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Immature Platelet Level in Stable Coronary Heart Disease (CHD) Patients with Diabetes Mellitus compared to Stable CHD Patients without Diabetes Mellitus

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Abstract. Coronary heart disease (CHD) causes high mortality and morbidity in many countries. Immature platelet reactivity is one of the major causes of CHD thrombus formation due to its larger size and stronger aggregation properties than normal platelets. Though still controversial, diabetes mellitus (DM), which is one of the CHD risk factors, is mentioned to have a strong association with a high immature platelet level. Since studies on immature platelet in stable CHD are limited, the authors intended to search for the difference between immature platelet level in DM and non-DM patients with stable CHD. This research was an observational analytic study with a cross-sectional design; 31 samples of CHD patients who underwent coronary catheterization were obtained. The characteristics of the data was collected by completing a pre-operation form and the immature platelets were counted using an automated cytometry tool, SYSMEX XE 2100. They were analyzed using Pearson's statistical analysis. There was no significant correlation between the immature platelet levels of DM and non-DM patients with stable CHD ($p>0.05$). There was a significant positive correlation between HbA1C and the immature platelet level (Immature Platelet Fraction, $p <0.05$; Immature Platelet Count, $p <0.01$) in stable CHD patients.

1. Introduction

Coronary heart disease (CHD) is one of the chronic diseases that is a major contributor to the morbidity rate, mortality rate and health care spending in both developing and developed countries. The National Heart, Lung and Blood Institute (NHLBI) explained that the enhancement risk for CHD occurs in those aged over 40 years in men and women by 49% and 32% respectively. From 2005 to 2008, NHLBI estimated that 16,300,000 Americans ≥20 years old had CHD and that they had a mortality rate as big as 126 over 100,000 populations [1]. Platelet reactivity related to immature platelets is the main driver of thrombus formation in CHD [2]. An immature platelet is a granule rich young platelet which contains the messenger RNA (mRNA) residue of megakaryocyte and Ribonucleic Acid (RNA). This makes protein biosynthesis possible. Immature platelets are also able to express cyclooxygenase-2 (COX-2) and they are of a bigger size than normal platelets [2–4].

Various research has proven that there is a relationship between peripheral immature platelets with coronary heart disease incidence. Immature platelets increase in the comorbid factors of CHD, such as

diabetes mellitus and smoking. Another research study stated that immature platelets are an independent predictor of mortality incidence in the Acute Coronary Syndrome (ACS) patients who underwent PCI for 12 months [2].

Immature platelets were counted using the Immature Platelet Fraction (IPF) and Immature Platelet Count (IPC) parameters. The IPC value, which was obtained by multiplying IPF with total platelet count, is considered to be the new marker of IPF for the stratification risk of a major cardiovascular event in CHD [5]. IPC is also related to platelet reactivity and it is an excellent predictor to use to evaluate the patient antiplatelet response to thienopyridine therapy, which is one of the primary therapies to prevent CHD restenosis [4,6]. Antiplatelets in CHD patients are one of the main therapies but according to some research, high immature platelet levels will decrease the effectiveness of antiplatelet therapy [5,7].

Up until today, a study comparing the immature platelet level of diabetes mellitus (DM) patients to non-diabetic mellitus patients with stable CHD has not been conducted yet. Therefore, researchers are interested in knowing more about the immature platelet level of diabetes mellitus patients and how it affects CHD incidence.

2. Methods

This research was an observational analytical study using a cross-sectional design. This study analyzed the difference in immature platelet level between the CHD patients with DM compared to those with CHD who were non-DM patients.

The samples were CHD patients in Surabaya who underwent heart catheterization at Instalasi Diagnostik Intervensi Kardiovaskular (IDIK) Dr. Soetomo General Hospital from September 2017 until December 2017. We included stable CHD patients who agreed to sign the informed consent form. We excluded the CHD patients who had hematologic abnormalities causing thrombocytopenia and those who refused to sign the informed consent.

The calculation of the minimum sample size was done using the hypothesis test formula for the analysis of the comparative numerical data with 2 non-pair group, with a confidence level of 95%. The power of the test was 95%, the standard deviation was 1.82 and the significant mean difference between immature platelets considered by the author was 1.5. The minimum sample size was 31 samples and the sampling method was total sampling.

