, Stabouli SV, Papamichael CM, Zakopoulos NA. Impact of obesity in intima media thickness of carotid arteries. *Obesity*. 2006; 14(10): 1708-15.
12. Saedi S, Ghadrdoost B, Pouraliakbar H, Zahedmehr A, Jebelli A. The association between increased carotid intima-media thickness and SYNTAX Score in coronary artery disease: A single center study. *Indian heart journal*. 2018; 70(5): 627-9.
13. Zuo G, Zhang M, Jia X, Zheng L, Li Y, Zhao H et al. Du X. Correlation between brachial-ankle pulse wave velocity, carotid artery intima-media thickness, ankle-brachial index, and the severity of coronary lesions. *Cell biochemistry and biophysics*. 2014; 70(2): 1205-11.

14. Kablak-Ziembicka A, Tracz W, Przewlocki T, Pieniazek P, Sokolowski A, Konieczynska M. Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart*. 2004; 90(11): 1286-90.
15. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao Let al. Yusuf S. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. *Circulation*. 2020; 142(7): 621-42.
16. Cho SH, Jeong MH, Park IH, Choi JS, Yoon HJ, Kim KH et al. Ahn Y. Endothelial dysfunction, increased carotid artery intima-media thickness and pulse wave velocity, and increased level of inflammatory markers are associated with variant angina. *Journal of cardiology*. 2009; 54(2): 183-91.
17. Kalkan K, Hamur H, Yildirim E, Ipek E, Ermis E, Ozturk Met al. Demirelli S. The comparison of angiographic scoring systems with the predictors of atherosclerosis. *Angiology*. 2018; 69(2): 158-63.
18. Darabian S, Hormuz M, Latif MA, Pahlevan S, Budoff MJ. The role of carotid intimal thickness testing and risk prediction in the development of coronary atherosclerosis. *Current atherosclerosis reports*. 2013; 15(3): 1-4.
19. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J cardiol*. 1983; 51: 606.
20. Sinning C, Lillpopp L, Appelbaum S, Ojeda F, Zeller T, Schnabel Ret al. Munzel T. Angiographic score assessment improves cardiovascular risk prediction: the clinical value of SYNTAX and Gensini application. *Clinical Research in Cardiology*. 2013; 102(7): 495-503.
21. Whincup PH, Nightingale CM, Owen CG, Rapala A, Bhowruth DJ, Prescott MH et al. Rudnicka AR. Ethnic differences in carotid intima-media thickness between UK children of black African-Caribbean and white European origin. *Stroke*. 2012; 43(7): 1747-54.
22. Azriana A, Handini MC, Sirait A. Gaya Hidup Suku Batak Yang Menderita Penyakit Jantung Koroner (Studi Ethnografi Di Rsud Dr. Pirngadi Medan Tahun 2018). *Jurnal Ilmiah Kohesi*. 32019.
23. Ibrahim T. Adat Istiadat Propinsi Aceh. Proyek Penelitian Kebudayaan Kementerian Pendidikan dan Kebudayaan: Kementerian Pendidikan dan Kebudayaan; 1997. p. 14.
24. Velde J. Surat-Surat dari Sumatera. Jakarta: Pustaka Azet; 1987.
25. Hidayah Z. Ensiklopedi suku bangsa di Indonesia: Yayasan Pustaka Obor Indonesia; 2015.
26. Nurdin A. Integrasi agama dan budaya: kajian tentang tradisi maulod dalam masyarakat Aceh. *El-Harakah (Terakreditasi)*. 2016; 18(1): 45-62.
27. Muna M. Tradisi Kenduri Blang Dalam Masyarakat Meunasah Baro Kabupaten Aceh Besar. Syiah Kuala 2018.
28. Apriana E. Kearifan lokal masyarakat aceh dalam konservasi laut. Serambi Saintia: Jurnal Sains dan Aplikasi. 2016; 4(1).
