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ORIGINAL

Relationship Between Growth Differentiation Factor-15 and Global Registry of Acute Coronary Events Score in Patients with Non-St Segment Elevation Acute Coronary Syndrome

Relación Entre el Factor de Diferenciación de Crecimiento-15 y La Puntuación Del Registro Global De Eventos Coronarios Agudos en Pacientes con Síndrome Coronario Agudo Sin Elevación Del Segmento St

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ABSTRACT

Introduction: one of the main causes of hospitalization and death is NSTE-ACS. A GRACE risk score tool specifically designed for risk stratification of acute coronary syndrome patients is needed. The GRACE score has limitations related to the uncertainty of atherosclerotic plaque rupture and difficulty in predicting. GDF-15 is one possibility that is necessary because the results depend on an assessment of risk at a point in time. Elevated circulating levels of GDF-15 are associated with poor prognosis in many acute and chronic conditions including heart disease. Research linking GDF-15 with GRACE scores is limited and requires further study. analyze the relationship between GDF-15 and GRACE Score in NSTE-ACS patients.
Method: analytical observational study with a cross-sectional method, 37 subjects were taken at Airlangga University Hospital in july-November 2024. GDF-15 levels were measured using the ELISA method using a Bio-rad reader. Analysis used the SPSS 25 series Spearman test.
Results: subjects (n=40) were predominantly aged 60,98±8,592, 70 % male, and 67,5 % had a history of hypertension. The median GDF-15 level was 574,53 with a minimum level of 77 ng/L and a maximum of 2913 ng/L, the mean GRACE score was 95,65±18,307 with the highest score of 147. Statistical analysis showed a strong relationship between GDF-15 and the GRACE (contingency coefficient 0,724 with p 0,001).
Conclusions: GDF-15 can be used as an alternative additional marker in GRACE score assessment.

Keywords: Ska; Nste-acs; Gdf-15; Grace Score.

RESUMEN

Introducción: una de las principales causas de hospitalización y muerte es el SCASEST. Se necesita una herramienta de puntuación de riesgo GRACE diseñada específicamente para la estratificación del riesgo de pacientes con síndrome coronario agudo. La puntuación GRACE tiene limitaciones relacionadas con la incertidumbre de la rotura de la placa aterosclerótica y la dificultad para predecirla. GDF-15 es una posibilidad necesaria porque los resultados dependen de una evaluación del riesgo en un momento dado. Los niveles circulantes elevados de GDF-15 se asocian con un mal pronóstico en muchas afecciones agudas y crónicas, incluidas las enfermedades cardíacas. La investigación que vincula GDF-15 con las puntuaciones GRACE es limitada y requiere más estudios. analizar la relación entre GDF-15 y GRACE Score en pacientes con SCASEST.

Método: estudio observacional analítico con método transversal, 37 sujetos fueron tomados en el Hospital Universitario de Airlangga en julio-noviembre de 2024. Los niveles de GDF-15 se midieron mediante el método ELISA utilizando un lector Bio-rad. El análisis utilizó la prueba de Spearman de la serie SPSS 25.
Resultados: los sujetos (n=40) tenían predominantemente edad de 60,98±8,592 años, 70 % hombres y 67,5 % tenían antecedentes de hipertensión. El nivel medio de GDF-15 fue 574,53 con un nivel mínimo de 77 ng/L y un máximo de 2913 ng/L, la puntuación GRACE media fue de 95,65 ± 18,307 con la puntuación más alta de 147. El análisis estadístico mostró una fuerte relación entre GDF-15. 15 15 y el GRACE (coeficiente de contingencia 0,724 con p 0,001).
Conclusiones: GDF-15 se puede utilizar como un marcador adicional alternativo en la evaluación de la puntuación GRACE.

Palabras clave: Ska; Nste-acs; Gdf-15; Grace Score.

