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Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as markers of stable ischemic heart disease in diabetic patients

An observational study

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Abstract

Ischemic heart disease (IHD) is a pressing public health concern with high prevalence, mortality, and morbidity. Although the value of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) as markers of the acute coronary syndrome are well recognized, there is a paucity of data deciphering their role in screening for stable ischemic heart disease (SIHD) in the presence of type 2 diabetes mellitus (T2DM). The present study investigates the value of NLR and PLR as markers of SIHD in T2DM. We evaluated the predictive value of NLR and PLR for SIHD by comparing T2DM patients having angiographically proven SIHD to T2DM patients without IHD at different cutoff levels by evaluating the area under the curve (AUC) obtained from receiver-operating-characteristic analysis. Raised NLR and PLR were significantly associated with SIHD ($P < .001$ for each). On performing AUC-receiver-operating-characteristic analysis, NLR of > 2.39 and PLR of > 68.80 were associated with the highest prevalence of SIHD (NLR, AUC: 0.652 [0.605–0.699]; CI: 95%; $P < .001$, PLR, AUC: 0.623 [0.575–0.671] CI: 95%; $P < .001$). The sensitivities and specificities for these cutoff values were 50% and 73% for NLR and 73% and 46% for PLR, respectively. NLR and PLR were significantly higher in SIHD compared to those without; however, these markers had limited predictive potential in the setting of T2DM.

Abbreviations: ACS = acute coronary syndrome, AUC = area under the curve, IHD = ischemic heart disease, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, ROC = receiver-operating-characteristic, SIHD = stable ischemic heart disease, T2DM = type 2 diabetes mellitus.

Keywords: inflammatory markers, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, ROC-AUC, stable ischemic heart disease

1. Introduction

Ischemic Heart Disease (IHD) grows as a public health challenge worldwide with increasing rates of prevalence, mortality, morbidity and economic burden. The paucity of cost-effective resources for diagnosing and screening IHD in developing countries results in delays in diagnosis and prompt administration of treatment.[1] Extensive literature linking inflammation to IHD has helped us recognize the value of various inflammatory markers as potential screening tools for the early diagnosis of ischemic heart disease.[2] C-reactive protein (CRP), vascular cell adhesion molecules (VCAMs), selectins, and cytokines, for example, Interleukin-4 (IL-4), are some of the markers explored earlier; however, these are expensive.[3] Neutrophil-lymphocyte ratio (NLR) and Platelet-lymphocyte ratio (PLR) have been studied as alternatives to the aforementioned biomarkers due to their cost-effectiveness and wide availability.

A high NLR has been observed to correlate significantly with the severity of IHD, the progression of atherosclerotic plaque, and major adverse cardiovascular events (MACE)[4,5] and a high PLR has also been recognized as a predictor of severe IHD[6]; however, most previous studies have focused on evaluating their predictive value for diagnosing acute coronary syndromes (ACS) or have correlated them with the severity of coronary artery stenosis. There is paucity of data evaluating

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the probable value of these economical tests as screening tools for stable ischemic heart disease (SIHD). Type 2 diabetes mellitus (T2DM), a frequent accompaniment of IHD, is another condition associated with the raised NLR and PLR.[7] Some investigators reported that a sub-group of their patients with T2DM had significantly raised NLR when accompanied with IHD compared to those without, but most of the studied patients had ACS, not SIHD.[8] The question of NLR's predictive value for SIHD, thence, still remains unanswered. In this study we decided to explore the predictive value of NLR and PLR for SIHD in the presence of pro-inflammatory milieu of T2DM.

2. Methods

2.1. Study design and subjects

This single-center, retrospective, cross-sectional study was conducted at the tertiary health care facility attached to a postgraduate medical teaching institution. The institutional ethics committee (IEC) approved this study. Owing to the study's retrospective design, taking participants' consent was not applicable. All patients with IHD, who underwent coronary angiography (CAG) in the department of Cardiology from January 2019 to December 2019, were screened for inclusion into this study. Patients aged 40 years or more, having T2DM along with SIHD and not having any pre-defined exclusion criterion, were recruited. For the study purpose, SIHD was defined as presence of spontaneous or inducible myocardial ischemia along with coronary artery diameter stenosis of at least 50% in the left main coronary artery or ≥ 70% in any other epicardial coronary artery and no deterioration in ischemic symptoms over preceding 2 months' period. The admission for angiography/intervention was based on the decision of the respective treating cardiologist. DM was diagnosed as per the American diabetes association guidelines.

