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The Correlation Between Interleukin-6 (IL-6) Levels and the Extent of Coronary Lesions Based on SYNTAX Scores in Patients with Acute Coronary Syndrome (ACS)

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ABSTRACT

Introduction: Atherosclerosis plays an important role in the pathogenesis of acute coronary syndrome (ACS). Inflammation plays a causal role in atherosclerosis. There are many inflammatory markers related to ACS, including C-reactive protein (CRP), homocysteine, matrix metal loproteinases, interleukin (IL)-6, IL-8, and IL-27. IL-6 is the sign of synthesis of acute phase proteins. Recently, the clinical trials related to ACS showed that IL-6 may be an indicator of increased risk for ACS. An Interleukin-6 (IL-6) examination is can be used to assess risk factors for acute coronary syndrome (ACS). Interleukin-6 is a marker of local inflammation of coronary plaque and peripheral blood circulation which increases the occurrence of coronary heart disease causing plaque instability and rupture. The SYNTAX scoring system has correlation assessed through angiography assessing the complexity of the severity of coronary artery stenosis. This study aims to determine the between Interleukin-6 (IL-6) levels and the extent of coronary lesions based on the SYNTAX score in patients with acute coronary syndrome (ACS).

Methods: This is a cross-sectional study of 45 patients with acute coronary syndrome (ACS) who were treated at H. Adam Malik General Hospital, Medan (February 2023 – May 2023). IL-6 levels were examined using the Electrochemiluminescent Immunoassay (ECLIA) method using Cobas e 411. The extent of the coronary lesion was calculated based on the SYNTAX score from coronary angiography which was calculated by two invasive cardiologist as suggested before using an online calculator. We used the Spearman correlation test and Mann Whitney test to analyze the data.

Results: There were 39 male subjects (86.7%) total. The mean age of the subjects was 54.89 ± 10.3 years old. Most of the subjects experienced STEMI in total 28 people (62.2%). The Median IL-6 levels was 19.22 pg/mL while the median of SYNTAX score level was 13.00. By using *cross-sectional* study and the spearman correlationa test, there is a significant correlation between IL-6 and the SYNTAX score with the correlation value obtained r = 0.343 (p = 0.021).

Conclusion: There is a significant relationship between IL-6 and the extent of coronary lesions based on the SYNTAX score in patients with acute coronary syndrome.

Keywords: Interleukin-6; acute coronary syndrome; SYNTAX score

INTRODUCTION

Cardiovascular disease is still a global threat and is a disease that plays a major role as the number one cause of death throughout the world. The World Health Organization (WHO) stated that in 2019 more than 17.9 million people died from cardiovascular disease or 31% of all global deaths. It is estimated that in 2030 there will be 23.6 million people dying from cardiovascular disease[1]. Based on data from Riset Kesehatan Dasar Riskesdas) in 2018, the incidence of cardiovascular disease in Indonesia is increasing, including 1.33 percents of North Sumatera population has been diagnosed[2].

Acute coronary syndrome (ACS) is a cardiovascular disease consisting of signs and symptoms of myocardial ischemia that occurs suddenly due to decreased blood flow to the heart. ACS includes unstable angina, myocardial infarction, up to sudden death, where damage to the heart muscle occurs, which is characterized by increased cardiac enzyme activity and a typical ECG picture, both ST-elevation myocardial infarction and non-ST segment elevation myocardial infarction[3].

Atherosclerosis is a chronic inflammation of blood vessels which plays an important role in the pathogenesis of acute coronary syndrome (ACS). Inflammatory cytokines cause activation of endothelial cells and contribute to the inflammatory response in patients with ACS. There are many inflammatory markers associated with ACS, including C-reactive protein (CRP), homocysteine, interleukin-6 (IL-6), IL-8 and IL-27[4,5].

