

# Association of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio and Coronary Artery Disease Among the Physicians

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**Introduction:** Cardiovascular diseases (CVDs) are major global health problem and are the third leading cause of death in the world. Most studies found the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were correlated with myocardial infarction and heart failure. Previous studies reported a higher risk of CVD among physicians but no study concerns NLR and the PLR to predict coronary artery disease (CAD) among the physicians.

**Purpose:** This study aimed to evaluate the role of blood features in the CBC, with a particular focus on NLR and PLR levels, in predicting the presence of CAD.

**Patients and Methods:** Data of Thai physicians who participated in the “Save Doctors’ Heart” project which was conducted between February 14 and October 31, 2022, were collected from personal information, work and health habits, physical examination, white blood cell (WBC), laboratory, cardiac testing, and presence of CAD. Prior to studying their association with CAD, optimal values of age and each blood parameter, NLR, and PLR were determined.

**Results:** Of 1161 physicians mean age was  $47.7 \pm 10.16$  years. By cardiac tests, CAD was identified in 11.3%. Significantly higher levels of WBC, neutrophils, NLR, and lower platelets were found in physicians with CAD. Except for lymphocytes and platelets which exhibited a reverse association with CAD, other factors were found as significant risk factors for CAD by univariate analysis. By multivariate analysis, the independent risk factors for CAD in order of their adjusted odds ratio (aOR) were age  $\geq 50$  years (aOR 9.34),  $NLR \geq 1.87$  (aOR 2.75), CAC score  $> 1$  (aOR 2.39), and  $PLR \geq 161.66$  (aOR 2.32).

**Conclusion:** NLR and PLR, older age and CAC score were found as independent factors predicting CAD. The findings of this study could potentially provide valuable insights into the relationship between blood parameters and CAD risk among physicians.

**Keywords:** blood cell count, coronary artery disease, lymphocyte, neutrophil, platelets

## Introduction

Cardiovascular diseases (CVDs) pose a major global health problem, presenting a considerable threat to the worldwide population with high mortality rates.<sup>1</sup> Coronary artery disease (CAD) is one important type of CVD, ranking as the third leading cause of death, accounting for approximately 17.8 million deaths annually worldwide.<sup>2</sup> The symptoms of CAD include chest pain, discomfort, dizziness, fainting, fatigue, etc. However, some individuals have non-specific symptoms. Hence, it is crucial for the early detection of CAD in at-risk individuals for early detection, especially among those who are at risk. Complete blood count (CBC) is the most common test for providing crucial hematologic information. Abnormal CBC may indicate underlying health disorders, such as infection or inflammation.<sup>3</sup> The relationship between the inflammatory response, hematologic markers, and CVDs has been a subject of research. Increasing evidence suggests inflammation develops and progresses atherosclerosis, endothelial lesions, plaque formation, and disruption,<sup>4</sup> which lead to acute coronary syndrome (ACS), including myocardial infarction (MI) and unstable angina.<sup>5</sup> Fewer studies showed an association between white blood cell (WBC) count and cardiovascular event parameters, both as prognostic markers for predicting

myocardial damage, severity, and mortality from CVD.<sup>6–8</sup> Most studies found that higher WBC counts, especially neutrophils, increase the risk of CAD and heart failure (HF).<sup>9–11</sup> Additionally, changes in the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) levels are correlated with MI and HF.<sup>12–17</sup>

Physicians, who bear significant responsibility for the health of the population, may also face health risks of their own. Previous studies reported a higher risk of CVD among physicians.<sup>18–20</sup> This can attribute to occupation-related stress, poor lifestyle and habits, and lack of exercise leading to high blood pressure (BP) and obesity, consequent to CVD.<sup>19,20</sup> Our hospital conducted the corporate social responsibility (CSR) project, “Save Doctors’ Heart”, to assess the cardiac health of Thai physicians, specifically CAD through cardiac tests. This study aimed to evaluate the role of blood features in the CBC, with a particular focus on NLR and PLR levels, in predicting the presence of CAD.