T2DM patients attending the Endocrinology outpatient department (OPD) with no historical, clinical or electrocardiographic evidence of IHD and/or of any other macro-vascular complication of diabetes, served as controls.

Patients with disease conditions having the potential to alter NLR and PLR, namely, thyroid disorders, active acute or chronic infections, chronic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis), active malignancy, hematological disorders (leukemia, clotting disorders), pregnancy or lactation, were excluded from the study. Subjects with insufficient demographic data and/or drug history (metformin, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker) were excluded.

2.2. Demographic and clinical data

Baseline characteristics including, age, gender, height, weight, smoking habit, hypertension, drug history including use of metformin, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker and instantaneous office blood pressure, were noted in all eligible subjects. All the patients included in this study were already diagnosed with T2DM according to the American diabetes association criteria. Body mass index (BMI) was calculated by the Quetelet index. Hypertension was defined as a systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg, respectively.

2.3. Determination of laboratory measurements

Blood samples for hematological analysis included total white blood cell (WBC) count, absolute counts of neutrophils, lymphocytes, platelets, and mean platelet volume (MPV). The hematological analysis was performed by Coulter LH 780 Hematology analyzer (Beckman Coulter corp., USA). NLR was calculated from the equation: NLR = absolute neutrophil count (cells/μL)/ absolute lymphocyte count (cells/μL). PLR was calculated using the equation: PLR = platelet count (cells/μL)/ absolute lymphocyte count (cells/μL). Besides, fasting plasma glucose, glycated hemoglobin (HbA1c), serum creatinine, alanine aminotransferase (ALT), alkaline phosphatase (ALP), total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol were measured.

2.4. Statistical methods

The data was analyzed using SPSS version 26.0 (IBM SPSS Statistics, Somers, NY) and R programming language version 3.6.3. Categorical data were presented as frequencies and proportions and compared using the Chi-square test or Fischer's exact t-test, as appropriate. Continuous data were presented as a median with an interquartile range and were compared using the Mann–Whitney U test. Multivariate logistic regression analysis was performed to determine the independent predictors of stable ischemic heart disease (SIHD). receiver-operating-characteristic (ROC) curve analysis was used to determine the optimum cutoff level of NLR and PLR for predicting SIHD. A P value of $< .05$ was considered statistically significant.

3. Results

A total of 2956 potential subjects were screened, including 1976 patients admitted for CAG (test group) and 980 T2DM patients attending Endocrinology OPD (control group). Of these, 1596 individuals had to be excluded from the test group due either to the absence of T2DM or to the presence of any of the predefined exclusion criteria. From the remaining 380 subjects, another 58 were excluded because of missing demographic data, and 61 were found to have evidence of ACS. Hence, 261 T2DM patients with SIHD finally qualified for the test group. Of the 980 potential controls, 520, with no symptomatic or electrocardiographic evidence of IHD, were screened further. Of them, 208 met 1 or more of the predefined exclusion criteria. In addition, 40 subjects with macrovascular complications of DM and 15 with insufficient demographic and drug history were also excluded. The remaining 257 subjects constituted the control group.

The baseline demographic data for the 2 studied groups, namely, T2DM with SIHD and T2DM without SIHD, are presented in Table 1, and their corresponding hematological parameters are shown in Table 2. Age distribution was higher in the SIHD group ($P < .001$), also the prevalence of male gender was significantly higher in the SIHD group ($P < .001$). As evident, both NLR and PLR were significantly higher in the SIHD group compared to the control group ($P < .001$).