Interleukin-6 (IL-6) is a 26-kDa pleiotropic immunomodulatory cytokine secreted by various cell types that plays an important role in many inflammatory processes. Interleukin-6 is a marker of acute phase protein synthesis that has a real prognostic value in acute coronary syndrome[6,7]. Several studies have explored the mechanism of IL-6 causing ACS, where IL-6 activates macrophages, infiltrates, and increases tissue factor expression[6].

Apart from using laboratory tests, coronary angiography examination is carried out to assess the extent of stenosis and to describe the severity of the coronary arteries. The Gensini score and SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and Cardiac Surgery) score are two common assessment of stenosis severity[5]. Compared to the Gensini score, coronary artery assessment using the SYNTAX score (SS) is considered by cardiologists as an angiographic tool that assesses the complexity of coronary artery disease. The SYNTAX score was developed specifically to describe the coronary vasculature by taking into account the number of lesions and their functional consequences, location, and complexity. A higher SYNTAX score, indicates a more complex disease state and worse prognosis[8]. The SYNTAX score is by far the most powerful angiographic tool in the prediction of events after PCI[9].

Studies by Gerin et al, 2017 and Ling et al, 2021, obtained significant correlation results between IL-6levels and the severity of acute coronary syndrome (ACS) based on the SYNTAX score. In addition, IL-6 levels independently predicted medium-high SYNTAX scores (SS > 22)[5,10]. Research studies on the relationship between interleukin-6 (IL-6) levels and the extent of coronary lesions based on the SYNTAX score in ACS patients have never been carried out in Indonesia, especially at H. Adam Malik General Hospital, Medan. This research was carried out at H. Adam Malik General Hospital, Medan, taking into account that this hospital is a referral hospital for the North Sumatra region and its surroundings.

METHOD

Research Population

This research is a cross-sectional analytic study with consecutive sampling, consisting of all patients diagnosed with Acute Coronary Syndrome (ACS) who were hospitalized at H. Adam Malik

General Hospital Medan in the period from February 2023 to May 2023. The inclusion criteria were ACS patients (STEMI, NSTEMI, UAP), have been examined for coronary angiography, and willing to participate in the study until it was completed. The study involved 45 ACS patients. Patients with cancers, infectious disease, chronic liver disease, post CABG or post PCI were excluded from the study.

Measurement of IL-6 and SYNTAX score

All the subjects who agred to join this research were were giving their informed consent before thecoronary angiography was held in the Cath-Lab of the Integrated Heart Installation at RSUP Haji Adam Malik Medan. Measurement of the area of coronary lesions based on the SYNTAX Score (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) is a scoring system developed to assess coronary vascular characteristics by assessing the overall number of lesions, lesion location, and lesion complexity which will be calculated and validated by the doctor Cardiovascular specialist when performing coronary angiography. Score calculation via the SYNTAX score application. For IL-6 examination, the material used is a serum blood sample taken when the patient was diagnosed with ACS. Samples are stored at -40 ^{0}C and can last for 6 months in the freezer, then examination of IL-6 levels is carried out simultaneously at one time. The measurement of IL-6 was carried out by ECLIA (Electrochemiluminescent Immunoassay) method using Cobas e 411. Based on Gerin et all in 2017, Normal IL-6 levels are < 7.81 pg/mL and in CAD patients ≥ 7.81 pg/mL[5].

Statistical analysis

Data were analyzed using SPSS version 20. Characteristics of the research subjects were presented in the form of tabulations and descriptions. The obtained data were not normally distributed. Therefore, the correlation between IL-6 levels and the total surface area of coronary lesions based on the SYNTAX score in ACS patients is analyzed by using the Spearman correlation test. The Mann Whitney test was used to see differences between the SYNTAX score and IL-6 levels. If a p value <0.05 is obtained then it is considered significant.

RESULT

Characteristics of subjects

Table 1.Baseline Characteristics of Research Subjects

Characteristic	N= 45 (%)
Sex	
Male	39 (86.7)
Female	6 (13.3)
Age (years old)	54,89 (10.3)
Smoking	
Yes	33 (73.3)
No	12 (26.7)
Hypertension	23 (51.1)
Diabetes Mellitus	14 (31.1)
ACS	
STEMI	28 (62.2)
NSTEMI	11 (24.4)
UAP	6 (13.3)

The baseline characteristic result was presented in Table 1, including average of age, gender, Interleukin-6 (IL-6) levels, SYNTAX scores and grouping of ACS categories.

