HEMATOLOGY PROFILE AND SEVERITY OF CORONARY ARTERY STENOSIS IN CORONARY HEART DISEASE

Andi Irhamnia Sakinah[1], Aryadi Arsyad[1], Andi Ariyandy[1], Muhammad Husni Cangara[1], Muzakkir Amir[1]

Correspondensi e-mail: aryadi.arsyad@med.unhas.ac.id

[1]*Universitas Hasanuddin Makassar, Indonesia*

ABSTRACT

A hematology profile test can be used as an inflammatory marker to identify cardiovascular disease, including coronary heart disease (CHD). This study aimed to analyze the routine hematology test for patients with coronary artery disease who undergo coronary angiography and its relationship to the severity of coronary artery stenosis. This observational analytic study was designed with a cross-sectional design. The samples from 15 patients were obtained using the purposive sampling technique. The severity of stenosis was determined according to PERKI 2017 guidelines. Data are presented in mean±SD, median (IQR), and percentage n (%). Parametric data were tested by independent t-test or one-way ANOVA, nonparametric data were tested by Mann-Whitney test or Kruskal Wallis test, while categorical data were tested by Fisher's exact test. This study showed that the levels of WBC, neutrophils, lymphocytes, basophils, RBC, hemoglobin, MCV, MCH, MCHC, PLT, RDW-CV, and MPV values were in the normal category. With a mean monocyte/lymphocyte ratio of 0.27 ± 0.06 which tends to increase, there was no difference in MLR values between the two groups based on the severity of coronary artery stenosis (p>0.05). Therefore, it can be concluded that there is no significant relationship between hematological parameters and coronary artery stenosis in CHD patients.

ARTICLE INFO

Keywords:
Complete Blood Count; Stenosis; CHD

PROFIL HEMATOLOGI DAN TINGKAT KEPARAHAN STENOSIS ARTERI KORONER PADA PENYAKIT JANTUNG KORONER

ABSTRAK

Pemeriksaan hematologi rutin dapat digunakan sebagai penanda inflamasi untuk mengidentifikasi penyakit kardiovaskular, termasuk penyakit jantung koroner (PJK). Penelitian ini bertujuan untuk menganalisis gambaran profil hematologi rutin pasien penyakit jantung koroner yang menjalani angiografi koroner serta hubungannya dengan stenosis lesi arteri coronaria. Penelitian analitik observasional ini dirancang dengan desain cross-sectional. Sampel dipilih dengan teknik purposive sampling dan diperoleh 15 subjek penelitian. Tingkat stenosis ditentukan sesuai panduan PERKI 2017. Data disajikan dalam mean±SD, median (IQR), dan persentase n (%). Data parametrik diuji dengan uji t independen atau one-way ANOVA, data nonparametrik diuji dengan Mann-Whitney test atau Kruskal Wallis test, sedangkan data kategorik diuji dengan Fisher's exact test. Hasil penelitian menunjukkan kadar nilai WBC, neutrofil, limfosit, basofil, RBC, hemoglobin, MCV, MCH, MCHC, PLT, RDW-CV, dan MPV berada dalam kategori normal. Dengan rerata monocyte/lymphocyte ratio 0,27 ±0,06 yang cenderung meningkat, tidak ditemukan adanya perbedaan nilai MLR antara kedua kelompok berdasarkan signifikasi stenosis arteri coronaria (p>0,05). Oleh karena itu, dapat disimpulkan bahwa tidak terdapat hubungan signifikan antara parameter hematologi dengan stenosis arteri coronary pada pasien PJK.

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Kata kunci:
Pemeriksaan Darah Lengkap; Stenosis; PJK

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Introduction

Coronary heart disease (CHD), was known as the leading cause of death in the world, with about 17.9 million deaths per year which increases every year (1). According to The Centers for Disease Control and Prevention (CDC), CHD was found approximately in 18.2 million people above 20 years old with 2 out of 10 CHD deaths occurring in adults over 65 years old in the United States (2). In Indonesia, the prevalence of CHD in 2013 was 1.5% based on clinical symptoms, so it is estimated that around 2,650,340 people suffer from CHD at the age of 15 years. In South Sulawesi, patients with CHD were still found quite a lot around 166,429 people (3).

