Research Article

# Leukocyte-Derived Inflammatory Indices (DNLR AND MLR) As Markers Of Isolated Coronary Artery Disease In Type 2 Diabetes Mellitus

Abin Varghese[1], Kuladeepa Ananda Vaidya[2]

[1] Research Scholar, Department of Pathology, Srinivas Institute of Medical Sciences and Research Centre, Mukka, Mangalore, Karnataka, India
[2] Professor, Department of Pathology, Srinivas Institute of Medical Sciences and Research Centre, Mukka, Mangalore, Karnataka, India
*Corresponding Author:
Abin Varghese
Research Scholar, Department of Pathology
Srinivas Institute of Medical Sciences and Research Centre
Mukka, Mangalore – 575018, Karnataka, India
Email: abinmlt@gmail.com
ORCID: 0000-0003-3728-8805

**Abstract**

**Background:** Type 2 diabetes mellitus (T2DM) is characterised by chronic inflammation, which is associated with increased cardiovascular risk. The derived neutrophil-to-lymphocyte ratio (dNLR) and monocyte-to-lymphocyte ratio (MLR) are inexpensive inflammatory biomarkers, but their comparative value in identifying isolated coronary artery disease (CAD) remains unclear.
Objective: To compare dNLR and MLR in T2DM patients with isolated CAD and those without vascular complications, and to evaluate their diagnostic performance.
**Methods:** This retrospective study included 414 T2DM patients with isolated CAD and 333 without macrovascular or microvascular complications. dNLR and MLR were calculated from routine complete blood counts. Group differences, ROC analysis, logistic regression, and likelihood-ratio testing were performed.
**Results:** Both dNLR and MLR were significantly higher in patients with isolated CAD. dNLR showed good diagnostic discriminant ability for isolated CAD (AUC 0.704), compared with MLR (AUC 0.587). After adjustment for age, sex, HbA1c, hypertension, dyslipidemia, and obesity, dNLR remained independently associated with isolated CAD (adjusted OR 3.50). Incorporating MLR into the adjusted dNLR model did not significantly improve model performance.
**Conclusion:** dNLR showed good discriminative ability and was an independent inflammatory marker for identifying isolated CAD in T2DM.dNLR outperformed MLR and provided greater diagnostic utility for identifying CAD.

**Keywords:** Type 2 diabetes mellitus; coronary artery disease; neutrophil-to-lymphocyte ratio; monocyte-to-lymphocyte ratio; inflammation; biomarker; ROC curve.

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with chronic, low-grade inflammation, which results in altered white blood cell subpopulations. This immune dysregulation contributes to endothelial dysfunction and atherosclerosis, leading to microvascular and macrovascular complications[1,2].Hyperglycemia and insulin resistance promote reactive oxygen species, AGE-RAGE signalling, and NF-κB activation. This results in endothelial activation, increased adhesion molecule expression, and monocyte recruitment into the arterial wall [3].Coronary artery disease in T2DM is an accelerated atherosclerotic process caused by the pathophysiological effects of diabetes on the vascular endothelium, resulting in more severe and unstable coronary lesions [4].dNLR (derived neutrophil-to-lymphocyte ratio) and MLR (monocyte-to-lymphocyte ratio) are inflammatory haematological indices used in CAD to reflect innate immune activation and relative lymphopenia. Higher values of these indices indicate more active atherosclerotic inflammation and are linked to cardiovascular mortality and disease severity among T2DM [5,6] .Most published studies have evaluated mixed vascular complications rather than isolated CAD. Therefore, the role of dNLR and MLR in patients with isolated CAD remains unclear. The present study addresses this gap by evaluating these indices in isolated CAD, after adjusting for established cardio-metabolic risk factors.
In this study, we explored differences in dNLR and MLR between T2DM patients with isolated CAD and those without other vascular complications. The study examined how these markers relate to glycemic control (HbA1c). Our analysis assessed their ability to distinguish between groups using ROC curves and determined whether combining the two markers provides additional diagnostic value beyond using either one alone, using adjusted logistic regression and nested-model comparison.

## 2. Methods

### 2.1 Study design and population

This retrospective, cross-sectional study compared two groups of patients with confirmed T2DM. Group A included patients with isolated CAD, positive for CAD but negative for other vascular complications. Group B consisted of patients without any complications, serving as controls. There were 414 patients in Group A and 333 in Group B.

### 2.2 Laboratory indices

dNLR was calculated as the absolute neutrophil count divided by the difference between the total white blood cell count and the absolute neutrophil count. MLR was calculated as the absolute monocyte count divided by the absolute lymphocyte count. Both indices were derived from a single complete blood count per patient.