INTRODUCTION

Cardiovascular disease is the leading cause of death, affecting about 17,9 million people each year. Cardiovascular diseases are a group of diseases that affect the heart and blood, including chronological, cerebrovascular, remark, and other conditions. According to WHO 2021, four out of five cases of death from cardiovascular disease are caused by strokes and heart attacks. And those under seventy years old account for one-third of deaths from cardiovascular disease. Acute Coronary Syndrome (ACS) is currently still the number one killer in the world including Indonesia, ACS disease is influenced by various risk factors, ranging from risk factors to potentially high levels of LDL, hypertension, smoking, and diabetes mellitus.[1] Basic health research data in 2018 stated that East Java's heart disease prevalence rate was 1,5 %.[2]

The accumulation of atherosclerotic plaque in the epicardial arteries, both obstructive and non-obstructive, is the cause of ACS.[3] ACS examination includes anamnesis, physical examination, electrocardiogram, and cardiac biomarkers. ACS is divided into three types, namely unstable angina (UA), non-ST Elevation Myocardial Infarction (NSTEMI), and ST Elevation Myocardial Infarction (STEMI). NSTEMI and UA are included in NSTE-ACS, a spectrum of diseases caused by an imbalance in myocardial oxygen supply and oxygen demand.[2]

Age, heart rate, systolic blood pressure, Killip class, creatinine levels, elevated myocardial biomarkers, cardiac arrest on admission, ST segment deviation, and 90 % of the risk factors for predicting mortality should be used clinically. The GRACE score was created especially for risk stratification of ACS patients because it is a leading cause of hospitalization and death.[3] The GRACE score can be used to assess the risk of NSTE-ACS quantitatively, this score provides the most accurate risk stratification both at hospital admission and discharge.[4] Kumar's research, 2021 shows that the GRACE score has high clinical significance for predicting in-hospital mortality in NSTE-ACS patients. A high GRACE score carries a higher risk of in-hospital death or death within six months of discharge.[3,5] The GRACE score is a validated scoring system and provides prognostic value for NSTE-ACS subjects, however, the GRACE score has several shortcomings, namely lack of access to the online website, nurse awareness, and time in the department due to blood test results. Creatinine and troponin are part of the GRACE score calculation.[5] According to research by Widera 2012, the GRACE score has limitations related to unpredictable atherosclerotic plaque rupture and the difficulty of predicting outcomes based on risk assessment at one time.[6] Inflammation associated with NSTE-ACS outcomes cannot be captured by the variables included in the GRACE score, therefore the GDF-15 marker is needed to improve risk assessment—outside the scoring system. GDF-15 levels in the blood circulation increase in ACS patients, and increased GDF-15 measured in individuals with acute myocardial infarction shows a correlation with inflammatory biomarkers.[5] Wang study, 2019, stated that the GRACE score and GDF-15 have a relationship, with the emergence of GDF-15 as a biomarker that has the potential to add clinical information and information discriminatory on GRACE score when hs troponin T was considered as an additional variable. *Growth Differentiation Factor*-15 is part of TGF-ß secreted by cells exposed to various types of stress.[7] Adipose tissue expresses GDF-15, a stress-induced cytokine brought on by damage to numerous organs, including the heart, lungs, colon, kidneys, liver, and pancreas.[6] Higher circulating GDF-15 levels are an independent predictor and prognostic factor after acute pulmonary thrombosis. This can provide information regarding the risk of kidney damage or transplantation in patients with arterial hypertension. Increased risk of cardiovascular disease is associated with high levels of GDF-15 in the blood.[8] Research lingking GDF-15 with GRACE scores is still limited and requires further study. The benefit of GDF-15 as a prognostic factor in ACS is known from many studies.

Research Objectives: to determine the relationship between GDF-15 and the GRACE score which has a risk value in patients with NSTE-ACS. Based on the background, researchers are interested in conducting research on the relationship between GDF-1 and GRACE scores in patients with NSTE-ACS.

METHOD

Ethical Approval

The study design used an observational analytical design, using serum samples taken from the clinical pathology laboratory of Airlangga University Hospital. This study was approved by the Health Research Ethics Committee of Airlangga University Hospital through a letter numbered: 099/KEP/2024.

Sample

Serum samples from patients diagnosed with NSTE-ACS were collected and stored in a freezer at-20°C at the Special Infection House Research Laboratory Installation. The sample collection process was carried out in August 2024 - November 2024. Samples that have been collected during that time will be continued to the stage of examining GDF-15 levels using an ELISA Reader (BioRad iMark Microplate Reader) and calculating GRACE scores using GRACE 2,0 and validated by the PPDS heart at Airlangga University Hospital.

