PREDICTIVE VALUE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO FOR CORONARY ARTERY DISEASE: A PROSPECTIVE STUDY.

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ABSTRACT

Introduction
The goal of the current investigation was to assess the relationship between the occurrence of coronary artery disease (CAD) and the neutrophil-to-lymphocyte ratio (NLR). Additionally, we wanted to provide an appropriate NLR cut-off for the diagnosis of CAD.

Methods
A total of 124 individuals underwent coronary angiography, and they were split into two groups: category 1 (people without coronary artery disease) and category 2 (those with coronary artery disease).

Results
The findings revealed a statistically significant positive correlation (p< 0.05) between heightened concentrations of WBC, neutrophils, monocytes, NLR, hs-CRP, CPK-MB, and troponin I with the presence of the disease. Based on the findings of subcategory analysis, it was observed that the association exhibited a greater degree of significance (p< 0.04) within the male demographic and among individuals of advanced age. Of all the markers evaluated, the NLR exhibited the most robust predictive capacity for CAD, as indicated by the highest odds ratio of 1.395 (95% CI: 0.941–2.360; p = 0.04). The determined optimal cut-off value for the diagnosis of CAD was found to be 2.12 (p< 0.001), based on the NLR. The current investigation additionally identified a correlation between the NLR and other biochemical indicators, specifically hs-CRP, CPK-MB, and troponin I, utilizing quartile analysis.

Conclusion
The NLR is a straightforward diagnostic indicator that has demonstrated efficacy in the identification of CAD within the Indian population. A defined threshold of 2.12 has been established for optimal diagnostic accuracy.

Recommendations
The utilization of NLR, owing to its cost-effectiveness and convenient accessibility, can be utilized as an initial screening modality, particularly in smaller healthcare facilities, to assess the need for employing more expensive and time-consuming imaging techniques in the diagnosis of coronary artery disease.

INTRODUCTION
The association between inflammatory markers and coronary artery disease (CAD) has been well-established in medical literature [1]. Among the various cellular components, the subtypes of white blood cells (WBCs), specifically the Neutrophil-to-lymphocyte ratio (NLR), have been found to exert a notable influence on the processes of atherogenesis and atherothrombosis [2]. NLR serves as a cost-effective and easily accessible biomarker, which holds potential in evaluating the susceptibility to cardiovascular diseases alongside conventional markers. The study conducted in the Indian subcontinent offers substantiation for the utilization of NLR as a prognostic and diagnostic instrument for CAD and its related mortality [3].

An elevated NLR, regardless of the presence of concurrent biomarkers, is suggestive of an augmented long-term mortality hazard in individuals diagnosed with stable CAD as well as those encountering acute coronary syndrome (ACS) [4].

Attempts have been undertaken to establish appropriate cutoff values for the NLR in various patient populations; however, it is important to note that these values may exhibit variability based on factors such as age and ethnicity. Several studies employed different methods to classify patients based on their NLR. These methods included dividing patients into groups based on NLR intervals such as tertiles, quartiles, and quintiles. Additionally, some studies utilized specific NLR cutoff points, such as NLR ≥ 2.5, NLR ≥ 2.7, NLR ≥ 3, and NLR ≥ 4. Furthermore, a few studies even employed an NLR cutoff point of NLR ≥ 5 [5]. Furthermore, the aforementioned investigations procured blood specimens at various time points, including upon admission, prior to surgical intervention, throughout the duration of hospital stay, or an average of three measurements during the course of hospitalization.

The primary objective of this study is to examine the correlation between NLR and CAD among individuals of Indian descent. Furthermore, the aim is to ascertain the clinical utility of NLR as a diagnostic and prognostic indicator within this specific population. The present study additionally seeks to propose an optimal cutoff value for the NLR that can be effectively utilized in clinical practice within this particular cohort.

METHODS

Study Design
A prospective study was conducted.

Study setting
The study was conducted at the Sri Jayadeva Institute of Cardiovascular Science & Research, Bengaluru, for a time period spanning from March 2021 to January 2022.

Participants
The study involved 124 individuals of both genders.

Inclusion criteria
The study cohort comprised individuals who were undergoing coronary angiography (CAG), admitted to the hospital due to their initial presentation of chest pain, diagnosed with myocardial infarction, and those admitted as emergent cases.

RESULT

Exclusion criteria
People taking lipid-lowering drugs (statins), those who have undergone recent major surgery, and those diagnosed with rheumatic heart disease were excluded from the study.

Ethical considerations
Written informed consent was taken from all the participants.

Variables
Comprehensive medical histories and thorough physical examinations were performed. Investigational factors included age, gender, diabetes mellitus (DM), hypertension (HTN), smoking status, cardiac biomarkers (CK-MB, troponin I), high-sensitivity C-reactive protein (hs-CRP), differential count, WBC count, mean platelet volume (MPV), erythrocyte sedimentation rate (ESR), and red cell distribution width (RDW).

