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Relationship between Platelet Indices and Coronary Heart Disease in Malaysian Population

Akhila Eswaran[1], Anil Philip Kunnath[1*], Goh Mun Hon[2], Yasmin Ayob Binti Ayob[2] and Ponnarasi Tharmajan[2]

[1]Division of Applied Biomedical Science and Biotechnology, School of Health Sciences, International Medical University, Malaysia

[2]National Heart Institute, Kuala Lumpur, Malaysia

[*]**Corresponding author:** Anil Philip Kunnath, Division of Applied Biomedical Science and Biotechnology, School of Health Sciences, International Medical University, Bukit Jalil, Kuala Lumpur, Malaysia, E-mail: anilphilip_kunnath@imu.edu.my

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Abstract

Coronary Heart Disease (CHD) is a major cause of mortality worldwide and in Malaysia. Early screening and diagnosis reduce the mortality rate of this disease by 15%-30%. CHD is caused by atherosclerosis and platelets have been found to play a major role in the development of atherosclerotic lesions. Although other biomarkers exist for CHD, platelet indices can be detected earlier and are routinely available. Hence this project was undertaken to study the relationship between platelet indices and CHD, as well as to find the diagnostic significance of platelet indices by comparing with other inflammatory biomarkers of CHD. This is a case control study carried out from July 2019 to September 2019, at the National Heart Institute, Kuala Lumpur, Malaysia. The study population consisted of 100 normal control subjects and 100 case study subjects. Once eligibility was confirmed, patient data was filled in the case study forms, while the observational laboratory data consisting of platelet indices, were collected from the Sysmex XN-1000 analyser. Statistical analysis was then carried out using the SPSS 16.0 Software, whereby an independent sample t-test was done and a p-value of less than 0.05 was considered statistically significant. Results showed that the levels of PDW, MPV and P-LCR were increased significantly (p-value less than 0.05) in CHD patients, while the levels of PC and PCT between the two groups showed no statistically significant difference. Nevertheless, it was found that these elevations could also be due to other risk factors, such as gender, smoking, Diabetes Mellitus, and hypertension. Hence, further research should be carried out to study the potential mechanisms behind the increase of platelet indices levels as a result of CHD alone, as it has the potential to be a beneficial risk predicting factor for CHD.

Keywords: Coronary Heart Disease (CHD); Platelet Count (PC); Platelet Distribution Width (PDW); Mean Platelet Volume (MPV); Platelet Larger Cell Ratio (P-LCR); Platelet Crit (PCT)

Introduction

Coronary Heart Disease (CHD) involves a group of conditions that arise due to thrombotic lesions in the coronary arteries. These include acute coronary syndrome, unstable angina, stable angina, myocardial infarction, and sudden cardiac death. CHD a major cause of mortality worldwide and in Malaysia. According to The National Health and Morbidity Surveys, the prevalence of cardiovascular diseases is expected to increase by 10% over the next 20 years [1]. Apart from that, data from the Acute Coronary Syndrome Registry shows that there is an increase in development of heart disease at a younger age in Malaysians, with mean ages of between 55.9 to 59.1 years, as compared to neighbouring countries which have mean ages of between 63.4 to 68 years [2].

Nevertheless, early screening and diagnosis reduces the mortality rate of this disease by 15%-30%. The most commonly used methods of investigation for coronary heart disease include electrocardiograms and imaging tests. Laboratory tests on the other hand, such as Troponin T, Creatine Kinase, and full blood count, are usually performed to evaluate the risk factors of CHD [3]. However, despite the advancement in diagnostic and therapeutic strategies, which has provided the opportunity for improvement in prevention of CHD, the main limitations that exist for these tests are high cost of risk predicting tests, non-availability of the tests especially in rural areas and a lack of standardization [3].

Atherosclerosis and its complications are the major causes of CHD. There are several risk factors that can contribute to the development of CHD. Some of which include, smoking, obesity, gender, hypertension, Diabetes Mellitus, and hypercholesterolemia [4,5]. Hence, recognizing new prognostic factors or related factors for CHD, while improving its risk stratification is important. Research on blood platelet physiology has shown that platelets play an important role in the pathogenesis of CHD.