## Materials and Methods

Our hospital conducted the “Save Doctors’ Heart” project between February 14 and October 31, 2022, among Thai physicians aged 35–75 without congenital heart diseases. The inclusion criteria were physicians who were available to measure personal health, blood tests, and cardiac testing. Exclusion criteria were those who had a history or current autoimmune/hematologic/bone marrow disease, infection, inflammatory bowel disease, active cancer, steroid or inflammatory drug use, inadequate cardiac investigations, or only suspicious CAD without definite confirmation. Data were collected from personal health information including age, gender, BMI, personal history (hypertension, diabetes mellitus, dyslipidemia), work and health habits (weekly work hours, fiber in the diet, smoking, exercise, stress), physical examination (weight, height, BP, cardiovascular system), laboratory (WBC count, absolute neutrophils, absolute lymphocytes, platelet count, BP, blood sugar, lipid profiles), cardiac testing, and presence of CAD.

Cardiac testing is based on abnormal basic testing results and the cardiologist’s discretion. Non-invasive cardiac investigations included a 12-lead electrocardiogram (EKG), coronary artery calcium (CAC) scanning, exercise stress tests and/or echocardiogram, or stress echocardiogram. Additionally, coronary computed tomography angiography (CCTA) or coronary angiogram (CAG) may be performed. The CAC score obtained from the CAC scanning measures the amount of calcified plaque in the coronary arteries. This score provides valuable information about the extent of atherosclerosis and the risk of developing CAD. The collected blood was transferred to a test tube containing EDTA as an anticoagulant and sent to the laboratory unit to be assessed within one hour after venipuncture and analyzed by a Sysmex XN-1500 analyzer. The hospital conducted daily internal quality assessments of the laboratory, and annual external quality assessments of the laboratory were performed annually.

## Ethics

The study received approval from the MedPark Institutional Review Board (COA-MPIRB 003/2023). A waiver of informed consent was obtained due to being a retrospective study. The data were collected from the archive of the CSR project (February to October 2022) between March 31 and May 31, 2023. The confidentiality of information was protected according to the Helsinki Declaration and was used only for research purposes. The individual identifiers were removed during data collection and were replaced with serial code numbers.

## Statistic

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were presented as mean  $\pm$  standard deviation (SD) for normally distributed data or median and ranges for non-normally distributed data. Categorical variables were presented as frequency and percentage. For clinical data, BMI was categorized as underweight/normal ( $<25$  kg/m<sup>2</sup>) or overweight/obese ( $\geq 25$  kg/m<sup>2</sup>). Personal history of hypertension, diabetes mellitus, and dyslipidemia, and/or abnormal values identified in the project for the respective disorders were categorized as having such disorders. The CAC score was classified as “no evidence” (score 0–1) or “evidence of CAD” (score  $> 1$ ).

The diagnostic performance, mean or median values of each blood component, NLR, and PLR to predict CAD were compared with the Area Under Curve (AUC). The optimal cut-off values of age and each blood feature were determined

using Receiver Operating Curve (ROC) analysis to categorize them into 2 groups to assess their risk of CAD. Except for NLR and PLR, each value of the blood feature was rounded to the nearest whole number.

Group comparisons by univariable analysis were made using Student's *t*-test or Mann–Whitney *U*-test for continuous variables and chi-square or Fisher's exact test for categorical variables, as appropriate. Clinically important features or significant by univariate analysis were included for a multivariate analysis by logistic regression to explore independent factors or risk for CAD. Only blood features of NLR and PLR, significant clinical features, and cardiac testing were included in the multivariate analysis. A *p*-value <0.05 was considered statistically significant.

## Results

Of 1244 physicians who participated in “Save Doctors’ Heart” project, 83 were excluded due to no CBC results/had it done elsewhere, CAD not confirmed, and history of the disease. A total of 1161 physicians were included in the study, the mean age was  $47.7 \pm 10.16$  years, and 55.6% were female. Among the 1153 physicians with available data, 28.7% were overweight/obese, 46.1% had high BP, 29.7% had high blood sugar, and 77.0% had dyslipidemia. The echocardiogram, stress echocardiogram, exercise stress test, and CAC score evaluation were performed on different numbers of physicians. For CCTA/CAG was conducted as indicated. Our details about cardiac testing were presented elsewhere. The presence of CAD was confirmed in 11.3% of physicians.