### 2.3 Statistical analysis

Normality was assessed using the Shapiro–Wilk test. As dNLR and MLR were non-normally distributed, continuous variables were compared using the Mann–Whitney U test, and categorical variables using the chi-square or Fisher's exact test. Correlations with HbA1c were assessed using Spearman's rank correlation. Diagnostic performance was evaluated by ROC analysis, and AUCs were compared using DeLong's test. Logistic regression was used to assess independent associations with isolated CAD, with adjustment for age, sex, HbA1c, hypertension, dyslipidemia, and obesity. Model performance was compared using the likelihood-ratio test and the Akaike information criterion. Statistical significance was set at $p<0.05$. Analyses were performed using SAS version 9.4.

## 3. Results

### 3.1 Baseline characteristics

**Table 1.** Baseline characteristics of T2DM patients with isolated CAD (Group A) versus no complications (Group B).

| Variable | Group A (Isolated CAD) | Group B (No complications) |
|---|---|---|
| Age, years | 70 (63–76) | 66 (58–73) |
| Male sex, n (%) | 273 (65.9%) | 177 (53.2%) |
| HbA1c, % | 7.90 (6.83–9.20) | 7.50 (6.70–8.50) |

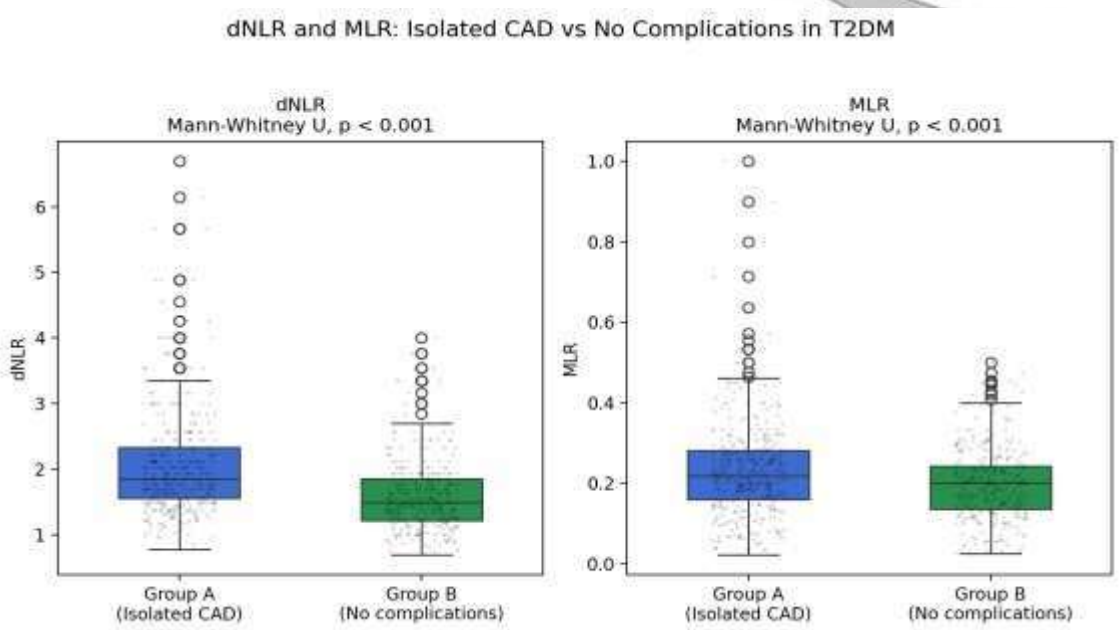
### 3.2 Primary comparison of dNLR and MLR

Both dNLR and MLR were significantly higher in patients with isolated CAD than in patients without complications (Table 2, Figure 1). The separation between groups was numerically and statistically larger for dNLR than for MLR.

**Table 2.** Comparison of dNLR and MLR between groups.

| Variable | N (A/B) | Group A (Isolated CAD) | Group B (No complications) | Test | Statistic | p |
|---|---|---|---|---|---|---|
| dNLR | 414/333 | 1.86 (1.56–2.33) | 1.50 (1.22–1.86) | Mann-Whitney U | U = 97,070.5 | <0.001 |
| MLR | 414/333 | 0.22 (0.16–0.28) | 0.20 (0.14–0.24) | Mann-Whitney U | U = 80,925.0 | <0.001 |

**Figure 1.** Distribution of dNLR and MLR by group.




**3.3 Correlation with HbA1c**

dNLR showed a weak but statistically significant positive correlation with HbA1c (Spearman r = 0.162, p<0.001). MLR showed no significant correlation with HbA1c (r = −0.033, p = 0.405), indicating that its distribution was largely independent of glycemic control at the time of sampling.