Platelet size is known to reflect platelet activity, whereby larger platelets are usually younger and metabolically more active due to the presence of intracellular granules. Hence, they adhere and aggregate more than smaller ones due to high concentration of thromboxane A2 [6-8]. As a result, they promote the development of atherosclerotic lesions and thrombus formation, leading to the development of CHD. Platelets also act as an indicator of platelet activation, and can therefore be related to the clinical presentation of CHD [9] Several studies have shown that platelet indices are generally elevated in the presence of CHD [10,11].

Although other biomarkers that are more sensitive do exist for CHD, platelet indices can be detected earlier, are also easily recordable, and routinely available in most clinical laboratories. Hence platelet indices would potentially make a good risk predictor for CHD and provide patients with the benefit of timely interventions [12,13].

Despite the platelet indices being able to assess the presence of platelet activation, it is still unclear if they can be considered as risk factors for CHD [14]. Hence the study was conducted to study the relationship between platelet indices and CHD, as well as to find the diagnostic significance of platelet indices by comparing with other inflammatory biomarkers of CHD.

Methodology

This is a case control study carried out from July 2019 to September 2019, at the Malaysian National Heart Institute. The study population consisted of 200 subjects. Out of which, the Normal Control Group (N-CHD group) consisted of 100 health screening clients, while the Case Study Group (CHD group) consisted of 100 CHD patients admitted to IJN for either coronary angiography or bypass surgery.

The general inclusion criteria consisted of the subject being a Malaysian, being between the ages of 18 to 75 years, having a Full Blood Count (FBC) test performed the general exclusion criteria however, were pregnant women, patients with decompensated heart failure, and patients with incomplete FBC test results.

Once eligibility was confirmed, the case study forms were filled for each patient. The data was obtained from the patient medical records and hospital information system. The data taken consisted of a detailed documentation of the patient medical history, cardiovascular-targeted examinations, as well as their biochemistry test results such as lipid profile.

The observational laboratory results on the other hand, were collected from the Sysmex XN-1000 haematology analyser. This consisted of the platelet indices; Platelet Count (PC), Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), Platelet Larger Cell Ratio (P-LCR), and Platelet Crit (PCT).

Results

Following the collection of data, statistical analysis was carried out using the SPSS 16.0 Software. The continuous data were expressed as mean±standard deviation, while categorical data were expressed as frequency and percentage (%) shown in **Tables 1 and 2.**

Table 1: Frequency and percentage of risk factors present in CHD and N-CHD groups.

Parameters	Total	CHD	N-CHD
Male (n%)	155 (77.5%)	87 (87%)	68 (68%)
Female (n%)	45 (22.5%)	13 (13%)	32 (32%)
Malay (n%)	90 (45%)	60 (60%)	30 (30%)
Chinese (n%)	78 (39%)	25 (25%)	53 (53%)
Indian (n%)	32 (16%)	15 (15%)	17 (17%)
Male Aged ≥ 45 (n%)	122 (61%)	80 (80%)	42 (42%)
Female Aged ≥ 55 (n%)	24 (12%)	9 (9%)	15 (15%)
BMI ≥ 25	135 (67.5%)	68 (68%)	67 (67%)
Hypertension (n%)	102 (51%)	75 (75%)	27 (27%)
Active Smoking (n%)	50 (25%)	38 (38%)	12 (12%)
Diabetes (n%)	63 (31.5%)	45 (45%)	18 (18%)
Physical Inactivity (n%)	138 (69%)	82 (82%)	56 (56%)

Table 2: Mean and standard deviation for the biochemistry results of the CHD and N-CHD groups.