Table 1 shows the overall median values of each blood feature according to the presence of CAD. It was observed that physicians with CAD had significantly higher levels of WBC, neutrophils, and NLR. Each increase of 1000 cells/mm<sup>3</sup> in WBC or neutrophils was associated with a 1.02-fold and 1.30-fold risk of CAD, respectively. On the other hand, the number of lymphocytes, platelets, and PLR was found to be lower among physicians with CAD, with platelets and PLR showing statistical significance. Each decrease of 1000 cells/mm<sup>3</sup> of lymphocytes or platelets reduced the risk of CAD by 0.86 folds and 0.99 folds, respectively.

We evaluated the diagnostic performance of each blood component, NLR, and PLR in predicting CAD. Among these features, NLR, neutrophils, and total WBC count demonstrated higher AUC values compared to the other features (Table 2). Optimal thresholds for predicting the risk of CAD were determined for age and various blood features. The cut-off values for these thresholds were as follows: age (50 years), WBC (6350 cells/mm<sup>3</sup>), neutrophils (3570 cells/mm<sup>3</sup>), lymphocytes (1476 cells/mm<sup>3</sup>), platelets (239,500 cells/mm<sup>3</sup>), NLR (1.86), and PLR (161.66).

The association between age, gender, personal illnesses, BMI, blood features, cardiac testing, and risk for CAD. Except for lymphocytes and platelets, which exhibited a reverse association with CAD, all others were at significant risk for CAD by univariate analysis. In the multivariate analysis, the risk factors for CAD in order of their adjusted odds ratio (aOR) were age  $\geq 50$  years (aOR 9.34), NLR  $\geq 1.87$  (aOR 2.75), CAC scores  $> 1$  (aOR 2.39), and PLR  $\geq 161.66$  (aOR 2.32). Table 3

**Table 1** Median Values of Blood Features According to the Presence of Coronary Artery Diseases

Blood Features	Total (n = 1161)	Blood Features by Presence of Coronary Artery Disease, Median (IQR)		P-value
		No coronary Artery Disease (n = 1030)	Presence of Coronary Artery Disease (n = 131)	
WBC (cells/mm <sup>3</sup> )	5500 (4700–6400)	5500 (4700–6300)	5800 (4900–7000)	0.006
Neutrophil (cells/mm <sup>3</sup> )	3150 (2596–3943)	3110 (2584–3898)	3445 (2785–4380)	0.001
Lymphocyte (cells/mm <sup>3</sup> )	1750 (1465–2090)	1752 (1477–2090)	1717 (1411–2090)	0.373
Platelets (cells/mm <sup>3</sup> )	253,000 (219,000–290,000)	255,500 (221,000–292,000)	231,000 (203,000–265,000)	<0.001
Neutrophil to lymphocyte ratio	1.80 (1.41–2.31)	1.77 (1.39–2.28)	2.02 (1.58–2.66)	<0.001
Platelets to lymphocyte ratio	142.83 (114.84–179.05)	144.67 (116.34–180.24)	135.95 (106.24–168.69)	0.023

**Table 2** Diagnostic Performance of Each Blood Component, Neutrophil to Lymphocyte Ratio and Platelets to Lymphocyte Ratio to Predict Coronary Artery Disease

Blood Component	AUC (95% Confidence Interval)	Sensitivity (%)	Specificity (%)	P-value
Total white blood cell (cells/mm <sup>3</sup> )	0.573 (0.519–0.627)	42.0	75.1	0.006
Absolute neutrophil count (cells/mm <sup>3</sup> )	0.588 (0.536–0.640)	49.6	65.4	0.001
Absolute lymphocyte count (cells/mm <sup>3</sup> )	0.476 (0.423–0.530)	33.6	75.0	0.373
Total platelets (cells/mm <sup>3</sup> )	0.387 (0.336–0.439)	56.5	62.6	<0.001
Neutrophil to lymphocyte ratio	0.596 (0.546–0.645)	61.8	55.4	<0.001
Platelet to lymphocyte ratio	0.439 (0.387–0.492)	74.0	37.3	0.023