29. Andriansyah D. Tradisi Kenduri Kuburan (Keunurie Jeurat) Pada Masyarakat Aceh di Desa Pulo Tengah Kecamatan Darul Makmur Kabupaten Nagan Raya Aceh: UNIMED; 2012.
30. Marzuki M. Tradisi Meugang dalam Masyarakat Aceh: Sebuah Tafsir Agama dalam Budaya. *El-Harakah (Terakreditasi)*. 2014; 16(2): 216-33.
31. Dara DGR, Putro KZ, Irsyad M. Analisis Adat Budaya Aceh Pada Tradisi Mee Buu Tujuh Bulanan Ibu Hamil. *Jurnal Pelita PAUD*. 2021; 6(1): 92-101.
32. Khazanah W, Ramadhaniah R, Rahma CSN. Konsumsi Natrium Lemak Jenuh Dan Serat Berhubungan Dengan Kejadian Penyakit Jantung Koroner Di Rumah Sakit dr. Zainoel Abidin Banda Aceh. *Jurnal Kesehatan*. 2019; 7(1): 40-4.
33. Iskandar I, Hadi A, Alfridsyah A. Faktor risiko terjadinya penyakit jantung koroner pada pasien Rumah Sakit Umum Meuraxa Banda Aceh. *AcTion: Aceh Nutrition Journal*. 2017; 2(1): 32-42.
34. Syarkawi S. Revitalisasi Adat Istiadat Dan Pembentukan Karakter; (Analisis Terhadap Adat Istiadat Dan Pembentukan Karakter Syari'at Di Aceh). *Lentera: Jurnal Ilmiah Sains dan Teknologi*. 11(2): 145179.
35. Bauer M, Caviezel S, Teynor A, Erbel R, Mahabadi AA, Schmidt-Trucksäss A. Carotid intima-media thickness as a biomarker of subclinical atherosclerosis. *Swiss medical weekly*. 2012; (43).
36. Mookadam F, Moustafa SE, Lester SJ, Warsame T. Subclinical Atherosclerosis: Evolving Role of Carotid Intima-Media Thickness. *Preventive cardiology*. 2010; 13(4): 186-97.
37. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. *Journal of Thoracic Oncology*. 2010; 5(9): 1315-6.
38. Geeta, Savita, Pachar B, Nahta P, Khatri J. Predictive value of ultrasound assessed carotid and femoral intima media thickness in coronary artery disease and its relation with age and gender. *journal of indian college of cardiology*. 2015; 5(1): 9-14.

39. Latheef K, Praveen M, Vanajakshamma V, Rajasekhar D. Correlation of coronary artery disease angiographic severity with intima-media thickness of carotid artery. *Journal of Indian College of Cardiology*. 2012; 2(4): 144-9.
40. Shah Ebrahim D, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides ANet al. Rumley A. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women. 1999.
41. Youn YJ, Lee NS, Kim J-Y, Lee J-W, Sung J-K, Ahn S-Get al. Choe K-H. Normative values and correlates of mean common carotid intima-media thickness in the Korean rural middle-aged population: the Atherosclerosis Risk of Rural Areas iN Korea General Population (ARIRANG) study. *Journal of Korean medical science*. 2011; 26(3): 365-71.
42. Zielinski T, Dzielinska Z, Januszewicz A, Rynkun D, Makowiecka Ciesla M, Tyczynski Pet al. Naruszewicz M. Carotid intima-media thickness as a marker of cardiovascular risk in hypertensive patients with coronary artery disease. *American journal of hypertension*. 2007; 20(10): 1058-64.
43. Pradono J, Werdhasari A. Faktor determinan penyakit jantung koroner pada kelompok umur 25-65 tahun di Kota Bogor, data kohor 2011-2012. *Buletin Penelitian Kesehatan*. 2018; 46(1): 23-34.
44. Kirişli H, Schaap M, Metz C, Dharampal A, Meijboom WB, Papadopoulou S-Let al. Meijjs M. Standardized evaluation framework for evaluating coronary artery stenosis detection, stenosis quantification and lumen segmentation algorithms in computed tomography angiography. *Medical image analysis*. 2013; 17(8): 859-76.