We included Age, Sex, WBC, PLT, MPV, ANC, ALC, NLR, PLR, and hypertension (HTN) in multivariate analysis to determine the independent predictors of SIHD. Age, Sex, and HTN were independent predictors of SIHD (Table 3). Increasing age, male gender, and the presence of HTN was associated with higher odds of SIHD by multivariate logistic regression analysis.

The accuracy of NLR and PLR in diagnosing SIHD was poor. The optimum cutoff value for NLR to predict SIHD was 2.39 using a ROC curve with a sensitivity of 50.0% and a specificity of 73.0% (NLR, area under the curve [AUC]: 0.652 [0.605–0.699]; CI: 95%; $P < .001$). The optimum cutoff value for PLR to predict SIHD was 68.80 using a ROC curve with a sensitivity of 73.0% and a specificity of 46.0% (PLR, AUC: 0.623 [0.575–0.671] CI: 95%; $P < .001$)(Table 4, Fig. 1).

Table 1

Demographic characteristics and drug history of Type 2 diabetic patients with stable ischemic heart disease and without ischemic heart disease.

Variables		Overall (n = 518)	Control (n = 257)	SIHD (n = 261)	*P* value
Age (yr)		53.00 [48.00, 59.00]	51.00 [46.00, 57.00]	55.00 [49.00, 62.00]	<.001
Sex, n (%)	Female	136 (26.3)	93 (36.2)	43 (16.5)	<.001
	Male	382 (73.7)	164 (63.8)	218 (83.5)	
BMI (kg/ m^2)		19.14 [15.06, 24.44]	15.06 [13.73, 16.45]	24.41 [22.23, 26.48]	<.001
HTN, n (%)	No	258 (49.8)	177 (68.9)	81 (31.0)	<.001
	Yes	260 (50.2)	80 (31.1)	180 (69.0)	
Smoking, n (%)	No	396 (76.4)	196 (76.3)	200 (76.6)	1
	Yes	122 (23.6)	61 (23.7)	61 (23.4)	
Metformin, n (%)	No	223 (43.1)	24 (9.3)	199 (76.2)	<.001
	Yes	295 (56.9)	233 (90.7)	62 (23.8)	
Statin, n (%)	No	232 (44.8)	208 (80.9)	24 (9.2)	<.001
	Yes	286 (55.2)	49 (19.1)	237 (90.8)	
ACEi, n (%)	No	383 (73.9)	242 (94.2)	141 (54.0)	<.001
	Yes	126 (24.3)	15 (5.8)	111 (42.5)	

Data are presented as median (interquartile range) or number (percentage). categorical variables were analyzed using the Chi-square test, and the Mann–Whitney U test was used for continuous variables. *P* values ≤ 0.05 were considered statistically significant.

ACEi = angiotensin converting enzyme inhibitor, BMI = body mass index, HTN = hypertension, IHD = ischemic heart disease, SIHD = stable ischemic heart disease.

Table 2

Hematological characteristics of patients with Type 2 Diabetes Mellitus with Stable Ischemic heart disease and without Ischemic heart disease.

Variables	Overall (n = 518)	Control (n = 257)	SIHD (n = 261)	*P* value
PPG (mg/dL)	213.00 [148.50, 298.00]	257.00 [190.00, 335.00]	168.00 [121.00, 232.75]	<.001
HbA1c (mmol/mol)	8.00 [6.70, 9.60]	7.80 [6.60, 9.60]	8.15 [7.18, 9.43]	.17
WBC [(n × 10^3)/mm^3]	8.40 [7.10, 10.00]	8.40 [7.00, 9.70]	8.50 [7.30, 10.20]	.107
PLT [(n × 10^3)/mm^3]	189.50 [140.00, 243.00]	188.00 [135.00, 240.00]	192.00 [146.00, 246.00]	.158
MPV (fl)	11.20 [9.80, 12.40]	11.30 [10.00, 12.50]	11.00 [9.80, 12.20]	.15
ANC [(n × 10^3)/mm^3]	4.90 [4.00, 6.10]	4.70 [3.80, 5.70]	5.10 [4.20, 6.60]	<.001
ALC [(n × 10^3)/mm^3]	2.30 [1.80, 2.90]	2.40 [2.00, 3.00]	2.10 [1.60, 2.70]	<.001
NLR	2.10 [1.58, 2.82]	1.88 [1.46, 2.46]	2.40 [1.77, 3.30]	<.001
PLR	83.23 [60.43, 115.20]	74.17 [53.33, 106.67]	91.76 [68.00, 127.00]	<.001

Data are presented as median (interquartile range) or number (percentage). categorical variables were analyzed using the Chi-square test, and the Mann–Whitney U test was used for continuous variables. *P* values ≤ 0.05 were considered statistically significant.