**Table 3** Personal Characteristics, Blood Features, and Cardiac Testing to Predict Coronary Artery Disease

Features	n	Coronary Artery Disease		Crude Odds Ratios (95% CI)	P-value	Adjusted Odds Ratios* (95% CI)	P-value
		No, n (%)	Yes, n (%)				
Age (year), n = 1161							
• < 50	729	711 (97.5)	18 (2.5)		–		–
• ≥ 50	432	319 (73.8)	113 (26.2)	13.99 (8.363–23.409)	<0.001	9.34 (3.998–21.819)	< 0.001
Gender, n = 1161							
• Female	645	618 (95.8)	27 (4.2)		–		–
• Male	516	412 (79.8)	104 (20.2)	5.78 (3.716–8.983)	<0.001	1.74 (0.931–3.250)	0.083
Body mass index, n = 1153							
• Not over	822	745 (90.6)	77 (9.4)		–		–
• Over - Obesity	331	277 (83.7)	54 (16.3)	1.89 (1.297–2.742)	0.001	1.29 (0.710–2.341)	0.404
Diabetes mellitus, n = 1161							
• No	816	761 (93.3)	55 (6.7)		–		–
• Yes	345	269 (78.0)	76 (22.0)	3.91 (2.690–5.681)	< 0.001	1.04 (0.589–1.847)	0.884
Dyslipidemia, n = 1161							
• No	267	251 (94.0)	16 (6.0)		–		–
• Yes	894	779 (87.1)	115 (12.9)	2.32 (1.347–3.982)	0.002	0.86 (0.409–1.791)	0.679
Hypertension, n = 1161							
• No	626	601 (96.0)	25 (4.0)		–		–
• Yes	535	429 (80.2)	106 (19.8)	5.94 (3.78–9.34)	< 0.001	1.48 (0.754–2.916)	0.253
White blood cells (/mm <sup>3</sup> ), n = 1161							
• < 6500	873	793 (90.8)	80 (9.2)		–	–	–
• ≥ 6500	288	237 (82.3)	51 (17.7)	2.13 (1.459–3.119)	<0.001	–	–

(Continued)

Table 3 (Continued).

Features	n	Coronary Artery Disease		Crude Odds Ratios (95% CI)	P-value	Adjusted Odds Ratios* (95% CI)	P-value
		No, n (%)	Yes, n (%)				
Neutrophil (/mm <sup>3</sup> ), n = 1161							
• < 3500	715	649 (90.8)	66 (9.2)		–	–	–
• ≥ 3500	446	381 (85.4)	65 (14.6)	1.68 (1.164–2.417)	0.006	–	–
Lymphocyte (/mm <sup>3</sup> ), n = 1161							
• < 1500	319	275 (86.2)	44 (13.8)		–	–	–
• ≥ 1500	842	755 (89.7)	87 (10.3)	0.72 (0.489–1.062)	0.098	–	–
Platelets (/mm <sup>3</sup> ), n = 1161							
• < 240,000	459	385 (83.9)	74 (16.1)		–	–	–
• ≥ 240,000	702	645 (91.9)	57 (8.1)	0.46 (0.318–0.664)	<0.001	–	–
Neutrophil to lymphocyte ratio, n = 1161							
• < 1.87	621	571 (91.9)	50 (8.1)		–		–
• ≥ 1.87	540	459 (85.0)	81 (15.0)	2.02 (1.387–2.927)	<0.001	2.75 (1.523–4.972)	0.001
Platelets to lymphocyte ratio, n = 1161							
• < 161.66	418	384 (91.9)	34 (8.1)		–		–
• ≥ 161.66	743	646 (86.9)	97 (13.1)	1.70 (1.125–2.557)	0.011	2.32 (1.153–4.674)	0.018
Echocardiogram, n = 730							
• Normal	298	291 (97.7)	7 (2.3)		–	–	–
• Abnormal	432	359 (83.1)	73 (16.9)	8.45 (3.834–18.640)	< 0.001	–	–
Exercise stress test, n = 534							
• Normal	331	331 (100.0)	–		–	–	–
• Abnormal	203	170 (93.7)	33 (16.3)	–	< 0.001	–	–
Stress echocardiogram, n = 663							
• Normal	643	569 (88.5)	74 (11.5)		–		–
• Abnormal	20	14 (70.0)	6 (30.0)	3.30 (1.229–8.838)	0.025	1.48 (0.494–4.408)	0.486
Coronary calcium score, n = 671							
• Score < 1	439	419 (95.4)	20 (4.6)		–		–
• Score ≥ 1	232	121 (52.2)	111 (47.8)	19.22 (11.457–32.239)	< 0.001	2.39 (1.207–4.743)	0.012