Parameters	CHD (Mean ± SD)	N-CHD (Mean ± SD)
Total Cholesterol (mmol/L)	4.181 ± 1.083	5.382 ± 1.014
Triglycerides (mmol/L)	1.705 ± 0.762	1.545 ± 0.872
Triglycerides (mmol/L)	1.705 ± 0.762	1.545 ± 0.872
HDL-Cholesterol (mmol/L)	1.17 ± 0.329	1.385 ± 0.342
LDL-Cholesterol (mmol/L)	2.284 ± 1.245	3.311 ± 0.916
Creatinine (µmol/l)	139.938 ± 150.451	82.798 ± 19.419
eGFR (MDRD) (ml/min/1.73 m^2) >60	59%	92%

An independent sample t-test was done to compare the differences in mean between the N-CHD and CHD groups, whereby a p-value of less than 0.05 was considered statistically significant, shown in **Table 3.**

Table 3: The frequency, mean, standard deviation and standard error means of platelet indices for the CHD and N-CHD groups.

	Condition	Total	Mean	Std. deviation	Std. error mean
Platelet count (× 109/L)	N-CHD	100	262.08	58.1879	5.81879
	CHD	100	265.17	100.0244	10.00243
Platelet Distribution Width (%)	N-CHD	100	11.173	1.56508	0.15651
	CHD	100	11.734	1.78745	0.17875
Mean Platelet Volume (fL)	N-CHD	100	9.948	0.72495	0.07249
	CHD	100	10.346	0.91744	0.09174
Platelet Larger Cell ratio (%)	N-CHD	100	24.417	5.84637	0.58464
	CHD	100	27.493	7.16576	0.71658
Platelet Crit (%)	N-CHD	100	0.2585	0.05353	0.00535
	CHD	100	0.2665	0.09982	0.00998

The graphs of mean and standard deviation for the statistically significant components were then plotted using the Microsoft Excel 2010 software, shown in **Figures 1 and 2.**

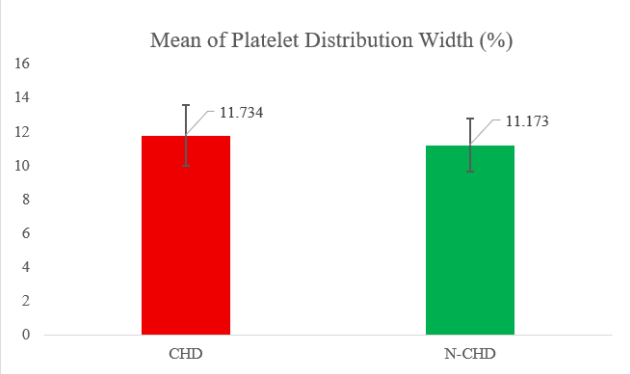

Figure 1: Differences in the means of platelet distribution width levels between CHD and N-CHD groups.

Table 4 depicts the components of platelet indices and their p-values, whereby the bolded components are statistically significant with p-values of less than 0.05. The levels of Platelet Distribution Width (PDW), Mean Platelet Volume (MPV) and

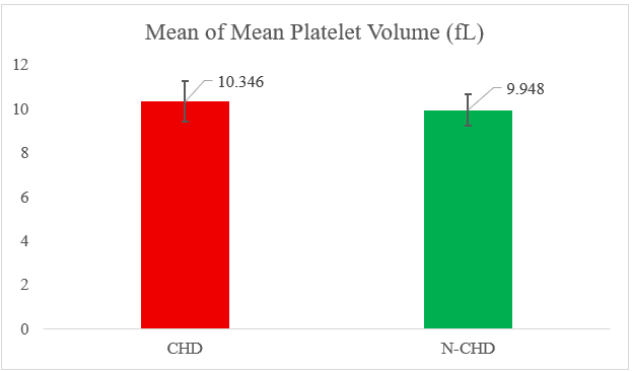

Figure 2: Differences in the means of mean platelet volume levels between CHD and N-CHD groups.

Platelet Larger Cell Ratio (P-LCR) between the two groups, were statistically significant as their p-values were all below 0.05. This indicates that there is a relationship between these components of platelet indices and CHD.

However, the levels pf Platelet Count (PC) and Platelet Crit (PCT) between the two groups, showed no statistically significant difference, as their p-values exceed 0.05. This indicates that there is no relationship between these components of platelet indices and CHD, shown in **Figure 3.**

Table 4: Independent sample T-test for platelet indices of the CHD and N-CHD groups.