ALC = absolute lymphocyte count, ANC = absolute neutrophil count, HBA1C = glycosylated Haemoglobin, MPV = mean platelet volume, NLR = neutrophil lymphocyte ratio, PLR = platelet lymphocyte ratio, PLT = platelet count, PPBS = post prandial blood sugar, SIHD = stable ischemic heart disease, WBC = white blood cell count.

Table 3

Multivariate logistic regression analysis of selected variables on in-SIHD.

Characteristic	OR	95% CI	*P* value
Age	1.03	1.01, 1.06	.017
Sex			
Female	Ref		
Male	2.98	1.86, 4.87	<.001
WBC [(n × 103)/mm3]	1.06	0.75, 1.53	.7
PLT [(n × 103)/mm3]	1.01	1.00, 1.01	.091
MPV (fl)	0.97	0.88, 1.07	.6
ANC [(n × 103)/mm3]	0.92	0.54, 1.49	.7
ALC [(n × 103)/mm3]	0.94	0.54, 1.67	.8
NLR	1.55	0.99, 2.84	.11
PLR	1.00	0.98, 1.01	.6
HTN			
No	Ref		
Yes	5.10	3.40, 7.74	<.001

P values ≤ 0.05 were considered statistically significant.

ALC = absolute lymphocyte count, ANC = absolute neutrophil count, CI = confidence interval, HTN = hypertension, MPV = mean platelet volume, NLR = neutrophil lymphocyte ratio, OR = odds ratio, PLR = platelet lymphocyte ratio, WBC = white blood cell count.

4. Discussion

It is a well-recognized fact that atherosclerosis is a chronic inflammatory disease as suggested by the intra-vascular imaging studies, histopathological evidence of inflammatory plaque changes and the abnormally raised levels of circulating inflammatory cellular and the biomarkers.[3,9] Previous studies have shown WBC count, absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) to be independently associated with ACS and SIHD; however, evaluation of these parameters as markers for IHD provided inconsistent results. These inconsistencies were caused by fluctuations in common physiological conditions like stress induced release of catecholamines and cortisol, which are known to cause neutrophil and lymphocyte proliferation.[10] However, NLR was found to be less dependent on these fluctuations, proving its superiority as an indicator or predictor of the inflammatory state.[11]

Similarly, the effect of these hematological parameters has also been extensively studied in T2DM wherein, the rise in NLR was found significantly linked with pre-diabetes, diabetes, as well as poor glycemic control[7]; consequently, this marker has even been proposed as a tool to monitor the disease control and its progression in diabetic patients. Despite these data, there remain some unanswered questions in this context including,

Table 4

Area under the curve by Receiver operating characteristics of Neutrophil lymphocyte ratio and Platelet lymphocyte ratio in Stable ischemic heart disease.

Area under the ROC curve							
	AUC	cutoff	*P* value	95% Confidence interval		Sensitivity	Specificity
NLR	0.652	2.390	.000	0.605	0.699	0.5	0.730
PLR	0.623	68.800	.000	0.575	0.671	0.73	0.460

NLR = neutrophil lymphocyte ratio, PLR = platelet lymphocyte ratio, ROC = receiver-operating-characteristic.