The pathophysiology of CHD has been started many years before the emergence of complaints due to the formation of atherosclerotic plaques. Accumulation of fatty plaque occurs as a low-grade inflammatory reaction in the tunica intima of the moderate arteries that is accelerated by existing risk factors. The inflammatory process then causes a gradual thickening of the inner lining of the coronary arteries and progressively shrinks the lumen of the blood vessels to varying degrees (4). As a result, atherosclerosis was formed as a chronic inflammatory disease that is triggered by an inflammatory response due to the accumulation of fat in the artery walls (5). This pathology was formed as a result of a complex reaction between vascular endothelium and immune cells while the development of this plaque was associated with the vascular inflammation that occurs (6).

Physiological and/or pathological disturbances in the arterial wall are maintained by abundant intravascular red blood cells. Physiologically, the viscosity of blood is mainly determined by the number of red blood cells, so the frictional force generated will be imposed on the artery walls. In pathological conditions, tissue damage that triggers the origination of the main source of redox-active iron is caused by either acute or chronic red blood cell collisions. Redox-active iron (Fe++) was known to be the main catalyst of all oxidative reactions in living cells and tissues (7). As a result, the vascular endothelium located in the branching and indentation areas of the coronary arteries is susceptible to penetration of blood lipoprotein particles which can accumulate into the proteoglycan-rich subendothelial layer of the arterial intima (5). The complex interaction between these two components and tissue reactions will initiate the formation of atherosclerosis (8).

Current research shows that the pathogenesis of atherosclerosis is closely related to the inflammatory process. Immunological reactions are an early sign of the atherosclerosis process that begins with an innate immune response that develops in the absence of antigen stimulation. White blood cell components such as macrophages, dendritic cells, and T cells (8–10) are mediators in the early initiation and development of atherosclerotic plaques.

As the basic cause of coronary heart disease is an inflammatory reaction, almost all cellular components of blood are certainly involved in the development of atherosclerosis (11). Previous studies have also shown the association of various hematological profiles with cardiovascular risk (12–14). In addition, complete blood tests are an easy and cheap test compared to other examinations for diagnosing CHD. Hence, the test can be carried out starting at first-level health facilities as primary health services. Therefore, this study aimed to examine the routine hematological profile of coronary heart disease patients undergoing coronary angiography and its relationship with stenosis severity of coronary artery lesions.

Methods

This cross-sectional study was carried out using medical record data of patients treated at RSUP Dr. Wahidin Sudirohusodo Makassar. Samples were taken using a non-probability sampling technique with a purposive sampling method that met the inclusion criteria.

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Coronary heart disease patients with the diagnosis of angina pectoris CCS (Canadian Cardiovascular Society) 3-4 (symptomatic), history of long-standing myocardial infarction, perioperative myocardial infarction, or history of positive ischemic stress test who were admitted to the hospital through clinic were included in this study. Patients with a history of type II diabetes mellitus, history of PCI (Percutaneous Coronary Intervention), history of using steroids or immunosuppressants in the last 3 months, fever or other infectious diseases (including a history of parotitis or salivary gland infection/inflammation) in the last 1 month, history of stroke, depression, Alzheimer's disease, cancer, and other autoimmune or immune diseases such as rheumatoid arthritis or Systemic Lupus Erythematosus were excluded in this study.

Data taken included the basic characteristics of the subjects such as age, sex, body mass index, blood pressure, risk factors for cardiovascular disease, laboratory results of routine hematology examinations, and results of coronary angiography. All data were taken through structured interviews and patient medical record documents in the ward. Body Mass Index (BMI) is categorized into five categories namely underweight, normal, overweight at risk, obese I, and obese II (15). Hypertension was defined as the presence of manifestations of hypertension or the presence of hypertensive heart disease in the medical record or while taking antihypertensive drugs. Dyslipidemia is a manifestation of lipid metabolism disorders that can be seen from the medical history, abnormal laboratory values, or while taking lipid-lowering drugs. The complete blood count and reference value for each hematological parameter are based on the value issued by the hospital laboratory as the place where the samples were examined. The results of coronary angiography were categorized into two groups, namely insignificant and significant. Samples were categorized as significant if they had (1) 70% stenosis of the right coronary artery—RCA left circumflex artery—LCA, and left anterior descending—LAD; and/or (2) 50% stenosis of the left main coronary artery—LMCA) (16). From the significant stenosis group, the samples were then categorized according to the number of branch vessels of the LMCA that had a significant stenotic lesion. Continuous variables with parametric distributions are presented in terms of mean±SD and tested by independent t-test, while non-parametric distributions are presented in median (IQR) and tested by Mann-Whitney test. Categorical data are presented in the form of frequency (n %) and tested by the Chi-Square test.