**3.4 Diagnostic performance**

The dNLR demonstrated acceptable ability to distinguish isolated CAD, with an AUC of 0.704 (95% CI 0.667–0.741), and an optimal cutoff at 1.564, yielding a sensitivity of 71.7% and specificity of 57.7%. In comparison, MLR showed a lower discriminative power, with an AUC of 0.587 (95% CI 0.546–0.628), and a cutoff at 0.244, with sensitivity of 41.1% and specificity of 75.4%. DeLong's test confirmed that dNLR performed significantly better than MLR (p<0.001).

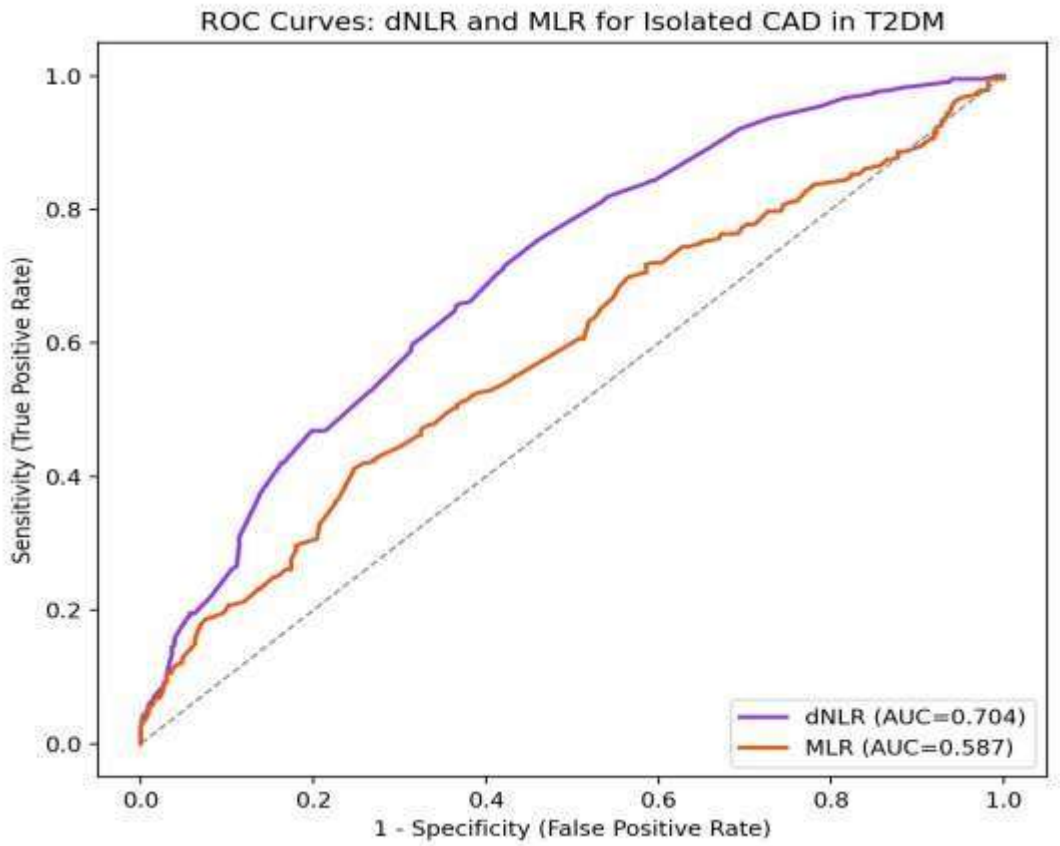
**Table 3:** ROC curve analysis for dNLR and MLR

| Marker | AUC | 95% CI | Optimal cutoff (Youden) | Sensitivity | Specificity | Youden J |
|---|---|---|---|---|---|---|
| dNLR | 0.704 | 0.667–0.741 | 1.564 | 0.717 | 0.577 | 0.294 |
| MLR | 0.587 | 0.546–0.628 | 0.244 | 0.411 | 0.754 | 0.164 |

**Table 4:** DeLong's test comparing the two AUC's

| Comparison | AUC difference | DeLong p |
|---|---|---|
| dNLR vs MLR | 0.117 | <0.001 |

**Figure 2:** ROC curves for dNLR and MLR in predicting isolated CAD status




**3.5 Logistic regression**

In unadjusted analyses, both dNLR and MLR were significantly associated with isolated CAD ($p<0.001$ for both). After adjustment for age, sex, HbA1c, hypertension, dyslipidemia, and obesity, both markers remained independent predictors of isolated CAD, with dNLR showing a stronger and more consistent association.