Blood specimens were obtained from the antecubital vein in order to conduct a comprehensive blood count and biochemical analysis. The study subjects were stratified into two cohorts according to angiographic results: Category 1 (n = 89; individuals lacking coronary artery disease - absence or insignificance of coronary artery disease) and Category 2 (n = 35; individuals presenting with coronary artery disease - stenosis exceeding 70%).

Biochemical Estimations
Blood specimens were obtained during the initial patient encounter in order to mitigate potential sources of bias. The laboratory evaluations encompassed the determination of the total leukocyte count, as well as the quantification of platelet count, neutrophil and lymphocyte counts, MPV, and RDW utilizing an automated blood cell counter. The laboratory analysis encompassed the assessment of Troponin I, CPK-MB, and hs-CRP. The measurement of ESR was performed. All of the aforementioned assessments were performed on a singular blood specimen.

Statistical Analysis
The statistical software package SPSS version 20 was utilized for the execution of data analysis. The statistical program was utilized to perform automated computations for the Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and WBC-to-platelet ratio (WBCPR). The study findings were reported in terms of quantitative variables, which were represented as the mean value along with the standard deviation. On the other hand, qualitative variables were conveyed in the form of percentages. A predetermined level of significance was established at $p < 0.05$.

Table 1: Demographic characteristics of participants

Characteristics	Percentage
Age (mean± SD)	57.35 ± 9.80
Male	71.0
Smoking	54.4
Family history of CAD	16.3
BMI (Kg/m^2) (mean± SD)	25.77 ± 3.17
Diabetes mellitus	27.4
Hypertension	62.7
Dyslipidemia	75.0

Table 1 shows the patients demographics. Table 2 presents a comparative analysis of baseline biochemical parameters observed in the two groups. Patients in Category 2, characterized by the presence of significant CAD, exhibited elevated levels of WBC count, neutrophils, and monocytes in comparison to patients in Category 1, who were not present with CAD. Patients in Category 1 exhibited a statistically significant ($p < 0.05$) decrease in their NLR with a mean value of 4.2 ± 2.8, in contrast to patients in Category 2 who had a higher NLR of 5.5 ± 3.5. Patients presenting with significant CAD exhibited a notably elevated RDW of 11.9 ± 1.5, in contrast to individuals lacking CAD, who displayed a lower RDW of 11.4 ± 2. Furthermore, patients classified under category 2 exhibited heightened concentrations of hs-CRP (3.2 ± 3.3 vs. 1.7 ± 4.1), CPK-MB (115.4 ± 151.5 vs. 50.4 ± 75.7), and troponin I (13 ± 17.8 vs. 6.2 ± 13.4) in comparison to patients categorized under category 1.

The NLR demonstrated a significant correlation with CAD in the male population and in individuals aged over 40 years. Patients in the CAD-positive group who had an ejection fraction (EF) less than 50% exhibited a marginally elevated mean NLR value of 5.45 ± 4.04, in contrast to those with an EF of 50% or greater, who had a mean NLR value of 4.65 ± 3.18.

Table 2: Comparison of Parameters between CAD-Free and CAD-Affected Populations (Category 1 vs. Category 2)

Variables	Categories	Mean	Standard deviation	P value	95% CI
WBC	Category 1	10165.6	3771.0	<0.0001	1.000
	Category 2	12035.8	4595.6		
Neutrophil	Category 1	7274.2	3923.8	<0.0001	1.164
	Category 2	9174.2	4531.8		
Lymphocyte	Category 1	2255.6	950.8	0.619	1.248
	Category 2	2181.0	921.5		
Eosinophil	Category 1	247.4	168.2	0.195	2.370
	Category 2	244.8	189.0		
Monocyte	Category 1	360.1	303.4	0.057	1.313
	Category 2	466.9	208.1		
Basophil	Category 1	0.6	5.5	0.652	0.970
	Category 2	1.2	12.8		
Platelet	Category 1	308340.0	120953.5	0.971	0.935
	Category 2	318687.4	159313.1		
MPV	Category 1	5.6	1.3	0.255	0.941
	Category 2	5.9	1.4		
NLR	Category 1	3.3	2.8	0.002	0.961
	Category 2	4.6	3.5		
PLR	Category 1	162.4	107.8	0.600	0.998
	Category 2	180.8	265.3		
RDW	Category 1	11.4	1.0	0.128	1.315
	Category 2	11.9	1.5		

hs-CRP	Category 1	1.7	3.2	0.381	1.108
	Category 2	3.2	3.3		
CPK-MB	Category 1	50.4	75.6	<0.0001	0.997
	Category 2	115.4	151.5		
Troponin I	Category 1	5.3	13.3	<0.0001	1.021
	Category 2	13.0	17.8		
ESR	Category 1	21.4	7.3	0.205	0.965
	Category 2	22.6	7.5		

A robust positive correlation was observed between elevated levels of WBC, neutrophils, monocytes, NLR, and troponin I, and the incidence of CAD. Among the various factors investigated, the NLR emerged as the most dependable prognostic indicator for CAD, exhibiting an odds ratio of 1.395 (95% CI: 0.941–2.360; p = 0.04). In order to evaluate the diagnostic precision, ROC analysis was employed, revealing that the negative likelihood ratio (NLR) exhibited the greatest AUC. Neutrophil count and troponin I demonstrated AUC values that closely trailed behind the NLR. According to the ROC analysis, a threshold of 2.12 (p< 0.001) was identified as an appropriate cutoff value for the NLR. This cutoff value demonstrated a sensitivity of 82.64% and a specificity of 62.46%. The analysis of quartiles further demonstrated a positive correlation between the levels of ACS markers and the mean value of NLR. Nevertheless, the analysis conducted using Pearson's correlation indicated that there was no noteworthy association observed between the neutrophil-to-lymphocyte ratio (NLR) and the left ventricle ejection fraction (LVEF) among patients diagnosed with CAD (coefficient of correlation: −0.08; p = 0.23).