Most of the subjects were male, of total 39 people (86.7%). The mean age of the subjects was 54.89 ± 10,3 years old with the youngest being 29 years old and the oldest being 75 years old. A total of 33 subjects (73.3%) were smokers. There was a history of hypertension in 23 subjects (51.1%) and 14 subjects (31.1%) had a history of DM. Based on the examination results, it showed that the majority of subjects experienced STEMI, totaling 28 people (62.2%).

SYNTAX score and IL-6

Using the Spearman correlation test, it shows that there is a significant correlation between IL-6) and the area of coronary lesions based on the SYNTAX score (p = 0.021) (table 2). The correlation value (r) obtained is 0.343 (the strength of correlation is moderate), meaning that there is a sufficient level of correlation and positive, where the correlation between the two variables in the same direction, wherw the higher of IL-6 level, the wider of the coronary lesion (the higher the SYNTAX score) in i ACS patients.

Table 2. Analysis of correlation between SYNTAX score and IL-6

Variables	N= 45	r*	p value
The severity of the coronary lesion, n (%)			
score ≤ 22 (low)	34 (75.6)		
score > 22 (mid-high)	11 (24.4)		
SYNTAX score, med (min-max)	13.00 (2 – 43,5)	0.343	0.021
IL-6 (pg/mL)	19.22 (1,5 – 190,2)		

**Spearman correlation*

Table 3 below shows that there were 6 subjects (group average = 11.58) who had IL-6 levels <7.81 and 39 subjects (group average = 24.76) who had IL-6 levels ≥7. 81. It was found that there was a difference in the area of coronary lesions based on the SYNTAX score in the two groups of normal IL-6 levels and the abnormal (high) group in acute coronary syndrome (ACS) patients with a p value of 0.022. Of the 39 people who had high IL-6 levels, there were 27 (69.2%) subjects with STEMI. Of the 6 people with normal IL-6 levels, there were more (66.7%) with a diagnosis of UAP. This shows that there is a significant relationship between Interleukin-6 levels and the ACS diagnosis category, where p is 0.000.

Table 3. Correlation between IL-6 levels, severity of the coronary lesion, and ACS classification

IL-6 (pg/mL)	severity of coronary lesion, n (mean)	p value**	ACS Classification, n(%)			p value***
			UAP	NSTEMI	STEMI	
Normal (<7.81)	6 (11.58)	0.022	4 (66.7)	1 (16.7)	1 (16.7)	<0.001
Higher (≥7.81)	39 (24.76)		2 (5.1)	10 (25.6)	27 (69.2)	
Total	45		6	11	28	