**Table 5.** Logistic regression: Model 1, unadjusted (marker alone); Model 2, adjusted for age, sex, HbA1c, hypertension, dyslipidemia, and obesity

| Model | Variable | OR / aOR (95% CI) | P | AIC |
|---|---|---|---|---|
| Model 1 (unadjusted) | dNLR | 3.27 (2.44–4.39) | <0.001 | 943.09 |
| Model 2 (adjusted) | dNLR | 3.50 (2.45–5.00) | <0.001 | 750.09 |
| Model 1 (unadjusted) | MLR | 29.51 (6.59–132.26) | <0.001 | 1009.03 |
| Model 2 (adjusted) | MLR | 17.51 (2.95–103.90) | 0.002 | 804.52 |

**3.6 Model comparison: dNLR alone, MLR alone, and combined**

Likelihood-ratio testing showed that adding dNLR to the MLR model significantly improved model performance in both unadjusted and adjusted analyses (both $p<0.001$). In contrast, adding MLR to the dNLR model provided only a small improvement before adjustment and no significant benefit after adjustment, indicating that dNLR contributed most of the predictive information for isolated CAD.

**Table 6**. Nested likelihood-ratio test comparisons between single-marker and combined models.

| Comparison | $\chi^2$ | df | p | ΔAIC |
|---|---|---|---|---|
| Combined vs dNLR-only (unadjusted) | 4.687 | 1 | 0.030 | 2.69 |
| Combined vs MLR-only (unadjusted) | 70.626 | 1 | <0.001 | 68.63 |
| Combined vs dNLR-only (adjusted) | 1.448 | 1 | 0.229 | −0.55 |
| Combined vs MLR-only (adjusted) | 55.876 | 1 | <0.001 | 53.88 |

## 4. Discussion

In this study, among T2DM patients with isolated CAD and those without macro- or microvascular complications, dNLR emerged as the more powerful leukocyte-derived index. dNLR demonstrated acceptable discrimination on its own, with an AUC of 0.70. Furthermore, dNLR showed a strong and independent association with isolated CAD even after adjusting for other risk factors, with an adjusted odds ratio of 3.50 and a p-value of less than 0.001. Its contribution to the model's fit remained significant despite full covariate adjustments. MLR was significantly higher in patients with isolated CAD and remained independently associated with it in an adjusted single-marker model. However, MLR did not add meaningful discriminative value when combined with dNLR and after adjusting for age, sex, HbA1c, hypertension, dyslipidemia, and obesity.

Our findings are partially consistent with previous studies showing that leukocyte-derived inflammatory ratios are associated with CAD in diabetes. dNLR has previously been associated with post-PCI mortality and major adverse cardiovascular events across large coronary cohorts [7]. Also, the albumin-dNLR composite score has similarly predicted long-term mortality after percutaneous intervention[8].The comparatively weaker and less independent performance of MLR mirrors mixed findings in the broader literature. Previous studies have consistently shown that elevated MLR is associated with coronary artery disease. Ji et al. found that MLR independently predicted the presence of CAD and was associated with more severe coronary lesions, with a cutoff value of 0.25. Similarly, a large study involving 12,093 patients with coronary heart disease reported that higher MLR had the strongest association with carotid plaque burden, highlighting its value as a simple marker of systemic atherosclerosis [6,9]. However, our study specifically evaluated patients with isolated CAD in type 2 diabetes and found that, although MLR remained an independent predictor, its discriminative performance was lower than that of dNLR. Neutrophils and monocytes both participate directly in atherosclerotic plaque formation, endothelial activation, and plaque destabilisation, while relative lymphopenia is associated with stress-related immune dysregulation and intensified vascular inflammation [10,11].dNLR, by incorporating both neutrophil elevation and lymphocyte depletion in a single ratio, may capture this combined signal more efficiently than MLR. This might help explain why dNLR remained independently significant in our adjusted models, whereas the impact of MLR was no longer evident after adjustment. Our results suggest that, of the two haematological parameters, dNLR is the more clinically promising for risk stratification towards isolated CAD in T2DM. MLR appears limited in this specific context once dNLR and standard risk factors are already available.

