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Correlation Monocyte Count, High Density Lipoprotein Cholesterol Levels and Monocyte High Density Lipoprotein Cholesterol Ratio with hsCRP Levels in Hypertension Patient

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Abstract

Background: Hypertension is a condition which blood pressure in blood vessels increases chronically. Previous studies have shown that hypertension is associated with an inflammatory process involving innate and adaptive immune responses. Hypertension led to increased levels of several inflammatory markers such as Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and C-Reactive Protein (CRP). Chronic inflammation is also characterized by an increase in the number of monocytes. Activation and spread of monocytes can be inhibited by High Density Lipoprotein Cholesterol (HDL-C). HDL-C can also inhibit the work of activated monocytes.

Objective: Aim of this study was to determine the relationship between the number of monocytes, high density lipoprotein levels, and the ratio of monocytes to high-sensitivity C-reactive protein concentrations in a population of people with high blood pressure.

Method: This study was conducted using a cross-sectional design in hypertensive patients who visited the heart disease and internal medicine polyclinic at Pertamina Hospital Cirebon with a total of 67 respondents with grade 2 hypertension according to JNC VII.

Results: Correlation between hsCRP with Monocyte Count was positive but not significant (p=0,311; r=0,126), hsCRP and HDL-C has negative correlation (p=0,273; r=-0,136), hsCRP and monocyte HDL rasio also had no significant correlation (p=0,121; r=0,191) **Conclusion:** There was no correlation between hsCRP with monocyte count, hsCRP, and Monocyte HDL Ratio (MHR) (P>0.05).

Keywords: *Hypertension, hsCRP, Monocyte, HDL, Monocyte HDL Ratio*

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INTRODUCTION

Hypertension is one of the causes of mortality and morbidity worldwide that beoming cause of death of around 8 million people each year, of the 1.5 million deaths that occur in Southeast Asia. World Health Organization (WHO) in 2011 report that prevalence hypertension case in world exceed one billion, two-thirds of whom are spread across developing countries in low to moderate income populations. This number predicted to continue increase sharply in 2025 with 29% of adults suffering from hypertension[1].

Currently, hypertension is a fairly major health problem in Indonesia which is often found in primary health services. Data from research conducted by Jabani, et al. (2021), states that 60.7% of people with grade 2 hypertension in Kendari City are women and 59.3% are men. Prevalence of hypertension has increased in the West Java region by 29.4% in 2013 to 39.6% in 2018[2]. West Java Provincial Health Office in 2023 reported that hypertension sufferers in Cirebon Regency were the second highest after Bogor Regency, with 678,232 people from data obtained in 2019.

Hypertension occurs because the heart pumps blood harder to meet the body's oxygen and nutrient needs[2,3]. American College of Cardiology (ACC) and the American Heart Association (AHA) define hypertension as blood pressure at or above 130/80 mmHg[4]. Early prognosis in patients with hypertension needs to be done so that it does not develop into more severe diseases such as cardiovascular[5]. Some predictor markers that can be used include the Monocyte HDL-C Ratio and hsCRP. Both markers are related to the inflammatory process and immunity. Factors that can affect hypertension include age, gender, genetics, obesity, smoking, alcohol consumption, stress conditions, the presence of inflammatory diseases and also infections. Based on this, further research is needed to determine the relationship between the number of monocytes, high density lipoprotein levels and the Monocyte High Density Lipoprotein (MHR) Ratio with highly sensitive C-Reactive Protein levels in patients with hypertension.

Previous studies have stated that hypertension is associated with an inflammatory process involving innate and adaptive immune responses[3]. Vascular inflammation can occur both at the onset and development of hypertension. Hypertension results in increased levels of several inflammatory markers[6], including increased cytokine release, production of reactive oxygen species (ROS) and the emergence of adhesion molecules, which are conditions found in hypertension[7]. Increased numbers of inflammatory markers such as Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and C-Reactive Protein (CRP) are found in patients with hypertension.