ELISA Assay

GDF15 examination using the sandwich ELISA method. Sample examination blood was taken from the patient and processed into serum to be used in this study. The examination was carried out after all samples were collected. Unopened reagent kits can be stored at 2-8oC for 1 month, but if more than 1 month then the components are stored separately. Micro ELISA plates, reference standards, and concentrated biotinylated Ab are stored at -20°C and can last for 6 months, HRP conjugates are stored at -20°C and are light-proof and can last for 6 months, reference standards and dilution samples, biotinylation detection AB diluent, HRP conjugate diluent, washing buffer, and substrate reagent are stored at 2-8°C and can last for 6 months. The working method of the GDF-15 examination is as follows:

Reagents, standard solutions, and samples were prepared in advance and then allowed to reach room temperature before use. Unused plates should be stored at 2-8°C. Standards were added as much as 50 µL to the plate, and make sure that biotinylated antibodies were not added to the plate containing the standards. Samples were added as much as 40 µL to the plate, and then 10 µL of anti-GDF15 antibody was added. Streptavidin-HRP as much as 50 µL was added to the sample and standard plates then homogenized and incubated for 60 minutes at 37°C. After that, the plate was washed 5 times using 300 µL of buffer, with each wash carried out for 30 seconds to 1 minute, then the plate was patted using tissue. Substrate solution A was added as much as 50 µL to each plate, followed by substrate solution B as much as 50 µL, and then the plate was incubated for 10 minutes at 37°C in the dark. Stop solution was added as much as 50 µL to each plate, which caused the blue color to change to yellow. Finally, the plate was read using a wavelength of 450 nm for 10 minutes.

Statistical Methods

Statistical data analysis uses descriptive analysis to see the distribution of gender, age, and history of hypertension. Analysis of the relationship between GDF-15 and GRACE scores in NSTE-ACS patients using the normality test (Shapiro-Wilk). Normally distributed data was followed by the Pearson test. Data that was not normally distributed was carried out by a normality test followed by the Spearman test. The significance of $P < 0,05$ is seen using SPSS, the strength of the relationship is obtained from looking at the r value.

RESULTS

GDF-15 Quality Assurance Results

This study used Bioenzy reagent (BZ-08127300-EB) NoZE805033 with storage at 2-8°C, expiry date of January 18, 2025. The detection limit was 5,57 ng/L.

Demographic Characteristics of Research Subjects

The research subjects were 40 subjects diagnosed with NSTE-ACS (NSTEMI and UA). The frequency distribution of research variables was obtained from secondary data collection from Airlangga University Hospital medical records. Age, gender, and history of hypertension are demographic characteristics of research subjects.

Table 1. Results of Analysis of Research Subject Characteristics

Characteristics		Total	
		N	%
Age (years)	Mean±SD	60,98±8,592	
Gender	Man	28	70 %
	Woman	12	30 %
History of Hypertension	Yes	27	67,5 %
	No	13	32,5 %

Quantitative characteristic variables are described by their average value (mean) and standard deviation, while qualitative characteristic variables are described by the number or frequency and proportion of each variable category in percent. The results are presented in table 1.

Based on the table1 age of the research subjects has an average value ± SD (60,98 ± 8,592). The maximum age of SKA sufferers is 83 years old while the minimum age is 48 years old. The characteristics of the majority of SKA sufferers are male (70 %) and female (30 %). Some SKA sufferers have a history of hypertension (67,5 %).

Analysis of GDF-15 Levels in NSTE-ACS Patients

The data on the results of the GDF-15 level examination of the research subjects were obtained from sample analysis at the Laboratory of the Special Infection Hospital (RSKI). Sample analysis used the ELISA method using the Bioenzy brand reagent kit, sample analysis was carried out in November 2024. The research data was tested for normality which stated that the GDF-15 levels were not normally distributed and a description of the results of the GDF-15 levels can be seen in Table 2 below.

Table 2. GDF-15 levels

Variables	N	Shapiro Wilk	Median (Min-Max)
GDF-15 levels	40	0,001*	574,53 (77-2913)
*Significant <0,05 Normality			

Based on the table 2. It can be seen that SKA patients have a minimum GDF-15 level of 77 and a maximum of 2913.

Analysis of GRACE Score Calculation Results in NSTE-ACS Patients

The data from the calculation of the subject's GRACE score were obtained from calculations using GRACE 2,0 the subject data was taken from medical records at Airlangga University Hospital and the GRACE score was validated by a PPDS cardiologist, the GRACE score calculation was carried out in November 2024. A description of the GRACE score calculation results can be seen in table 3 below.

Table 3. GRACE Score Calculation

Variables	Shapiro Wilk	Category	SKA	
			N	%
GRACE Score	0,103*	Mean±SD	95,63±18,307	
		Rise high (140)	1	2,5 %
		Moderate increase (109-140)	6	15 %
		Low (<108)	33	82,5 %
*Significant >0,05 Normality				

Based on the table. It can be seen that the normality test is normally distributed and SKA patients who experienced a moderate increase in GRACE scores were (15 %), a high increase was (2,5 %), and (82,5 %) had low results.