**Mann-Whitney Test
***Pearson Chi Square

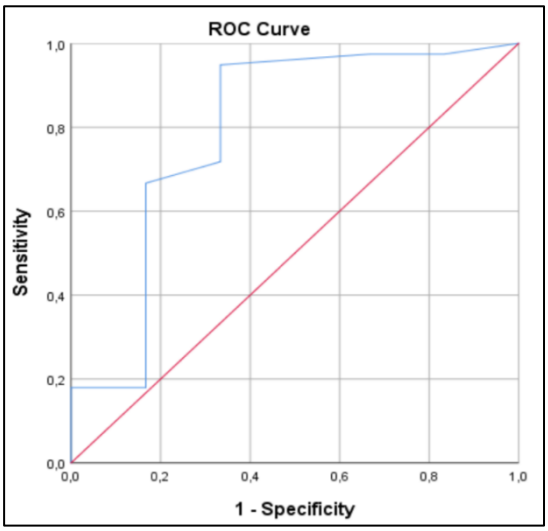

Figure 1. ROC curve of IL-6 and SYNTAX score

Assessment of the ability of IL-6 as a predictor of the severity of coronary lesions using ROC. The area produced by the ROC curve is the Area Under Curve (AUC) which is used to indicate the level of accuracy of IL-6's ability to predict predictors of the severity of coronary lesions based on the SYNTAX score. The AUC of the IL-6 value in predicting the severity of coronary lesions based on the SYNTAX score was 79.3% (good category), with a p value = 0.022 and a 95% CI of 55.1% - 100% (Fig.1). This shows that the IL-6 value as a good predictor of the extent of coronary lesions based on the SYNTAX score in acute coronary syndrome (ACS) patients ($p < 0.05$ or $p = 0.022$).

DISCUSSION

Most of our research subjects were male, 39 people (86.7%) of whom 33 subjects (73.3%) had a smoking habit. This is also in line with research conducted by Gerin et al, 2017 on 118 patients with coronary artery disease who were to undergo PCI. All research subjects were tested for Interleukin-6 and it was found that most of the subjects were male (40 people, 68.9%). The mean age of the subjects was 58.2 years with the youngest being 47 years old and the oldest being 69 years old. A total of 33 subjects (56.89%) had a smoking habit[5].

Risk factors for acute coronary syndrome (ACS) include age and gender, with the incidence rate in men being much higher than in women, but the incidence in women will increase after menopause around the age of 50 years. This is because the hormone estrogen has a protective effect against the occurrence of atherosclerosis, where in people aged >65 years, 20% of CHD is found in men and 12% in women. Increasing age will cause an increase in CHD sufferers, because blood vessels experience progressive changes and occur continuously over a long period of time. The earliest changes begin at the age of 20 years in the coronary arteries. Other arteries begin to modify only after the age of 40 years, occurring in men aged 35-44 years and increasing with increasing age[11].

Smoking, whether active or passive can cause cardiovascular disease through a series of processes such as enhanced oxidative stress, hemodynamic and autonomic changes, endothelial dysfunction, thrombosis, inflammation, hyperlipidemia. Individuals who smoke about one cigarette per day have a 48% higher risk of coronary heart disease compared to non-smokers. Some chemicals in tobacco smoke can cause excessive formation of reactive oxygen species (ROS) which results in

smooth muscle cell proliferation, DNA damage, inflammation, all of which lead to coronary heart disease[12].

There was a history of hypertension in 23 subjects (51.1%) and 14 people (31.1%) with a history of DM in this study. Based on the examination results, it showed that the majority of subjects experienced STEMI, totaling 28 people (62.2%). In line with research conducted by Ling et al, 2021. They conducted a retrospective study of 201 ACS patients who were to undergo PCI. All research subjects were tested for Interleukin-6 (IL-6). From the characteristics of the research subjects, the majority of the subjects were male, totaling 136 people (67.7%), with a history of hypertension in 127 people (63.2%) and a history of DM in 49 people (24.4%).[10]

Type 2 DM that is not managed properly will cause various chronic complications, both microangiopathy such as retinopathy and nephropathy and macroangiopathy such as coronary heart disease. The mechanism of CHD in type 2 DM is very complex and is associated with atherosclerosis which is influenced by various factors including hypertension, hyperglycemia, dyslipidemia, smoking, family history of CHD, and obesity. According to the American Heart Association in May 2012, at least 65% of DM sufferers died from heart disease or stroke[13]. Blood pressure that continues to increase in the long term will cause the formation of plaque which will narrow the blood vessels, and in certain circumstances where high blood pressure can crack the plaque so that plaque fragments can block the blood vessels, where it is known that blood vessels are an entry point for oxygen and energy. to the heart. In addition, increased blood pressure due to hypertension can increase resistance to pumping blood, so that the heart's workload will increase[14].