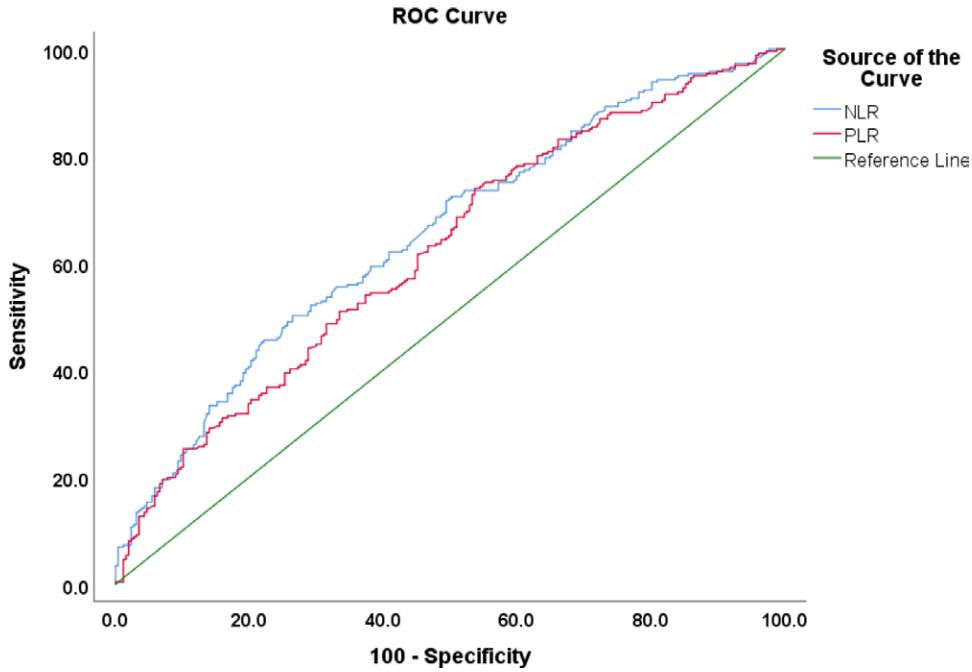

Figure 1. Area under the curve by Receiver operating characteristics of Neutrophil lymphocyte ratio and Platelet lymphocyte ratio in Stable ischemic heart disease.

whether the hematological markers of inflammation retain their value as indicators of IHD in presence of preexisting inflammatory milieu of T2DM which by itself causes raised NLR; and secondly, since previous studies focused on evaluating their IHD correlation either in ACS patients or in mixed populations with majority of patients having ACS, the strength of the predictive value of these markers in SIHD per se is not known. Hence, in the current study, we explored the predictive value of NLR and PLR for SIHD in the presence of pro-inflammatory milieu of T2DM.

Owing to the pivotal role of leukocytes in inflammation, total WBC count was expected to be a good predictor of IHD. On the contrary, specific subsets of lymphocytes, namely T-regulatory cells and T-helper-2 cells, were found to play a protective role in atherosclerosis[12] and lower lymphocyte count was demonstrated to be a good prognostic marker for ACS and SIHD being significantly associated with longer survival in IHD patients.[13] In confluence with these observations, the current study also revealed that the leukocyte and the neutrophil counts were significantly higher in patients with SIHD, while the absolute lymphocyte count was considerably lower in this group as compared to controls.

On evaluating the validity of NLR and PLR as markers of SIHD, our data demonstrated that high NLR and PLR strongly correlated with SIHD in patients with T2DM. However, the predictive value of these markers for SIHD in patients with T2DM was limited. On performing AUC-ROC analysis, NLR of > 2.39 and PLR of > 68.80 were associated with the highest prevalence of SIHD (NLR, AUC: 0.652 [0.605–0.699]; CI: 95%; $P < .001$, PLR, AUC: 0.623 [0.575–0.671] CI: 95%; $P < .001$). The sensitivities and specificities for these cutoff values were 50% and 73% for NLR and 73% and 46% for PLR, respectively.