Ethical Clearance

This study has been approved to be carried out on humans by the Health Research Ethics Commission, Hasanuddin University Makassar with the number 76/UN4.6.4.5.31/PP36/2020 with the protocol number UH19121106.

Results

Total samples that meet the inclusion criteria and is included in this study were 15 patients. The demographic characteristics included age, gender, ethnicity, education, occupation, risk factors or comorbid cardiovascular disease, i.e. body mass index, hypertension, dyslipidemia, smoking history, and previous history of acute myocardial infarction. Diabetes mellitus as a comorbid was not presented because it was part of the exclusion criteria.

Table 1. Demographic Characteristics of The Study Population

Characteristics	n	%
Age (years)		
≤ 55 years old	5	33,3

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> 55 years old	10	66,7
Gender		
Male	10	66,7
Female	5	33,3
Race		
Buginese	7	46,7
Makassar	2	13,3
Toraja	1	6,7
Mandar	1	6,7
Others	4	26,7
Education		
Elementary School	2	13,3
High School	8	53,3
Undergraduate	2	13,3
Graduate	3	20,1
Job		
Unemployment	4	26,7
Private employee	6	40
BUMN employee	1	6,7
Civil servant	4	26,7
Body Mass Index (kg/m^2)		
Normal	6	40
Overweight		
At-Risk	5	33,3
Obese I	2	13,3
Obese II	2	13,3
Hypertension		
No	4	26,7
Yes	11	73,3
Dyslipidemia		
No	9	60
Yes	6	40
History of Acute Myocardium Infarct		
No	9	60
Yes	6	40
History of Smoking		
Never	6	40
Had/Current	9	60

In Table 1, it was found that most of the patients were over 55 years old (66.7%) with a mean age of 57.26 ± 9.5 years. In both age categories, 60% in the age group 55 years and 70% in the age group >55 years were male. The median value of BMI was 23.87 (3.14) kg/m2, and more than half of the sample was in the overweight category (9 patients), i.e. 100% being in the insignificant stenosis group and 33.3% in the significant stenosis group. In addition, the risk factors for cardiovascular disease, namely dyslipidemia and a history of smoking were also shown by most of the patients, i.e. 11 patients (73.3%) and 9 patients (60%), respectively.

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Table 2. Cross Tabulation of Clinical Characteristics with Coronary Artery Stenosis

Patients Characteristics	Stenosis		*p value*
	Insignificant (n=6)	Significant (n=9)	
Age (years)	52,16 ±8,18	60,65 ±9,15	<0,05
Male (%)	2 (33,3)	8 (88,9)	<0,05
Hypertension (%)	4 (66,7)	7 (77,8)	0,54
Dyslipidemia (%)	3 (50)	3 (33,3)	0,45
Smoking (%)	2 (33,3)	7 (77,8)	0,17
History of AMI (%)	1 (16,7)	5 (55,6)	0,12
BMI (kg/m^2)	23,95 (3,96)	22,86 (3,39)	0,13
WBC			0,60
Below normal	0	0	
Normal	6 (100)	8 (88,9)	
Above normal	0	1 (11,1)	
NEU			0,29
Below normal	1 (16,7)	5 (55,6)	
Normal	5 (83,3)	4 (44,4)	
Above normal	0	0	
LYMPH (%)			1,00
Below normal	0	0	
Normal	6 (100)	8 (88,9)	
Above normal	0	1 (11,1)	
MONO (%)			0,32
Below normal	0	0	
Normal	4 (66,7)	3 (33,3)	
Above normal	2 (33,3)	6 (66,7)	
EOS (%)			0,39
Below normal	1 (16,7)	0	
Normal	1 (16,7)	3 (33,3)	
Above normal	4 (66,7)	6 (66,7)	
BASO (%)			1,0
Below normal	0	0	
Normal	6 (100)	8 (88,9)	
Above normal	0	1 (11,1)	
RBC			0,68
Below normal	0	1 (11,1)	
Normal	5 (83,3)	7 (77,8)	
Above normal	1 (16,7)	1 (11,1)	
HGB			1,0
Below normal	0	1 (11,1)	
Normal	6 (100)	8 (88,9)	
Above normal	0	0	
HCT			0,61
Below normal	4 (66,7)	4 (44,4)	
Normal	2 (33,3)	5 (55,6)	
Above normal	0	0	
MCV			1,00
Below normal	1 (16,7)	1 (11,1)	
Normal	5 (83,3)	8 (88,9)	
Above normal	0	0	
MCH			0,40
Below normal	1 (16,7)	0	
Normal	5 (83,3)	9 (100)	
Above normal	0	0	
MCHC			1,0