Chronic inflammation and atherosclerosis are indicated by an increase in the number of Monocytes[8]. Monocytes, which are inflammatory cells, are known to have an active role in the formation of atheromatous plaque at the vascular level and endothelial dysfunction. Monocytes are one of many types of inflammatory cells that play a role in inflammation during the pathogenesis of cardiovascular disease[9]. Monocytes activity inhibited by High Density Lipoprotein Cholesterol (HDL-C). Role of HDL-C in hypertension is to inhibit the attraction of activated monocyte cells attached to damaged/disturbed target organs or tissues, so that the inflammatory process can be inhibited. A decrease in HDL levels can also trigger the formation of plaque in the blood vessels that can triggers the emergence of atherosclerosis which is one of the causes of increased blood pressure[10].

Monocytes and HDL-C are two important components of the immune system and lipoproteins in atherosclerosis so that the Monocyte-HDL-C Ratio (MHR) can be used to predict the severity of atherosclerosis. Ratio of monocytes to HDL-C may be a new predictor of prognosis in cardiovascular disease. MHR is said to have advantages because it has proinflammatory and anti-inflammatory pathways. Several previous studies have stated that MHR is used as a prognostic marker in cardiovascular disease and mortality prognosis in acute ischemic stroke[11], both diseases are also related to hypertension. Increased MHR may reflect an imbalance between inflammation and anti-inflammation in the atherosclerosis process in hypertensive patients[12].

Other studies have shown that the Monocyte HDL-C ratio and hsCRP can be used as an indicator of cardiovascular risk in people with hypertension[13]. Discussion of the relationship between MHR and C Reactive Protein which is directly associated with hypertension has not been studied to date. Previous research conducted by Ni Made Dharma Laksmi (2020) linked MHR and Major Cardiovascular Events (MCIs), obtained significant results as predictors of MCIs. Another study conducted on patients with Type 2 Diabetes Mellitus with diabetic nephropathy showed the same thing, there was a significant increase in this condition[14]. CRP as one of the pro-inflammatory markers initiated by hypertension needs to be further reviewed in its relationship with MHR which has pro-inflammatory and anti-inflammatory pathways, it is possible that there is a significant relationship between the two markers in hypertension.

METHOD

This research is a descriptive analytical study with a cross-sectional design on hypertensive patients undergoing treatment at the internal medicine polyclinic and heart polyclinic of Pertamina Hospital Cirebon. Sampling technique in this study used the Nonprobability sampling technique with the consecutive sampling method. Consecutive sampling is a sampling technique from a population that meets the inclusion and exclusion criteria so that the required number of samples is 67 samples. Inclusion criteria in this study were patients with primary hypertension with grade 2 without distinguishing gender and age range. Hypertensive patients who have a history of malignancy, are suffering from liver disease, have infections, consume anti-inflammatory drugs and consume pain relievers are not used as samples in this study.

Research Tools

Equipment used in this study was a sphygmomanometer, Cobas Integra 400 Plus (Roche), Sysmex XN 1000 (Sysmex), Finecare ™ FIA Meter Plus (Wondfo). A sphygmomanometer is used to measure the patient's blood pressure. Cobas Integra 400 Plus (Roche) was used to determine High Density Lipoprotein (HDL-C), AST, and ALT levels. Sysmex XN 1000 (Sysmex) was used to calculate the absolute monocyte count. Finecare™ FIA Meter Plus (Wondfo) was used to measure hsCRP levels.

Research Materials

Specimen materials used were serum and EDTA (Ethylene Diamine Tetra Acetate) blood. Serum was used to determine HDL-C, AST, ALT and hsCRP levels. The absolute monocyte count was measured from EDTA blood samples. Reagents for HDL-C, AST and ALT examinations were produced by Roche diagnostic GmbH. Reagents from Sysmex corporation were used for monocyte count examinations. hsCRP was measured using reagents produced by Finecare (Wondfo).

Data Analysis

The data obtained in this study will be processed statistically using SPSS Version 21 software. Normality test using Kolmogorov Smirnov. Correlation test between hsCRP with Monocyte Count, HDL-C, and Monocyte-HDL Ratio used Spearman Test because all of that data were not normally distributed.

RESULTS

Characteristics of Research Subjects

Total sample in this study was 67 people with grade 2 hypertension that consist of 28 male patients and 39 female patients who were undergoing treatment at the internal medicine and heart clinic at Pertamina Hospital Cirebon. Characteristics of research subjects based on gender, age, Body Mass Index, duration of suffering, number of Monocytes, HDL-C levels, HDL monocyte ratio and hsCRP levels obtained from the Medical Record Installation unit and direct data collection from the research population as shown in Table 1.