Numerous studies demonstrated the positive correlation between NLR and the severity of IHD as estimated by 2 scoring systems, namely, SYNTAX and Gensini scoring systems.[3] A study by Arbel et al and Iranirad et al demonstrated that NLR > 3 was associated with advanced obstructive IHD and a worse prognosis.[14,15] In these studies, however, the severity of IHD was categorized by the number of vessels involved. In 2 studies by Kaya et al and Sonmez et al, patients with SIHD were investigated, and NLR cutoff values of 2.5 and 1.95 were proposed.[16,17] In the study by Sonmez et al, although patients with DM were included, only a few subjects with the disease were analyzed; moreover, these patients were compared to controls without SIHD (n = 71).[17] Similarly, the study by Kaya et al also studied SIHD in a small sample population of DM (n = 47).[16] In 2018, a large meta-analysis involving 17 studies and 7017 cases was conducted to investigate NLR as a predictor of IHD.[4] This study analyzed data from 3 studies with SIHD, 2 studies with ACS, and 12 studies that broadly included mixed patients with IHD. cutoff values for NLR ranging from 1.95 to 3.97 were proposed.[4] However, none of the above-mentioned studies exclusively studied patients with DM and SIHD. Fernando et al conducted a study in patients with T2DM (n = 150), testing the significance of NLR

in subjects with and without IHD (n = 100, n = 50, respectively). It was observed that NLR had significant predictive outcomes in detecting IHD (AUC under ROC = 0.997, 95% CI = 0.993–1.000). This study demonstrated a higher mean NLR for patients with IHD than our study (4.09 ± 1.67 vs 3.06 ± 2.91).[18] The study, however, did not differentiate ACS and SIHD, which may be the cause for the disparity.

In the present study, although we found NLR to be significantly elevated in SIHD compared to the controls, it could not adequately predict the presence of SIHD. This may be reasoned that NLR is more indicative of an acute response than a chronic inflammatory response, as seen in SIHD.[8] The co-existence of a pro-inflammatory state as that seen in T2DM, which by itself is independently associated with high NLR,[7] might have further masked any substantial difference in the levels of inflammatory markers that 1 may expect. The association between higher platelet count and cardiovascular disease has received support from recent studies.[19] Due to the thrombotic nature of the disease process, platelets have been indicted for playing a significant role in the initiation and progression of the thrombus.[20] Higher platelet counts were observed in states with underlying inflammation due to the increased stimulation of megakaryocyte proliferation in the bone marrow.[21] In the present study, we did not observe a significant relationship between high platelet count and the presence of SIHD. However, the Platelet-Lymphocyte ratio was observably higher in patients with SIHD when compared to the controls. By combining the pro-thrombotic response of platelets and controlled inflammatory response by lymphocytes, PLR has been proven to be a more reliable indicator of inflammation.[22] PLR was found to be positively associated with the severity of coronary atherosclerosis in ACS and was also found to be an independent predictor of severe IHD when the latter was stratified using Gensini score.[23,24] In a study by Cho KI et al, high PLR was reported to be an independent predictor of long-term adverse events after percutaneous intervention in ACS but not in SIHD.[25] In a study by Yüksel M. et al, PLR of > 111 predicted severe atherosclerosis (n = 388); however, this study primarily comprised of subjects with no history of T2DM (n = 296).[6] In the present study, exclusively involving subjects with T2DM, we propose a cutoff value of PLR > 68.80.Area under the ROC curve for PLR in the present study and the Yüksel M. et al study was comparable (0.623, 0.575–0.671, 95% CI; $P < .001$ vs 0.645, 95% CI: 0.587–0.703; $P < .001$).[6]

5. Conclusion

NLR and PLR are inflammatory cellular markers that have been studied for their association with IHD, more so in patients presenting with ACS. In this study, we explored their role as rapid and inexpensive markers of SIHD in the pro-inflammatory milieu of T2DM.With a cutoff NLR value of > 2.39, we could predict the presence of SIHD in T2DM with a sensitivity of 50% and a specificity of 73%. Similarly, at PLR cutoff value of > 68.80, the SIHD could be predicted with a sensitivity of 73% and specificity of 46%. Hence, NLR and PLR are significantly higher in diabetics with SIHD, compared to the once without IHD; these ratios, however, have limited predictive potential in this setting.

6. Limitations

Our study has some limitations including: this was a single-center study with a relatively small sample size; silent ischemia was ruled out by stress test only in those control group subjects who either had symptoms or EKG findings that raised suspicion of IHD.

A larger multi-center study may be conducted for further clarification on this subject.

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