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Below normal	0	0	
Normal	5 (83,3)	8 (88,9)	
Above normal	1 (16,7)	1 (11,1)	
PLT (10^3/µL)			1,0
Below normal	0	1 (11,1)	
Normal	6 (100)	8 (88,9)	
Above normal	0	0	
RDW-CV (%)			1,0
Below normal	0	0	
Normal	5 (83,3)	8 (88,9)	
Above normal	1 (16,7)	1 (11,1)	
PDW (fL)			0,30
Below normal	4 (66,7)	5 (55,6)	
Normal	1 (16,7)	4 (44,4)	
Above normal	1 (16,7)	0	
MPV (fL)			0,40
Below normal	0	0	
Normal	5 (83,3)	9 (100)	
Above normal	1 (16,7)	0	

**Abbreviations: WBC = White Blood Cells; NEU = Neutrophil; LYMPH = Lymphocyte; MONO = Monocyte; EOS = Eosinophil; BASO = Basophil; RBC = Red Blood Cells; HGB = Hemoglobin; HCT = Hematocrit; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin; MCHC = Mean Corpuscular Hemoglobin Concentration; PLT = Platelet; RDW-CV = Red Distribution Width – Coefficient of Variation; PDW = Platelet Distribution Width; MPV = Mean Platelet Volume.*

Coronary angiography results showed that there were 6 patients (40%) with insignificant coronary stenosis and 9 people (60%) with significant stenosis. Cross-tabulations for each of these characteristics with coronary stenosis significance are presented in Table 2.

Hematological examinations, showed that almost all blood parameters, both in the insignificant and significant stenosis groups, were in the normal category: WBC (93,3%), NEU (60%), LYMPH (93,3%), BASO (93,3%), RBC (80%), HGB (93,3%), MCV (86,7%), MCH (93,3%), MCHC (86,7%), PLT (93,3%), RDW-CV (86,7%), and MPV (93,3%), respectively. Both HCT and PDW parameters were mostly found to be in the category below the normal value with the percentages of 53.3% and 60%, respectively. However, MONO and EOS parameters are in the category above the normal value with percentages (53.3%) and (66.7%), respectively.

The four leukocyte ratios: neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), and eosinophil/ leukocyte ratio (ELR) were also investigated in this study as they were described in several previous studies as CHD predictors (17–20). However, none of the parameters showed a significant difference in values between groups based on the significance of coronary artery lesion stenosis ($p>0.05$), although it appears that MLR values tend to increase (Figure 1).

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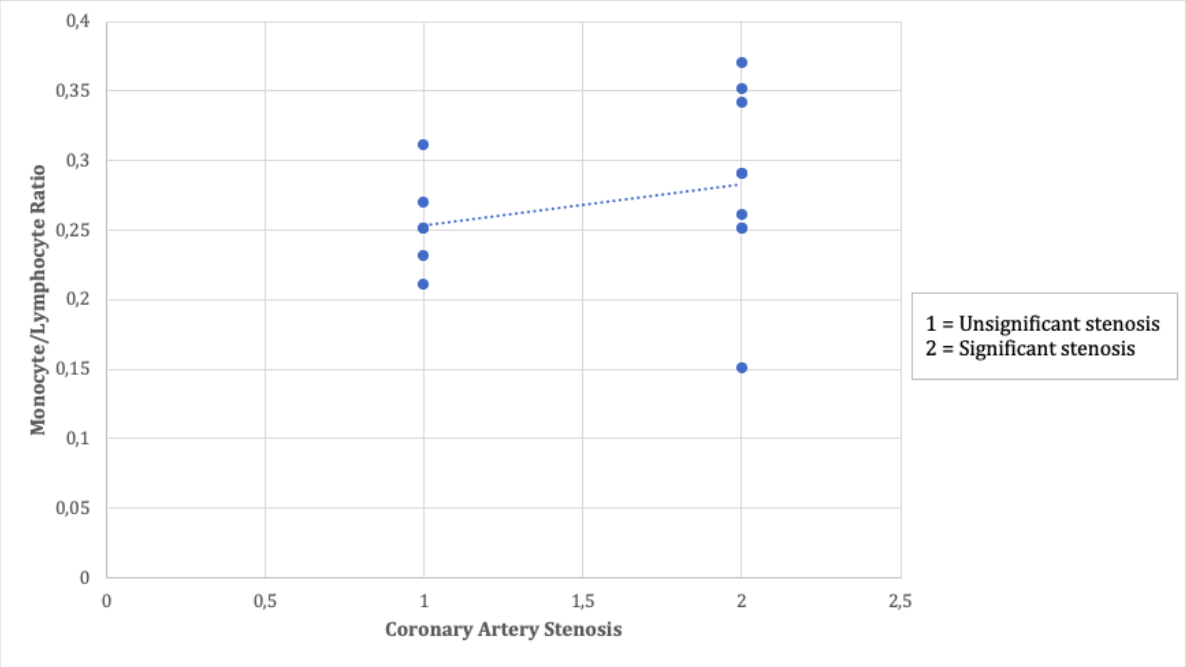