Table 1. showed that patient grade 2 hypertension mostly in 35 to 82 years old with an average age of 59.18 years. Average Body Mass Index is 25.06 with the lowest value of 17.3 and the highest of 35.9 which is one of the risk factors for hypertension.

Hypertension sufferers in this study were grade 2 hypertension sufferers who underwent outpatient treatment at a heart and internal medicine clinic. Grade 2 hypertension in this study had systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg. Average value of systolic blood pressure respondent was 169.3 (160-197) mmHg and diastolic blood pressure was 93.57 (70 - 137) mmHg.

Monocytes obtained in this study was in the range of 260 - 1300 cells / μL with an average of 606.12. This shows that there is a variation in the number of monocytes in patients with grade 2 hypertension, with a fairly large standard deviation (174.173).

hsCRP levels were measured using the Fluorescent Immunoassay method, obtaining an average level of 5.440 mg/L, the standard deviation value of 5.3069 in the range of 0.5 - 18.2 mg/L.

Table 1. Characteristic Research Subject

Characteristic	N	Mean ± SD	Median (Min-Max)
Gender Male Female	28 (42%) 39 (58%)		
Age (years)		59.18 ± 9.91	60 (35-82)
Body Mass Index (kg/m^2)		25.06 ± 3.83	24,6 (17.3-35.9)
Systolic Blood Pressure (mmHg)		169.43 ±9.00	169 (160-197)
Diastolic Blood Pressure (mmHg)		93.57 ±10.52	90 (70-137)
Monocyte Count (cell/μL)		606.12 ±174.17	570 (260-1300)
HDL-Cholesterol (mg/dL)		47.46 ±11.96	45 (21-98)
hsCRP (mg/L)		5.44 ±5.31	11.85 (0.5-18.2)
Monocyte HDL Ratio MHR)		13.57 ± 5.31	12.7 (4.40-37.10)

Based on the results of the Kolmogorov-Smirnov normality test on each research variable, the significance value of the number of monocytes was 0.081> 0.05, so the data on the number of monocytes was normally distributed. Meanwhile, the data on the variables of HDL-C levels, HDL Monocyte Ratio, and hsCRP levels were not normally distributed with a p value <0.05. The research data were then analyzed for the relationship between variables using the Pearson correlation test for normally distributed variables, while for non-normally distributed data using the Spearman correlation test with 95% confidence level (Table 2).

Spearman test between all variable in this study showed that there was not significant correlation between Monocyte Count, HDL-C levels, and HDL Monocyte Ratio with hsCRP levels with (p>0.05). Besides, unsignificant p value, correlation ratio in this study also showed that there was in very low correlation category (Table.2).

Table 2. Correlation Test Monocyte Count, HDL-C, and Monocyte HDL Ratio (MHR) with hsCRP

Variable	**hsCRP**		
	N	**p**	**r**
Monocyte Count	67	0,311	0,126
HDL-C	67	0,273	-0,136
Monocyte HDL rasio	67	0,121	0,191

DISCUSSION

Result from this study show that average patient with grade hypertension in 59 years old. According to Riskesdas 2018 data, the prevalence of hypertension in Indonesia tends to increase with a prevalence rate of > 31.6 percent at age > 35[15]. Obesity is one of the risk factor of hypertension. Obesity parameters that are usually used are body mass index (BMI) that obtained based on the calculation between body weight and height. BMI data in this study showed that grade 2 hypertension sufferers were quite balanced, this is indicated by the average BMI value which is at 25.06 which is the threshold value for obesity (> 25)[16]. This study did not use body mass index as a variable to be analyzed, as previous research conducted on 184 respondents who were overweight or obese stated that obesity levels that were not too high did not have a significant relationship with the incidence of hypertension[17]. Average systolic blood pressure patient in this study was 169.4 mmHg and average diastolic blood pressure patient was 93.57 mmHg that categorized as Grade 2 Hypertension.