The sample's characteristic data was collected when the samples showed up for catheterization preparation through anamneses and a physical and laboratory examination. A blood sample was collected at IDIK Dr. Soetomo General Hospital. The sample characteristics were observed using the pre-cath form and the immature platelet levels were observed using laboratory tools and automated flow cytometry, SYSMEX XE 2100 at Gedung Diagnostic Center (GDC) of Dr. Soetomo General Hospital.

The data was analyzed using SPSS 22.0. The sample characteristic data included age, sex, CHD family history, history of diabetes mellitus, hypertension, dyslipidemia and smoking habits. These characteristics were processed as descriptive statistic data. They were shown descriptively as the mean and standard deviation or as the median and frequency in percentage form. The data distribution was tested using the Saphiro Wilk test. The T2 independent sample comparison test was conducted only if both sample group were homogenous. The α value was 0.05, which had mean that the IPC and IPF difference between two sample groups were significant only if the p value were < 0.05. The Pearson method was conducted to analyze the correlation between immature platelet level and diabetes mellitus.

3. Results

This study was conducted in the IDIK of Dr. Soetomo General Hospital from October 2017 until December 2017. This study enrolled 31 CHD patients who underwent catheterization that met the research criteria.

3.1 Samples Characteristics

There were 32 subjects that consisted of 23 males (71.9%) and 9 females (28.1%). The youngest age was 34 years old while the oldest was 78 years old. The mean age was 57 years old. The risk factors for CHD obtained from the subjects were hypertension (53.1%), hypercholesterolemia (62.5%), smoking (56.3%) and DM (46.9%). The subject's baseline characteristic data has been shown in Table 1.

Table 1. Baseline characteristics of the samples.

Variables	Non-diabetes mellitus *(N=17)*	Diabetes mellitus *(N=15)*	*p*
Unmodifiable Factors			
Males, n (%)	14 (60.9%)	9 (39.1%)	0.453[a]
Females, n (%)	4 (44.4%)	5 (55.6 %)	
Age, mean ± SD	57.44 ± 11.036	8 ± 6.109	0.809[b]
Modifiable Factors			
Hypertension, n (%)	7 (41.2%)	10 (58.8%)	0.067[a]
Hypercholesterolemia, n (%)	8 (40%)	12 (60%)	0.017[a]
Smoking, n (%)	12 (66.7%)	6 (33.3 %)	0.178[a]
Aspilet Consumption, n (%)	13 (52.0%)	12 (48.0 %)	0.426[b]
Clopidogrel Consumption, n (%)	11 (52.4%)	10 (47.6 %)	0.691[b]

[a] Pearson's chi square test
[b] Fisher's test

The table implies that there is a significant relationship between hypercholesterolemia and DM. Furthermore, we analyzed the correlation between hypercholesterolemia and IPF/IPC. The result was a non-significant correlation between hypercholesterolemia with IPF and IPC (P>0.05) as shown in Table 2. Therefore, the significant correlation between hypercholesterolemia and DM could be ignored in this research.

Table 2. The relationship between hypercholesterolemia and IPF/IPC.

Variable	Immature platelet fraction (*p*)	Immature platelet count (*p*)
Hypercholesterolemia	0.537	0.537

3.2. Analysis Result

The researchers divided the immature platelets into two values, namely IPF and IPC. The results showed there to be a statistically significant correlation between IPF and IPC level, implying that the higher IPF level, the higher the IPC level would be in turn (Table 3).

The mean IPF and IPC levels in the CHD non-DM group were 3.89 ± 1.689 and 994 ± 409.86, respectively. The mean IPF and IPC on CHD in the DM group was 4.050 ± 2.002 and 1075 ± 564.76 respectively. Further analysis of the correlation between DM and the IPF/IPC level showed that DM influences the IPF and IPC level, although it was not significant (Table 4).

Table 3. Correlation between IPF and IPC.

Variable	Immature platelet count (*N=32*)	
	r	*p*
Immature Platelet Fraction (N=32)	0.781	<0.001

Table 4. IPF and IPC level on CHD with DM and CHD without DM comorbid.

Variable	Non DM (Mean ± SD)	DM (Mean ± SD)	p
Immature Platelet Fraction	3.89 ± 1.689	4.050 ± 2.002	0.667
Immature Platelet Count	994 ± 409.860	1075 ± 564.760	0.896

We also analyzed the correlation between HbA1C and IPF/IPC using a cross-tabulated test. There was a significant correlation between HbA1C and the IPF level, in that the higher the HbA1C level, the higher the IPF level would be in turn (P<0.05) (Table 5).