DISCUSSION

The present study proposes a suggested cutoff value for the NLR that exhibits a notable degree of sensitivity and specificity in the accurate diagnosis of CAD among individuals of Indian descent. The NLR test, which is obtained from the enumeration of leukocytes in the peripheral blood, is a widely accessible and cost-effective diagnostic tool with global availability. Prior investigations have established a correlation between NLR and unfavorable prognoses in diverse cardiac pathologies [5, 6]. Extensive research has been conducted to evaluate its potential in the screening of individuals who are at risk of CAD across all stages of the condition. Numerous investigations conducted in India, akin to analogous studies conducted globally, have put forth suggested cutoff values for NLR in the diagnosis of CAD. In a study conducted by Fernando *et al*. (2015), it was proposed that a threshold of ≥2.26 be utilized for the purpose of identifying CAD in patients with diabetes [7].

The NLR has demonstrated potential in assessing coronary plaque burden and the severity of atherosclerosis, as validated by multiple imaging modalities including coronary angiography and CT scans [8]. In a study conducted by Sari *et al*. (2015), it was observed that the NLR exhibited the highest predictive capability for CAD when compared to other biomarkers [9]. In elderly individuals, it has been observed that those diagnosed with CAD exhibit elevated levels of NLR. A previously reported threshold of 1.96 has been identified specifically for geriatric populations [10]. When compared to the total WBC count, an increased NLR has also been linked to increased cardiac mortality in patients with stable CAD [11].

In the present investigation, the NLR emerged as the most robust prognostic indicator for CAD. Specifically, a threshold value of 2.12 (p< 0.001) was identified as appropriate for individuals of Indian descent, exhibiting superior diagnostic accuracy in terms of sensitivity and specificity when contrasted with prior scholarly inquiries.

Neutrophilia's involvement in CAD potentially encompasses the liberation of inflammatory mediators, which can inflict harm upon tissues. Lymphopenia, conversely, may arise as a consequence of elevated levels of steroids attributable to stress induced by CAD and heightened inflammation, thereby culminating in an augmented NLR among individuals with CAD [2, 12]. An increased NLR amalgamates the prognostic potential of both leukocyte subtypes into a singular risk factor, thereby conferring significant diagnostic utility.

The present study additionally investigated the potential relationship between NLR and left ventricular ejection fraction (LVEF). However, it is noteworthy to mention that no statistically significant correlation was observed, which can be attributed to the considerable proportion of patients exhibiting compromised LVEF. Additional investigation is warranted in this domain.

CONCLUSION

In conclusion, this study highlights the NLR as a potent diagnostic tool for CAD in individuals of Indian descent. Elevated NLR levels were strongly associated with CAD, providing valuable clinical insights. A suggested cutoff value of 2.12 offers high sensitivity and specificity for this population. NLR's ability to assess coronary plaque burden and atherosclerosis severity underscores its diagnostic value, with specific guidance for the Indian context. These findings align with global research, emphasizing NLR's role in CAD diagnosis and risk assessment. However, further investigation is needed regarding NLR and left ventricular ejection fraction (LVEF). Overall, this study enhances our understanding of CAD diagnosis and emphasizes NLR's potential as a valuable adjunctive marker for assessing CAD risk in individuals of Indian descent.

Limitations
The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendation
Considering the prompt and timely immunological response exhibited by neutrophils and lymphocytes, along with their circulation within the bloodstream, it is advisable to utilize the NLR as a biomarker for CAD. This recommendation is supported by the straightforward, readily quantifiable, and cost-effective nature of NLR assessment. In accordance with prior international recommendations, the study substantiates the utilization of NLR as an economically viable biomarker for prognosticating forthcoming cardiovascular risk.

Acknowledgement

List of abbreviations
CAD- Coronary artery disease
NLR- Neutrophil-to-lymphocyte ratio
WBC- White Blood cells
ACS- Acute coronary syndrome
DM- Diabetes mellitus
HTN- Hypertension
CK-MB- Cardiac biomarkers
Hs-CRP- high-sensitivity C-reactive protein
MPV- Mean platelet volume
ESR- Erythrocyte sedimentation rate
RDW- Red cell distribution width
PLR- Platelet-to-lymphocyte ratio

WBCPR- WBC-to-platelet ratio
EF- Ejection fraction
LVEF- Left ventricle ejection fraction
CAG- Coronary angiography

Source of funding

Conflict of interest

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