## 5. Conclusion

Among leukocyte-derived inflammatory indices, the derived neutrophil-to-lymphocyte ratio (dNLR) emerged as a significantly discriminative marker of isolated coronary artery disease (CAD) in patients with T2DM, compared with the monocyte-to-lymphocyte ratio (MLR). dNLR maintained a strong, independent association even after adjusting for factors such as age, sex, glycemic control, hypertension, dyslipidemia, and obesity. MLR was elevated in cases of isolated CAD and showed an independent association when analysed alone. When combined with dNLR, MLR added no significant discriminative value. These results support further prospective studies to evaluate dNLR as a cost-effective cardiovascular risk assessment tool in T2DM.

## 6. Limitations

Because this is a retrospective cross-sectional study, causal relationships cannot be established. Only a single CBC measurement was available for each patient, preventing assessment of temporal changes. Residual confounding from unmeasured factors may also have influenced the findings. Established inflammatory markers such as high-

sensitivity C-reactive protein and the conventional neutrophil-to-lymphocyte ratio were not included for comparison.

## 7. Conflict of interest

The authors declare no conflicts of interest. The authors received no financial support or other benefits that could have influenced the conduct or reporting of this study.

## 8. Declarations

The study was conducted following approval from the Institutional Ethics Committee and adhered to the principles of the Declaration of Helsinki.

## 9. References


1. Nedosugova LV, Markina YV, Bochkareva LA, Kuzina IA, Petunina NA, Yudina IY, et al. Inflammatory Mechanisms of Diabetes and Its Vascular Complications. Biomedicines. 2022 May 18;10(5):1168. doi:10.3390/biomedicines10051168 PubMed PMID: 35625904; PubMed Central PMCID: PMC9138517.
2. Pezhman L, Tahrani A, Chimen M. Dysregulation of Leukocyte Trafficking in Type 2 Diabetes: Mechanisms and Potential Therapeutic Avenues. Front Cell Dev Biol. 2021 Feb 22;9:624184. doi:10.3389/fcell.2021.624184
3. Katakami N. Mechanism of Development of Atherosclerosis and Cardiovascular Disease in Diabetes Mellitus. J Atheroscler Thromb. 2018;25(1):27–39. doi:10.5551/jat.RV17014
4. Naito R. Coronary artery disease in type 2 diabetes mellitus: Recent treatment strategies and future perspectives. WJC. 2015;7(3):119. doi:10.4330/wjc.v7.i3.119
5. Fan W, Zhang Y, Gao X, Liu Y, Shi F, Liu J, et al. The Prognostic Value of a Derived Neutrophil-Lymphocyte Ratio in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. Clin Appl Thromb Hemost. 2021 Jan 1;27:10760296211034579. doi:10.1177/10760296211034579
6. Ji H, Li Y, Fan Z, Zuo B, Jian X, Li L, et al. Monocyte/lymphocyte ratio predicts the severity of coronary artery disease: a syntax score assessment. BMC Cardiovasc Disord. 2017 Dec;17(1):90. doi:10.1186/s12872-017-0507-4
7. Liu GQ, Zhang WJ, Shangguan JH, Zhu XD, Wang W, Guo QQ, et al. Association of Derived Neutrophil-To-Lymphocyte Ratio With Prognosis of Coronary Heart Disease After PCI. Front Cardiovasc Med. 2021 Sep 17;8:705862. doi:10.3389/fcvm.2021.705862
8. Xiu WJ, Yang HT, Zheng YY, Wu TT, Hou XG, Jiang ZH, et al. ALB-dNLR Score Predicts Mortality in Coronary Artery Disease Patients After Percutaneous Coronary Intervention. Front Cardiovasc Med. 2022 Mar 15;9:709868. doi:10.3389/fcvm.2022.709868
9. Ma M, Liu Y, Wang L, Yang R, Li Z, Gao S, et al. Relationship Between Monocyte-to-Lymphocyte Ratio as Well as Other Leukocyte-Derived Ratios and Carotid Plaques in Patients with Coronary Heart Disease: A RCSCD-TCM Study. JIR. 2022 Sep;Volume 15:5141–56. doi:10.2147/JIR.S375759
10. Chistiakov DA, Grechko AV, Myasoedova VA, Melnichenko AA, Orekhov AN. The role of monocytosis and neutrophilia in atherosclerosis. J Cellular Molecular Medi. 2018 Mar;22(3):1366–82. doi:10.1111/jcmm.13462
11. Suzuki T, Futami-Suda S, Igari Y, Watanabe K, Ouchi M, Suzuki K, et al. Low-molecular-weight lipoprotein (a) and low relative lymphocyte concentration are significant and independent risk factors for coronary heart disease in patients with type 2 diabetes mellitus: Lp(a) phenotype, lymphocyte, and coronary heart disease. Lipids Health Dis. 2013 Dec;12(1):31. doi:10.1186/1476-511X-12-31