Table 5. Correlation between HbA1C and IPF/IPC

Variable	HbA1C	
	r	p
Immature Platelet Fraction	0.781	<0.001
Immature Platelet Count	0.413	0.067

Furthermore, we tried to analyze the independent contribution of each of these variables to the immature platelet level using the multivariate regression test. The correlation between IPF and some of the risk factors were analyzed, including smoking, hypercholesterolemia, blood glucose level, HbA1C, creatinine serum, clopidogrel and aspilet therapy. Clopidogrel was found to be the most influence on the IPF level. The clopidogrel value was negative (β = -0.576) and significant (p<0.05). Subjects who received clopidogrel had the lowest immature platelet level.

Table 6. Multivariate analysis table.

Variable	Immature platelet fraction	
	β	*p*
Clopidogrel	-0.576	0.01

4. Discussion

4.1 Characteristics of subjects

This study enrolled 32 subjects with stable CHD who met the research criteria. The gender proportion of the subjects was 71.9% male and 28.1% female. We can conclude that the male gender is one of the risk factors for CHD. The average age for all of the subjects was 57 years old. The data implied that the manifestation of CHD starts at the age of 40 [8].

Various modifiable risk factors were found in the subjects, including hypertension (53.1%), hypercholesterolemia (62.5%), smoking (56.3%) and diabetes (46.9%). The hypertensive condition affects the vascular endothelial layer directly, causing endothelial dysfunction and leading to the formation of atherosclerotic plaque. Hypercholesterolemia is known as the main component of atherosclerosis development. This research showed that hypercholesterolemia had the highest proportion. The high proportion of smoking in this study also supports the theory that smoking can increase the risk of CHD incidence [9].

Almost 50% of subjects had DM as a CHD risk factor. Diabetes mellitus is related to abnormalities in the lipid metabolism, obesity, systemic hypertension and the raised risk of thrombogenesis that contributes to the development of CHD [10].

4.2 Immature platelet

Two values for the immature platelet parameters were obtained; IPF (3.959 ± 1.8) and IPC (1029.88 ± 477.0). The Pearson correlation test found there to be a highly significant positive

correlation (coefficient 0.781) between the IPF level and the IPC level. This result means that the higher the IPF level, the higher the IPC level would be as well. This result is in line with the previous research that said that the IPC value is obtained by multiplying IPF with the platelet count [6,11]. It could be concluded that given the strong relationship between IPF and IPC, an immature platelet level can be interpreted just by using one of the parameters.

From this study, we found that DM had a positive effect on IPF and IPC but that this effect was not statistically significant. In other words, DM is associated with an increase in immature platelet level but it cannot be generalized to all populations aside from the research sample. This insignificant correlation could result from the small sample size, the controlled glycemic index of some of the DM subjects, the presence of other factors which would affect immature platelets (i.e. hypercholesterolemia, hypertension, and smoking history) or the possibility of non-valid measurement tools [12]. Compared to the patients with DM status, the correlation analysis between HbA1c and IPF/IPC level had a different result. HbA1c, a parameter used to evaluate and control the glycemic index for a 3-month period, gave positive and statistically significant correlation results. This means that if the HbA1c level is high, then the IPF level would also be high.

Some of the mechanisms that are involved in the hyperglycemic condition related to an immature platelet level are thromboxane synthesis and calcium mobilization. This will cause adhesion at the cell's surface, which has a direct effect on the C protein given the hyper-reactivity of the platelet. The osmotic effect generates activity in the platelets and it suppresses the effect of NO and PGI2, which are low in the DM condition. The raised osmosis also causes a bigger platelet size [13].

4.3 Clopidogrel

Clopidogrel had a stronger correlation to IPF than the other clopidogrels. It had a negative ($\beta = -0.576$) and significant correlation to the IPF level. Subjects undergoing clopidogrel therapy had a lower IPF level. On the contrary, aspilet didn't have a better correlation with a lower IPF level compared to clopidogrel.

Aspilet has a lower relationship associated with high platelet levels in circulation [14] and it only has a short half-life (2–6 hours). Aspilet binds irreversibly to platelets in the first 2-6 hours and it will last during the age of the platelet. If the platelet age becomes shorter, as in the immature platelet condition (<1 day), then there will be many more new platelets produced by the spinal cord. this would result in a lot of platelets that will not bind to the aspilet.

5. Conclusion

There is a non-significant difference in the immature platelet levels between stable CHD in DM patients and the stable CHD in non-DM patients. However, there is a significant positive correlation between glycemic control and the immature platelet fraction level.

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