Analysis of the Relationship between GDF-15 Levels and GRACE Scores in NSTE-ACS Patients

The GDF-15 levels and GRACE scores were analyzed for normality first using the Shapiro-Wilk test. From the results of the Shapiro-Wilk test, the data were not normally distributed because the p-value <0,05 because the data was not normally distributed, the relationship was then sought through the Spearman test. The Spearman test can be seen in table 5.

Table 4. Interpretation of Spearman Rank Correlation

Spearman r	Correlation Coefficient
0,00-0,25	Very weak relationship
0,26-0,50	Relationship is sufficient
0,51-0,75	Strong relationship
0,76-0,99	Very strong relationship
1,00	Perfect relationship

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Table 5. Relationship between GDF-15 levels and GRACE scores

N = 40	GRACE Score Results
GDF-15 levels	rs = 0,724[a] ps = 0,001b

[a]Correlation Coefficient > 0,7 [b]Significant p< 0,005 Spearman

Based on table 5 the results of the analysis using the test *Spearman* obtained p = 0,001 for GDF-15 levels with GRACE scores, it can be concluded that there is a relationship between GDF15 levels and GRACE scores. The r value indicates that the strength of the relationship between GDF 15 levels and GRACE scores is strongly positive.

DISCUSSION

Quality assurance of the examination results in this study was carried out by conducting internal quality assurance before the examination. Internal quality assurance includes the GDF-15 examination reagent has been checked the lot number and its validity period has not expired when used. The standard examination of GDF-15 using the Bioenzy reagent (BZ-08127300-EB) ELISA method with lot number ZB805033 showed good results.

This study involved 40 subjects, 28 of whom were male and 12 of whom were female. These results are supported by research conducted by Firdaus 2018, which shows that there are 21 female SKA sufferers compared to 39 male sufferers.[9] The progressive decrease in estrogen levels after puberty in male subjects often experiences ACS 10-15 years earlier than female subjects who experience ACS at menopause.[10] Estrogen protects the heart in premenopausal or premenopausal conditions through several mechanisms, including preserving the lipoprotein profile. This is consistent with the fact that estrogen levels have a positive relationship with (HDL-C) and a negative relationship with total cholesterol, (LDL-C), (VLDL-C) and triglycerides. By generating nitrogen oxide, which stabilizes endothelial cells, estrogen modifies vascular tone. Increasing antioxidant effects and modifying fibrinolytic proteins, but this heart protection is lost with menopause.[10,11]

The research subjects had an average age of 60,98±8,592 years, in line with the research. Ramdhani 2013, Stated that the age group of subjects with SKA was 41-60 years old, which was the largest age group of sufferers.[11] The greatest risk factor for coronary heart disease development and death following atherosclerosis is advanced age.[10] The majority of SKA sufferers are over 45 years old in men, while in women they are around 55 years old. As age increases, Blood vessels will constantly undergo small modifications that may have an impact on heart function.[7] Advanced age is also related to the increase in time in the process of fat deposition on the walls of blood vessels, the process of blood vessel fragility occurs due to reduced elasticity of blood vessels and reduced cells from fibrous tissue and the accumulation of increasing lipids.[8]

Subjects affected by SKA have other risks such as a history of hypertension, as seen in table 1, there are 27 subjects with a history of hypertension, while there are 13 subjects who do not have a history of hypertension. This is consistent with studies carried out by Amrullah, 2022 Namely the frequency of hypertensive subjects as many as 58 people. Chronic arterial hypertension is a cardiovascular risk factor associated with the development of atherosclerosis, factors that need to be considered for the relationship between hypertension and atherosclerosis include genetic risk, insulin resistance, hyperactivity, and angiotensin, in addition, hypertension is also associated with the development of myocardial infarction.[12] Hypertensive patients with ACS tend to be elderly, and female and have a higher prevalence of comorbidities.[13]

Hypertension affects the heart because it increases the burden on the heart which causes left ventricular hypertrophy and accelerates the development of atherosclerosis because high blood pressure continuously traumatizes the walls of the coronary arteries, making it easier for coronary atherosclerosis to occur. When blood vessels narrow, blood flow in the coronary arteries, which carry oxygen to the heart, is reduced.[11]

The results showed that GDF-15 levels in 3 subjects increased to levels >1,800 ng/L, This study supports previous findings that GDF-15 levels were >1,800 ng/L were associated with increased mortality. In connection with the increasing prevalence of cardiovascular risk factors, GDF-15 levels have predictive significance for patients with ACS. Information regarding the short-term and long-term prognosis of ACS patients can be found in GDF-15 levels. The results of the study show that the addition of GDF-15 measurements can add information on clinical characteristics and cardiovascular risk factors so that it can improve risk stratification.