**Note:** \*Adjusted for age, gender, NLR, PLR, echocardiogram, stress echocardiogram, and calcium score.

**Abbreviations:** NLR, Neutrophil to lymphocyte ratio; PLR, Platelets to lymphocyte ratio.

## Discussion

Although the WHO Health Evidence Network reported that population screening for CVDs does not result in a reduction of morbidity and mortality,<sup>1</sup> it remains crucial to recognize the potential benefits of screening for individuals who are at risk. Therefore, it is necessary to carefully weigh the benefits and costs when considering an appropriate cardiac screening test, especially in countries with limited resources. The use of CBC as a tool for assessing the inflammatory

response in the development and progression of atherosclerosis and cardiovascular events should yield potential benefits.<sup>9</sup>

Our study discovered a significant association between CAD and increased WBC count, neutrophils, and NLR, along with a decrease in platelets and PLR. Although lower lymphocyte was found among the physicians with CAD, the difference was not statistically significant. Among these factors, elevated NLR, WBC count, and neutrophils had superior predictive performance for CAD compared to other parameters. When considering blood features and other clinical characteristics, independent risk factors for CAD included age  $\geq 50$  years, NLR  $\geq 1.87$ , PLR  $\geq 161.66$ , and a moderate to extensive CAC score. Age  $\geq 50$  years carried the highest risk of CAD (9.34-fold) compared younger group. Our study discovered that the risk for CAD of NLR (2.75-fold) and PLR (2.32-fold) was comparable with the risk associated with a CAC score  $>1$  (2.39-fold). These findings are consistent with previous studies linking NLR and PLR to CVDs such as MI, heart failure, and death.<sup>8,12–14,17</sup>

Several studies showed an association between an elevated WBC and neutrophil count with an increased risk of cardiovascular events.<sup>6–11</sup> A cohort study conducted in healthy young men reported an elevated WBC  $> 6900$  cells/mm<sup>3</sup> was associated with a 2.17-fold increase in the risk for CAD compared to elevated lipids or family history of CAD. It was found that each increment of 1000 cells/mm<sup>3</sup> in WBC count led to a 1.17-fold increased risk for CAD.<sup>11</sup> Their results were consistent with this study which found a 1.02-fold risk of CAD with an increase of 1000 cells/mm<sup>3</sup> in WBC count or a 2.13-fold risk with WBC  $\geq 6500$  cells/mm<sup>3</sup>. Previous studies found a direct association between high neutrophil or low lymphocyte counts with CAD, HF, and death.<sup>21–24</sup> For neutrophils, one study reported that a high ( $>6600/\mu\text{L}$ ) or low ( $<1560/\mu\text{L}$ ) neutrophil had better function than total CBC for independently predicting death or MI in patients with high risk for CAD.<sup>10</sup> Our results, similar to previous study, also reported a 1.68-fold risk of CAD with neutrophils count  $\geq 3500$  cells/mm<sup>3</sup> or 1.3-fold for an increase of every 1000 neutrophils/mm<sup>3</sup>.

The study of patients with chest pain found low lymphocytes ( $<1900$  cells/mL) had a 2.45-fold increased risk for MI but high CBC or neutrophils were not.<sup>25</sup> Lymphopenia may be led by increased lymphocyte apoptosis.<sup>26,27</sup> Our study was the same as their report regarding lower lymphocyte counts among the physicians who had CAD compared to the unaffected individuals. Although we found a 0.72-fold risk with lymphocytes  $<1500$  cells/mm<sup>3</sup> or 0.86-fold risk with a decrease of every 1000 lymphocytes/mm<sup>3</sup>, they were not statistically significant.