Acute coronary syndrome (ACS) is a clinical presentation of coronary atherosclerosis and plaques rupture. Elevated blood level of interleukin-6 conferred an increased risk of adverse prognosis in ACS patients[15]. Some studies have microscopically explored the mechanism by which IL-6 promotes ACS, proving that IL-6 promotes macrophage activation, infiltration, and increased expression of low-density lipoprotein (LDL) receptors, thereby enhancing macrophage uptake of LDL and inducing increased expression of tissue factor. These mechanisms contribute to the inflammatory process of atherosclerosis[6].

ACS patients were separated based on SS values cited in prior studies, with one group of patients with low SS values (SS≤ 22, n=34) and one group with intermediate-high SS values (SS>22, n=11).

In this study, we found that the median IL-6 level in ACS patients was 19.22 pg/mL and the median SYNTAX score was 13. These results are in line with the study by Gerin et al, 2017 which found that of 118 patients who underwent coronary angiography, there were 58 ACS patients with a mean IL-6 level of 21.0 pg/mL and a mean SYNTAX score of 10.7[5]. Ling et al's 2021 study found that there were 168 patients with SS ≤22 (83.6%) and 33 patients with SS >22 (16.4%), with the median IL-6 level in patients with SS ≤22 being 6.5 pg /mL and in patients with SS >22 it is 14.0[10].

Using the Spearman correlation test in this study, it showed that there was a significant relationship between IL-6 and the area of coronary lesions based on the SYNTAX score with a correlation value of r = 0.343 (p = 0.021), where in the high IL-6 group (levels ≥7. 81 pg/mL) for 39 patients, the coronary lesion area using the SYNTAX score was 24.76. A retrospective study conducted by Ling et al, 2021 on 201 ACS patients, showed that IL-6 levels were significantly correlated with SYNTAX scores (r= 0.479, p value <0.001), where in the interleukin-6 group the average was 14.0 pg/mL (high) was obtained in the SYNTAX Score group >22 (high)[10]. Gerin et al, 2017 in 118 patients who underwent coronary angiography showed a significant correlation between IL-6 and SYNTAX score (r= 0.484, with p<0.001). 5 The study of Djuric et al, 2021 also showed a positive relationship significant relationship between IL-6 and ACS severity based on the SYNTAX score (p = 0.017)[16].

Inflammatory processes are involved in the pathogenesis of atherosclerosis. Interleukin-6 as a multifunctional cytokine, plays a role in regulating the inflammatory response after injury. It contributes to connective tissue remodeling by increasing metalloproteinase gene expression. Focal overexpression of metalloproteinases causes destabilization and degradation of the fibrous cap plaque leading to atherosclerotic plaque instability[17]. Elevated IL-6 levels may reflect hidden plaque inflammation and are encountered in the early stages of ACS[15].

In this study, using Pearson chi square, it was found that there was a significant relationship between IL-6 levels and the severity of ACS (ACS classification) (p value <0.001). This is in line with Yang et al, 2021 study that ACS patients have significantly higher levels of IL-6 compared to healthy people[6]. ACS patients with elevated IL-6 should be monitored more closely than those with normal IL-6. Higher IL-6 levels early after the onset of STEMI are indicative of larger infarct size and decreased cardiac function[15].

From the ROC curve in this study, it was found that the AUC of IL-6 levels in predicting the severity of coronary lesions based on the SYNTAX score was 79.3% (p= 0.022, with a 95% CI of 55.1% - 100%). This shows that IL-6 levels can be used to predict the extent of coronary lesions based on the SYNTAX score in ACS patients with moderate levels of ability (AUC >70%-80%). This is in accordance with research by Gerin et al, 2017 which states that the optimal cut-off for IL-6 is 7.81 pg/mL to assess the presence of coronary artery disease lesions (ROC 0.78, sensitivity 78.3% and specificity 70.7 %)[5].

CONCLUSION

In this study, there was a significant relationship between Interleukin-6 and the area of coronary lesions based on the SYNTAX score in patients with acute coronary syndrome (r = 0.343; p = 0.021) so this examination is useful for predicting the area of coronary lesions based on the SYNTAX score. The ability of IL-6 levels to predict the extent of coronary lesions based on the SYNTAX score in ACS patients at Haji Adam Malik Hospital in Medan was 79.3%.