Figure 1 *Scatter Plot Of MLR Values Based On The Significance Of Coronary Artery Stenosis Lesions*

Discussion

A total of 15 patients were included in this study with an age range ranging from 41-78 years, with the majority being male over the age of 55 years which is a risk factor for coronary heart disease that cannot be modified. In addition, it was also found that most of the samples had modifiable risk factors, namely hypertension, smoking, and excess body mass index (21). The statistical tests showed that there was a relationship between age and sex with coronary artery stenosis in CHD patients. This is per the theory of cellular aging, both related to normal physiological and pathological vascular aging such as atherosclerosis, with impaired cell proliferation which can interfere with cell survival. This is due to the accumulation of damage to the cell nucleus and mitochondrial DNA, an increase in reactive oxygen species (ROS), and a proinflammatory state (22), as previously described that the process of atherosclerosis formation begins with an inflammatory response in vascular tissue (6). Regarding gender, it is also known that the effect of estrogen on women provides great protection against the occurrence of metabolic diseases, this is shown by 2 women over 55 years old (13%) of 15 patients. In addition, the role of gender in the formation of atherosclerosis is also associated with the anatomy and physiology of the heart itself, such as larger heart (LV) size, less contractility, a higher rate of apoptosis, a larger coronary artery size, and higher blood pressure in men (23).

Based on laboratory results, as we found most of the hematological parameters were normal in the two groups, there was also no significant relationship between these hematological parameters and coronary artery stenosis in CHD patients undergoing coronary angiography ($p>0.05$). This is in line with the research of Sbrana, S et al (24) but other studies (12,25–28) showed different findings which exhibited a significant relationship between the two variables. Previous studies have established that the risk factors found in this study also play a role in the formation of oxidative stress which in turn triggers the activation of hematopoiesis which can manifest in changes in blood cell count and proportion (29–31). This difference in findings may be due to a mismatch of study design with a small sample size as a result of limited data access in the Covid-19 pandemic and also bias from data collection. This bias could have occurred because blood sampling was not performed

concurrently with coronary angiography. Secondary data used also can be a risk of bias in the methodology so that the results are not significant.

Atherosclerosis as pathogenesis of CHD is not only associated with endothelial dysfunction, lipid metabolism disorders, and vascular inflammatory reactions but has also been categorized as a systemic inflammatory disease. Blood cells (and their derivatives—related to the immune response such as monocytes, macrophages, lymphocytes, dendritic cells) are known to play important role in plaque development to tissue ischemia (32). Subendothelial LDL retention can trigger monocyte recruitment and migration in atheroma formation (33). Monocytosis is associated with an increased risk of cardiovascular disease and cardiovascular disease-related mortality in various populations and clinical patients and is considered an independent risk factor for atherosclerotic disease (34). A study with 871 samples also showed an association between increased monocytes and the risk of heart disease at 10 years (35). Lymphocytes are also considered to play role in cardiovascular disease, with lymphocytopenia being a common finding of chronic systemic inflammatory conditions and thought to play a role in accelerated atherosclerosis (36). A possible explanation for lymphopenia in cardiovascular disease, especially acute myocardial infarction and heart failure, are the result of increased cortisol during the stress response. In addition, it should be considered that T-lymphocytes can modulate smooth muscle proliferation during the vascular repair so that the possibility of lymphocyte depletion is not only a marker but also a contributing factor to decreased myocardial function (37). Therefore, the integration of these two parameters in the MLR value can be a better risk factor for assessing the severity of coronary artery lesions. In this study, we found an increase in monocytes and lymphocytes that tend to be normal in the significant stenosis group, which led to an increase in MLR levels but did not show a significant difference between the two groups based on the significance of coronary artery lesion stenosis ($p<0.05$). This study certainly contradicts some previous studies with larger sample sizes and numbers (26,38) which could not be carried out in this study.