Independent samples test										
		Levene's test for equality of variances		t-test for equality of means						
		F	Sig	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	95% confidence interval of the difference	
									Lower	Upper
PC	Equal variances assumed	14.392	0	-0.267	198	0.79	-3.09	11.57182	-25.90983	19.72983
	Equal variances not assumed			-0.267	159.121	0.79	-3.09	11.57182	-25.94417	19.76417
PDW	Equal variances assumed	2.136	0.145	-2.361	198	0.019	-0.561	0.23758	-1.02951	-0.09249
	Equal variances not assumed			-2.361	194.605	0.019	-0.561	0.23758	-1.02956	-0.09244
MPV	Equal variances assumed	6.368	0.012	-3.404	198	0.001	-0.398	0.11693	-0.62859	-0.16741
	Equal variances not assumed			-3.404	187.951	0.001	-0.398	0.11693	-0.62866	-0.16734
PLCR	Equal variances assumed	4.538	0.034	-3.326	198	0.001	-3.076	0.92481	-4.89975	-1.25225
	Equal variances not assumed			-3.326	190.331	0.001	-3.076	0.92481	-4.9002	-1.2518
PCT	Equal variances assumed	24.426	0	-0.706	198	0.481	-0.008	0.01133	-0.03034	0.01434
	Equal variances not assumed			-0.706	151.589	0.481	-0.008	0.01133	-0.03038	0.01438

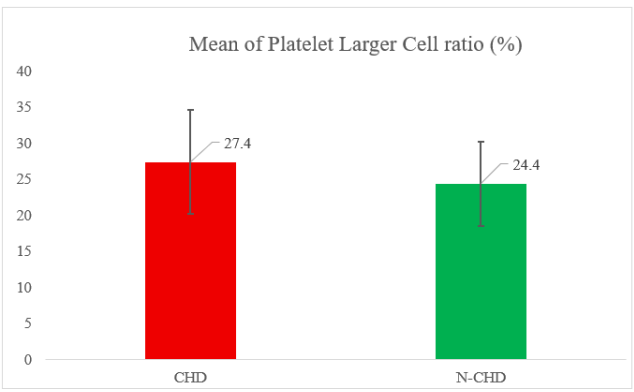

Figure 3: Differences in the means of platelet larger cell ratio levels between CHD and N-CHD groups.

Discussion

Coronary atherosclerosis is a major cause of mortality and it develops as a result of atherosclerosis. Platelets play a major role in the development of atherosclerotic plaques as they adsorb and accumulate on damaged arterial walls, promoting atherosclerosis [15].

Based on the statistical analysis carried out, three out of five components showed statistically significant results. Firstly, Platelet Distribution Width (PDW), which had a p-value of 0.019 when compared between the two groups. PDW is a measure of variation in platelet size distribution, with a range from 8.3% to 56.6% [16,17]. Based on the results obtained as

shown in **Figure 1**, the mean value of PDW in the CHD group (11.734) is higher than that of the N-CHD group (11.173), with a difference of 0.561%. This correlates with previous studies such as that carried out by Patil KS et al., on the comparison of platelet indices in acute coronary syndrome, which indicated elevations in PDW levels amongst CHD patients. This is because, high values of PDW is found to be an indicator of volume variability in platelet size, which suggests an increased production of larger reticulated platelets, a condition that is present in patients with CHD [18]. Nevertheless, the means of both these groups are still within the normal range, leading to the suggestion that this increase may be caused by other factors.

A study carried out by Buch A. et al. on platelet volume indices in type 2 diabetic patients showed that PDW and MPV levels can be increased in the presence of Diabetes Mellitus as it is associated with increases in platelet aggregation [19]. This could be a potential cause for the CHD group having higher PDW and MPV levels as compared to the N-CHD group in our study, as the number of CHD patients with Diabetes Mellitus (45) was much higher than that in the N-CHD group (18).

Another study conducted on the impact of cigarette smoking on platelet parameters, by Swaminathan et al., stated that smokers show significantly high values of PDW, MPV and P-LCR, which increases their risk of developing CHD [20]. Based on the data obtained **(Table 1)** the percentage of smokers in the CHD group (38%) is higher than that in the N-CHD group (12%), indicating that this could be a contributing factor to the increase in PDW levels amongst CHD patients. Therefore, although the levels of PDW are higher in CHD patients, this difference may not be caused by CHD alone as other factors such as smoking, Diabetes Mellitus, and gender, play a role in its elevation as well.