REFERENCES

1. World Health Organization(WHO). Cardiovascular diseases (CVDs). 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Kemenkes RI. Riset Kesehatan Dasar (Riskesdas). 2018. Available from: https://kesmas.kemkes.go.id/assets/upload/dir_519d41d8cd98f00/files/Hasil-riskesdas-2018_1274.pdf
3. Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI). Pedoman Tatalaksana Sindrom Koroner Akut Edisi 3. Jakarta; 2018.
4. Libby P. Targeting Inflammatory Pathways in Cardiovascular Disease: The Inflammasome, Interleukin-1, Interleukin-6 and Beyond. Cells. 2021 ;10(4):951.
5. Gerin F, Durmus E, Yaman A, Sunbul M, Mammadov C, Bozbay M, et al. Relation of interleukin-6 level with coronary artery disease severity in patients undergoing coronary angiography. Eur J Ther. 2020;23(3):117–21.
6. Yang C, Deng Z, Li J, Ren Z, Liu F. Meta-analysis of the relationship between interleukin-6 levels and the prognosis and severity of acute coronary syndrome. Clinics. 2021;76:e2690.
7. Freitas IA de, Lima N de A, Silva Jr GB da, Castro Jr RL de, Patel P, Lima CC de V, et al. Novel biomarkers in the prognosis of patients with atherosclerotic coronary artery disease. Rev

Port Cardiol. 2020 Nov;39(11):667–72.

8. Sianos G, Morel M-A, Kappetein AP, Morice M-C, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005 Aug;1(2):219–27.

9. Généreux P, Palmerini T, Caixeta A, Stone GW. A Guide to Calculating SYNTAX Score. Interv Cardiol Rev. 2012;7(1):21.

10. Ling Y, Weng H, Tang S. The relationship between IL-6 levels and the angiographic severity of coronary artery disease following percutaneous coronary intervention in acute coronary syndrome patients. BMC Cardiovasc Disord. 2021 Dec 3;21(1):578.

11. Ten Haaf ME, Bax M, ten Berg JM, Brouwer J, van't Hof AW, van der Schaaf RJ, et al. Sex differences in characteristics and outcome in acute coronary syndrome patients in the Netherlands. Netherlands Hear J. 2019 May 15;27(5):263–71.

12. Morris PB, Ference BA, Jahangir E, Feldman DN, Ryan JJ, Bahrami H, et al. Cardiovascular Effects of Exposure to Cigarette Smoke and Electronic Cigarettes. J Am Coll Cardiol. 2015 Sep;66(12):1378–91.

13. Al-Lamki L. Acute Coronary Syndrome, Diabetes and Hypertension: Oman must pay more attention to chronic non-communicable diseases. Sultan Qaboos Univ Med J. 2011 Aug;11(3):318–21.

14. Konstantinou K, Tsioufis C, Koumelli A, Mantzouranis M, Kasiakogias A, Doumas M, et al. Hypertension and patients with acute coronary syndrome: Putting blood pressure levels into perspective. J Clin Hypertens. 2019 Aug 12;21(8):1135–43.

15. Li H, Cen K, Sun W, Feng B. Predictive Value of Blood Interleukin-6 Level in Patients with Acute Coronary Syndrome: A Meta-analysis. Immunol Invest. 2021;50(8):964–76.

16. Djuric P, Mladenovic Z, Spasic M, Jovic Z, Maric-Kocijancic J, Prokic D, et al. Hyperhomocysteinemia and inflammatory biomarkers are associated with higher clinical SYNTAX score in patients with stable coronary artery disease. Vojnosanit Pregl. 2021;78(7):736–44.

17. Mossmann M, Wainstein MV, Mariani S, Machado GP, de Araújo GN, Andrades M, et al. Increased serum IL-6 is predictive of long-term cardiovascular events in high-risk patients submitted to coronary angiography: an observational study. Diabetol Metab Syndr. 2022 Aug ;14(1):125.