We found a significant association between CAD and platelet (0.99-fold risk with a decrease of every 1000 platelets/mm<sup>3</sup> or 0.46-fold with  $\geq 240,000$  platelets/mm<sup>3</sup>). However, the results from the Danish population reported a high platelet count (301,000–450,000/L) was associated with an increased risk of CVD (1.32-fold) and mortality (1.43-fold).<sup>28</sup> The finding may be attributed to various influencing factors, such as the effect of heparin-induced thrombocytopenia, the use of antiplatelet drugs for hypertension or diabetes, the laboratory use of EDTA for blood test, or even diurnal variation or sleep pattern of the individuals.<sup>29–31</sup> These medications could potentially influence platelet counts and contribute to the observed differences in effect to an association between platelet counts and CAD risk.

Other studies demonstrated a direct association between higher NLR and cardiac morbidity and mortality.<sup>10,13,15</sup> For instance, one study found an NLR  $> 4.71$  was associated with a higher risk of MI or death.<sup>10</sup> Others found elevated NLR was correlated with higher mortality in MI patients.<sup>15</sup> The authors who found NLR as a good predictor for 1-year mortality in MI patients undergoing surgery also supported its use as a prognostic indicator before the intervention, discharge, and long-term follow-up.<sup>13</sup>

Contrary to our initial finding of a relationship between low platelet counts and CAD, our study revealed that a high PLR was associated with CAD. This suggests that the utilization of PLR may have mitigated the impact of confounding factors on platelet count. Our results regarding the higher value of PLR and CAD were in line with the previous report. The study in Chinese patients post coronary angiogram found patients with PLR  $> 171$  had a 2.39-fold increased risk for 3-vessel CAD compared to those with PLR  $< 101$ .<sup>32</sup>

Although our findings were generally consistent with previous studies regarding the higher risk of CAD or MI with high WBC count, neutrophils, NLR, and PLR, there were some differences in specific values of each blood parameter and the level of significance. These discrepancies may be attributed not only to variations in the characteristics of the participants in each study but also to differences in reported outcomes and the duration of follow-up periods. Hence, it is essential to carefully consider these factors for their clinical implications.



We were aware of some limitations in our study. Firstly, we lacked data on medications that could potentially impact blood features, particularly platelet counts. This absence of information might have influenced our findings. Secondly, our study focused solely on CAD as the outcome, without considering other CVDs, long-term outcomes, or mortality. Furthermore, the severity of CAD and long-term outcomes were not available. Expanding the scope to encompass CVDs, severity of CAD, and long-term follow-up could provide a better understanding of the relationship between blood features and cardiovascular health.

Nevertheless, our study had some strengths. Firstly, despite focusing solely on physicians, the findings were consistent with existing data, suggesting that the role of blood features can be extended to the general population. Secondly, the confirmation of CAD through cardiac testing enhanced the reliability of the study's conclusions, as it ensured accurate identification of the condition. Thirdly, by determining the optimal values of each blood feature and their derivatives (NLR and PLR) in relation to CAD, our study should provide valuable insights into their association, contributing to the existing body of knowledge. Lastly, the incorporation of clinical features and cardiac testing in predicting NLR and PLR should have made the findings more robust. Furthermore, our findings were practical in clinical settings because CBC is a cost-effective screening test for physicians to assess their risk for CAD, even absence of symptoms. This test can serve as an initial step before considering cardiac testing.

## Conclusion

NLR and PLR, along with older age and CAC score, were independent predictive features for CAD in physicians. The relationship between specific blood parameters and CAD risk among physicians may facilitate early detection and appropriate management of the disease in healthcare professionals. By improving doctors' cardiac health, this project can have a positive impact not only on their well-being but also on the overall quality of patient care provided to the population.

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## Disclosure

The authors report no conflicts of interest in this work.

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