Correlation test between Monocytes and hsCRP in this study showed there was no significant correlation between two variables (p>0.05). Possible reason was mechanism of hypertension involves many components and mechanisms other than the monocyte cells themselves. Monocytes play a role in inducing hypertension through the mechanism of inflammatory reactions, formation of atherosclerotic plaques, oxidative stress and salt and water balance. These mechanisms, such as in the formation of atherosclerotic plaques, not only involve monocyte cells but also lipoproteins and endothelial cells. Disturbances that occur in lipoproteins and endothelial cells will also change the dynamics of blood flow or turbulence. Turbulence in the blood vessels allows someone to experience thrombosis which can affect blood pressure. Based on this, the number and activity of monocytes are things that must be controlled in managing atherosclerosis. Risk factors that can worsen the condition of blood vessels such as high blood pressure and unbalanced cholesterol levels can accelerate the recruitment and activation of monocytes[16]. This is in line with research conducted by Sofia Cedestrom, et al., on 30,154 men and women aged 50 to 64 years, concluding that increased hsCRP had a weak relationship with the presence of coronary atherosclerosis[18].

Relationship between the variables in this study can also be influenced by other cells besides monocytes that contribute to the mechanism of hypertension, namely Neutrophil cells and lymphocyte cells. Both cells play a role in the immune response to infection and inflammation. An increase in the number and activity of both cells can be associated with an increase in hsCRP levels. Neutrophil cells also play a role in the mechanism of atherosclerosis, namely in chronic inflammation in atherosclerotic plaques through the release of cytokines (IL-1, IL-6, and TNF-α), inflammatory mediators, and proteolytic enzymes; producing various reactive oxygen species (ROS); releasing their cytoplasmic granules containing proteolytic enzymes; and interacting with endothelial cells through adhesion and chemotaxis molecules, facilitating their migration into the arterial walls affected by atherosclerosis[19,20]. The role of lymphocyte cells in the process of atherosclerosis through regulation of immune responses, production of cytokines (IFN-γ, IL-17, and IL-10), and interaction with macrophages and cells[21,22].

Correlation test between HDL levels and hsCRP levels showed that there was no significant correlation between those two variables. This was also indicated by an average value of 47.46 mg/dL. HDL levels measured were HDL levels when the research data was taken, so they do not yet describe the effect of changes in HDL levels in helping to inhibit the process of atherosclerosis. HDL that interacts with chylomicrons, very Low-Density Lipoprotein, and other lipoproteins will be converted into cholesterol esters[23]. HDL undergoes significant changes in both its composition and structure. HDL enriched with SAA (Serum Amyloid A) shows a reduced capacity to inhibit LDL oxidation and bind biglycan, thereby reducing the atheroprotective effect of HDL. SAA can induce the production of chemokine MCP-1 (monocyte chemoattractant protein-1) in human monocytes. Another study stated that SAA stimulates monocytes and macrophages, resulting in blood vessel inflammation, also involving hsCRP, through increasing foam cell formation by increasing the expression of oxidized LDL receptors such as lectins. The functionality of HDL plays a role in reducing the risk of atherosclerosis [24] including in this case related to hypertension. This condition allows the relationship between monocytes and hsCRP to be not significantly related.

This study found that RMH did not have a significant relationship with hsCRP levels in patients with grade 2 hypertension, although RMH was used as a marker of inflammation and chronic inflammatory reactions displayed by abnormal endogenous factors including cytokines, end products of glaciation, lipoproteins, or hyperglycemia. These factors allow for complex interactions in the occurrence of hypertension that can be interrelated with each other which can cause the relationship between variables to not be seen significantly.

Presence of other infections that are not realized or known by the patient or hypertension sufferers do not inform the researcher of this condition which is indicated by the average value of hsCRP levels being high, namely 5.44 (>2 mg/L) and the number of hypertension sufferers with high hsCRP levels is greater than hypertension sufferers with normal hsCRP. This condition can possibly provide statistical test results that are not significantly related.

Other factors that can support the conclusion of this study are that respondents do not smoke, do not consume caffeinated drinks, genetic factors, no complications of other diseases, and good rest patterns. These factors allow the relationship between variables to be insignificant.

This study has limitations, Neutrophil cells and Lymphocyte cells also play a role in the process of inflammation and atherosclerosis. In addition, hsCRP levels with high tendency values indicate the possibility of inflammation / other infectious diseases in hypertensive patients who are not aware of or not informed to researchers. This condition may affect the relationship between variables in this study[25].

CONCLUSION

Monocytes, HDL-C levels, and the monocyte HDL-C ratio are not significantly related to hsCRP levels in patients with grade 2 hypertension at Pertamina Hospital Cirebon.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interest: The authors declared that they have no competing interests.

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