Mean Platelet Volume (MPV), is the average size of platelets found in blood, and is maintained at 7.2-11.7 femtolitres (fL) [21,22]. The difference in MPV levels between the two groups were statistically significant with a p-value of 0.001. In the presence of CHD, platelet production is found to be decreased, thereby causing the younger platelets to become bigger and more active, resulting in the increase of MPV levels. Elevated MPV therefore indicates an increase in platelet production rate and platelet activation, which can be found in patients with CHD [18]. This can be observed in our study as patients with CHD had higher levels of MPV (10.346 fL) as compared to the N-CHD group (9.948 fL), with a difference of 0.398 fL. Although there was a significant difference between the two groups, the MPV levels in both cases were still within the normal range. This difference may be caused by other factors such as Diabetes Mellitus, smoking, gender and age [19,20,23].

A study carried out by Ranganath et al., on women on estrogen therapy, showed that MPV levels in post-menopausal women were lower prior to receiving estrogen therapy. This is because post-menopausal women have low platelet activation as a result of having low estradiol levels [23]. Hence, post-menopausal women have lower MPV levels compared to men. Hence, this could be another factor affecting the increase in MPV levels in the CHD group, as the percentage of males having CHD (87%) is much higher than that of females (13%), of which, 84.6% are potentially in the post-menopausal stage with ages above 50.7 years [24].

The Platelet-Large Cell Ratio (P-LCR) is defined as the percentage of platelets which exceeds that of the normal platelet volume (12 fL) in the total platelet count [25]. In this study, a statistically significant difference with a p-value of 0.001 was obtained when the P-LCR values were compared between the two groups. The findings from our study showed that the levels of P-LCR in the CHD group were much higher than that in the N-CHD group, with a difference of 3%. Previously conducted research such as that done by Abdinur MA et al., on the levels of platelet indices in the presence of CHD, showed results similar to that of this study, whereby patients with CHD have increased production of P-LCR [15,18].

The findings from this study showed that the Platelet Count (PC) was maintained within the normal range, (150-450) × 109/L in both groups. Platelet Crit (PCT) on the other hand, is the volume occupied by platelets in the blood as a percentage, and is normally maintained at 0.22-0.24% [17]. The levels of PC and PCT between the two groups showed no statistical significance as they both had p-values of 0.790 and 0.481 respectively when compared between the CHD and N-CHD groups. This correlates with findings from previous studies carried out on the levels of platelet indices in the presence of CHD, in which both PC and PCT did not show any statistically significant results [15,18]. However, other studies such as that carried out by Seong AC et al., have shown that PCT and PC levels can be elevated in the presence of CHD, but due to other factors such as Diabetes Mellitus, hypertension and smoking [26].

There were several limitations faced while conducting this study. Firstly, the study population had to be reduced to 200 from 500, as we were unable to gain access to more patient medical records due to the three-month time constraint. Apart from that, there were several influencing factors of CHD present such as, Diabetes Mellitus, smoking, gender, age and hypertension. Thus, it is not possible to conclude that the elevation in platelet indices was solely due to CHD, as the influencing factors stated above could have contributed to the increase as well.

Conclusion

In conclusion, the platelet indices PDW, MPV and P-LCR showed statistically significant differences between the CHD and N-CHD groups, indicating that there is an elevation of these components in patients with CHD. Hence, based on the study carried out, the measurement of platelet indices has the potential to be developed into a beneficial risk predictor for

CHD, as they have some reference value for the early prediction and prevention of patients with CHD. This is also because, it is routinely available, more affordable as compared to other tests, and can be detected early. Nevertheless, it cannot be concluded that the elevations in these platelet indices are solely due to CHD alone, as several other influencing factors were present in this study. Thus, further research can be carried out using a larger population size to understand the association between platelet indices and CHD in the absence of other influencing factors.

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Disclosure

The authors report no conflicts of interest in this work.

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