The insignificance of these findings could be influenced by the incomparable group based on the statistical result in the variables of age ($p<0.05$) and gender ($p<0.05$), thus becoming one of the risks of research bias. In addition, several risk factors or other confounding factors were not determined such as physical activity, diet, mental health conditions, and drug use.

The limitations of this study are the small sample size with a single-center research design. On the other hand, this study only focuses on hematological parameters, while to bring a new value it is necessary to compare it with standard biomarkers that have been used routinely and widely. At last, the limitation is the lack of control of confounding factors that can affect the results of the study.

Conclusion

It was found that most of the routine hematological parameters were in the normal category and specifically on the leukocyte ratio there was no significant relationship between MLR values with the severity of coronary artery lesions based on the significance of coronary artery stenosis.

Suggestion

This research needs to be continued with a larger sample and adjusted by other independent variables related to inflammation which plays a role in the process of atherosclerosis formation. Multi-center research design can also be continued to represent the general population in Indonesia.

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KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
UNIVERSITAS HASANUDDIN FAKULTAS KEDOKTERAN
KOMITE ETIK PENELITIAN KESEHATAN
RSPTN UNIVERSITAS HASANUDDIN
RSUP Dr. WAHIDIN SUDIROHUSODO MAKASSAR
Sekretariat : Lantai 2 Gedung Laboratorium Terpadu
JL.PERINTIS KEMERDEKAAN KAMPUS TAMALANREA KM.10 MAKASSAR 90245.
Contact Person: dr. Agussalim Bukhari..,M.Med,PhD, SpGK. TELP. 081241850858, 0411 5780103. Fax : 0411-581431

REKOMENDASI PERSETUJUAN ETIK

Nomor : 76/UN4.6.4.5.31/ PP36/ 2020

Tanggal: 27 Januari 2020

Dengan ini Menyatakan bahwa Protokol dan Dokumen yang Berhubungan Dengan Protokol berikut ini telah mendapatkan Persetujuan Etik :

No Protokol	UH19121106	No Sponsor Protokol	
Peneliti Utama	**Andi Irhamnia Sakinah**	Sponsor	
Judul Peneliti	IL-6 Saliva dan Profil Hematologi Sebagai Prediktor Derajat Stenosis Arteri Koroner Pada Penderita Penyakit Jantung Koroner		
No Versi Protokol	2	Tanggal Versi	**22 Januari 2020**
No Versi PSP	2	Tanggal Versi	**22 Januari 2020**
Tempat Penelitian	**RSUP dr. Wahidin Sudirohusodo dan Laboratorium HUMRC Lt 6 RSUH Makassar**		
Jenis Review	☐ Exempted ☒ Expedited ☐ Fullboard Tanggal	Masa Berlaku **27 Januari 2020** sampai **27 Januari 2021**	Frekuensi review lanjutan
Ketua Komisi Etik Penelitian Kesehatan FKUH	Nama **Prof.Dr.dr. Suryani As'ad, M.Sc.,Sp.GK (K)**	Tanda tangan	
Sekretaris Komisi Etik Penelitian Kesehatan FKUH	Nama **dr. Agussalim Bukhari, M.Med.,Ph.D.,Sp.GK (K)**	Tanda tangan	

Kewajiban Peneliti Utama:

- Menyerahkan Amandemen Protokol untuk persetujuan sebelum di implementasikan
- Menyerahkan Laporan SAE ke Komisi Etik dalam 24 Jam dan dilengkapi dalam 7 hari dan Lapor SUSAR dalam 72 Jam setelah Peneliti Utama menerima laporan
- Menyerahkan Laporan Kemajuan (progress report) setiap 6 bulan untuk penelitian resiko tinggi dan setiap setahun untuk penelitian resiko rendah
- Menyerahkan laporan akhir setelah Penelitian berakhir
- Melaporkan penyimpangan dari prokol yang disetujui (protocol deviation / violation)
- Mematuhi semua peraturan yang ditentukan

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