The findings of this study are consistent with Kempf (2007). claimed that the chance of death within 1 year was highly correlated with increasing GDF-15 levels. Individuals with a GDF-15 level of 1200 ng/L had a decreased 1-year mortality rate, while patients with GDF-15 levels of 1800 ng/L had a relatively high 1-year mortality rate.[13] The ECG gains prognostic information from the GDF-15 measurement taken upon admission. Patients with normal ECG results have GDF-15 levels <1200 ng/L and abnormal ECG results have GDF-15 levels >1800 ng/L.[14]

For patients with ACS, the GRACE score is a popular, validated, and advised risk stratification measure. The GRACE score predicts adverse events after the index ACS.[12] the GRACE score can be widely applied to assess the cumulative risk of death in ACS patients. In a study conducted by Fox, 2006 Based on 48,389 patients supported the validity of the GRACE score for in-hospital and post-discharge mortality. Initial patient stratification aimed to identify patients suitable for reperfusion therapy based on clinical syndrome and ST-segment elevation.[15]

The results showed that there was 1 subject with a score above 140 who was male and had a history of hypertension. Research is in line with research by Yan, 2023. Revealing that male patients with a history of hypertension and diabetes have high scores and high mortality rates, The GRACE score is a point system for assessing hospital mortality rates. It determines the long-term mortality of patients with ACS and has good predictive value for coronary complications and other diseases.[14]

The results of the GRACE score calculation in NSTE-ACS patients showed that the majority of subjects were classified into the low-risk category, This is consistent with the findings of research by Kumar, 2021 Which showed that the majority of subjects were in the low-risk category followed by the intermediate and high-risk categories. The GRACE score results showed that in-hospital and six-month post-discharge mortality was significantly greater in the high-risk group compared with the intermediate and low-risk groups without in-hospital mortality. The GRACE score was a significant independent predictor of in-hospital mortality.[15]

The results of the analysis show that there is a strong relationship between GDF-15 levels and GRACE scores, with a p-value <0,05 and r r-value>0,5. This is in accordance with previous research that examined the relationship between GDF-15 levels and GRACE scores. Validated scoring methods, such as the GRACE score, provide information for additional prognostic assessment, but their ability to differentiate outcome groups is lacking, a deficiency that is related to the difficulty of predicting outcomes based on assessments at a single point in time. In addition, inflammation associated with NSTE-ACS is not fully captured by the variables included in the GRACE score. GDF-15 levels are associated with cardiovascular risk factors such as diabetes, smoking, and cholesterol, and in the elderly, GDF-15 biomarkers may help reflect additional pathways.[16]

GDF-15 contributes to left ventricular hypertrophy and systolic dysfunction in older adults, as well as endothelial dysfunction and plaque buildup.[17] The results of the study showed an increase in height in 3 subjects who had a history of hypertension and recurrent attacks. Research according to Zhang, 2016 shows that high levels of GDF-15 indicate a risk of death from ACS and recurrent MI. High levels of GDF-15 are associated with a predictive role indicating the degree of myocardial damage and the likelihood of recurrent myocardial infarction. Prolonged increases in GDF-15 levels after ischemia and reperfusion may be related to increased levels of oxidative stress and inflammation.[18,19] Increased GDF-15 levels in subjects with a history of hypertension are the results of research conducted by Uc & Sivri, 2019 stated that GDF-15 levels were significantly higher in patients with grade-2 essential hypertension., aortic stiffness indicates several conditions such as atherosclerosis, acute coronary events, and intimal thickness. Hypertension accelerates the decrease in aortic and arterial elasticity through increased distension pressure and increased matrix synthesis pressure due to vascular hardening.[20]

Research Limitations

A limitation of the study is that it did not exclude patients with recurrent attacks which could cause bias and most of them were in the low category.

CONCLUSION

Research shows a strong relationship between GDF-15 and GRACE contingency coefficient of 0,724 with p 0,001 It was concluded that GDF-15 could be used as an alternative additional marker in GRACE score assessment.

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