45. Suzuki T, Wang W, Wilsdon A, Butler KR, Adabag S, Griswold MEet al. Mosley TH. Carotid Intima-Media Thickness and the Risk of Sudden Cardiac Death: The ARIC Study and the CHS. *Journal of the American Heart Association*. 2020; 9(19): e016981.
46. Coskun U, Yildiz A, Esen OB, Baskurt M, Cakar MA, Kilickesmez KOet al. Yildiz S. Relationship between carotid intima-media thickness and coronary angiographic findings: a prospective study. *Cardiovascular Ultrasound*. 2009; 7(1): 1-5.
47. Cakar MA, Sahinkus S, Aydin E, Vatan MB, Keser N, Akdemir R, Gunduz H. Relation between the GRACE score and severity of atherosclerosis in acute coronary syndrome. *Journal of Cardiology*. 2014; 63(1): 24-8.
48. Neeland IJ, Patel RS, Eshtehardi P, Dhawan S, McDaniel MC, Rab STet al. Quyyumi AA. Coronary angiographic scoring systems: an evaluation of their equivalence and validity. *American heart journal*. 2012; 164(4): 547-52. e1.
49. Metwally YG, Sedrak HK, Shaltout IF. The relationship between coronary artery severity and insulin resistance in patients with impaired glucose tolerance and metabolic syndrome. *The Egyptian Journal of Internal Medicine*. 2020; 32(1): 1-7.
50. Rampidis GP, Benetos G, Benz DC, Giannopoulos AA, Buechel RR. A guide for Gensini Score calculation. *Atherosclerosis*. 2019; 287: 181-3.
51. Hensley B, Huang C, Martinez CVC, Shokoohi H, Liteplo A. Ultrasound Measurement of Carotid Intima-Media Thickness and Plaques in Predicting Coronary Artery Disease. *Ultrasound in Medicine & Biology*. 2020; 46(7): 1608-13.
52. Matsushima Y, Takase B, Uehata A, Kawano H, Yano K, Ohsuzu Fet al. Kurita A. Comparative predictive and diagnostic value of flow-mediated vasodilation in the brachial artery and intima media thickness of the carotid artery for assessment of coronary artery disease severity. *International journal of cardiology*. 2007; 117(2): 165-72.
53. Zhang M, Wen X, Zhou C, Huang J, He Y. Carotid intima-media thickness and plaques in internal carotid artery as surrogate markers of lower limb arterial lesions in Chinese patients with diabetic foot. *Brazilian Journal of Medical and Biological Research*. 2019; 52.
54. Liu D, Du C, Shao W, Ma G. Diagnostic role of carotid intima-media thickness for coronary artery disease: a meta-analysis. *BioMed Research International*. 2020; 2020.
55. Carnethon MR, Bertoni AG, Shea S, Greenland P, Ni H, Jacobs Jr DRet al. Liu K. Racial/ethnic differences in subclinical atherosclerosis among adults with diabetes: the Multiethnic Study of Atherosclerosis. *Diabetes care*. 2005; 28(11): 2768-70.
56. Pursnani S, Merchant M. South Asian ethnicity as a risk factor for coronary heart disease. *Atherosclerosis*. 2020; 315: 126-30.
57. Kandou GD. Makanan etnik Minahasa dan kejadian penyakit jantung koroner. *Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal)*. 2009; 4(1): 42-8.
58. Ahmad T, Dhama K, Tiwari R, Chaicumpa W, Hui J: Bibliometric analysis of the top 100 most cited studies in apolipoprotein E (ApoE) research. *Narra J* 2021; 1(1):e2

59. Zahra Z, Ramadhani CT, Mamfaluti T, Pamungkas SR, Firdausa S: Association between depression and HbA1c levels in the elderly population with type 2 diabetes mellitus during COVID-19 pandemic. Narra J 2022; 2(1):e51