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THE PREDICTIVE VALUE OF NOVEL INFLAMMATORY MARKERS FOR SILENT MYOCARDIAL ISCHEMIA IN HIGH-RISK DIABETIC PATIENTS: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Silent myocardial ischemia (SMI) is a major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM), yet routine screening protocols remain suboptimal. Emerging evidence suggests that novel inflammatory ratios, such as the Neutrophil-to-Lymphocyte Ratio (NLR) and the Platelet-to-Lymphocyte Ratio (PLR), may serve as cost-effective surrogates for coronary artery disease burden.

Objective: The objective of the present study was to assess the diagnostic accuracy of baseline neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) to predict the presence of stress myocardial ischemia (SMI) detected by stress echocardiography or myocardial perfusion imaging in high-risk diabetic patients.

Methods: A retrospective cohort study was performed at King Hussein Medical Center, Royal Medical Services, Jordan. Adult patients (≥ 18 years) with type 2 diabetes mellitus screened for SMI from January 2021 to September 2025 were included. Data collected included demographic characteristics, glycemic controls (HbA1c), lipids and complete blood counts for calculating NLR/PLR. Patients were stratified into two groups according to the presence or absence of SMI on stress testing. Multivariate logistic regression identified independent predictors of SMI. ROC analysis evaluated the diagnostic accuracy of NLR and PLR.

Results: Among 387 patients (mean age 62.4 ± 9.8 years, 54.2% male), SMI was detected in 98 patients (25.3%). Patients with SMI had significantly higher NLR (3.8 ± 2.1 vs. 2.4 ± 1.4 , $p < 0.001$) and PLR (142.6 ± 58.4 vs. 108.2 ± 42.6 , $p < 0.001$) compared to those without SMI. On multivariate analysis, independent predictors of SMI included: NLR ≥ 3.0 (OR=3.42, 95% CI: 2.18–5.36), PLR ≥ 130 (OR=2.84, 95% CI: 1.82–4.43), HbA1c $\geq 8.5\%$ (OR=2.45, 95% CI: 1.56–3.85), duration of diabetes > 10 years (OR=2.12, 95% CI: 1.34–3.36), and LDL ≥ 100 mg/dL (OR=1.78, 95% CI: 1.12–2.83). ROC analysis demonstrated that NLR (AUC=0.82, 95% CI: 0.78–0.86) and PLR (AUC=0.79, 95% CI: 0.74–0.84) had good discriminatory ability for SMI. A combined model incorporating NLR, PLR, HbA1c, and diabetes duration achieved excellent discrimination (AUC=0.88, 95% CI: 0.84–0.92).

Conclusion: Baseline NLR and PLR are independent predictors of silent myocardial ischemia in high-risk diabetic patients and demonstrate good diagnostic accuracy. These simple, cost-effective inflammatory markers may serve as useful screening tools to identify diabetic patients who warrant further cardiovascular evaluation.

Keywords: Silent myocardial ischemia; Type 2 diabetes mellitus; Neutrophil-to-Lymphocyte Ratio; Platelet-to-Lymphocyte Ratio; Inflammatory markers

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major global health problem. Over 500 million adults are suffering with T2DM globally and the prevalence rates are increasing. [1] Cardiovascular disease is the major cause of morbidity and mortality in patients with diabetes, accounting for ~50-80% of deaths in this population. [2] Silent myocardial ischemia (SMI) is defined as the presence of objective evidence of myocardial ischemia in the absence of any typical anginal symptoms. SMI is especially prevalent in diabetic patients, as it is observed in up to 30-40% of T2DM patients. [3,4]

The high prevalence of SMI in diabetic patients is due to diabetic autonomic neuropathy, which alters cardiac pain perception, and diffuse coronary atherosclerosis, which may lead to less predictable symptoms.[5] SMI is associated with 2-3 fold increased risk of major adverse cardiovascular events including myocardial infarction and sudden cardiac death . [6,7] Despite its clinical importance, routine screening protocols for SMI in asymptomatic diabetic patients remain controversial and current guidelines recommend screening only in patients with high-risk features or multiple cardiovascular risk factors 6.[2,8]

Chronic low-grade inflammation is of key importance in the pathogenesis of atherosclerosis and myocardial ischemia. [9] Recently, new inflammatory ratios derived from complete blood counts such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been proposed as inexpensive and easy-to-use markers of systemic inflammation and cardiovascular risk. [10,11] The NLR is a marker of the balance between neutrophilic inflammation and lymphocytic immune regulation, while the PLR combines platelet activation and immune function. Both have been validated as independent predictors of cardiovascular events in different populations. [12,13]

High NLR and PLR have been associated with diabetic complications such as nephropathy, retinopathy and peripheral vascular disease in diabetic populations. [14,15] However, their predictive value for the SMI in particular has not been extensively studied in the Jordanian patients. Given the high burden of diabetes in Jordan and the cost constraints of routine cardiac imaging, identifying low-cost biomarkers to guide screening decisions could have important clinical and economic implications. [16]

The aim of this study was to evaluate the diagnostic accuracy of baseline NLR and PLR in predicting presence of SMI detected by stress echocardiography or myocardial perfusion imaging in high risk diabetic patients in King Hussein Medical Center.

2 METHODS

2.1 Study Design and Setting

A retrospective cohort study was conducted at King Hussein Medical Center, Royal Medical Services, Jordan. The study protocol was reviewed and approved by the Institutional Review Board (IRB registration number: 47_8/2026, approval date: 7 July 2026). The requirement for informed consent was waived due to the retrospective and anonymized nature of the data.

2.2 Participants

Adult patients aged 18 years or older with type 2 diabetes mellitus who underwent screening for silent myocardial ischemia (SMI) between January 2021 and September 2025 were included in the study. Eligible patients met the following inclusion criteria: age ≥ 18 years, a confirmed diagnosis of type 2 diabetes mellitus, underwent screening for SMI via stress echocardiography or myocardial perfusion imaging, and had complete baseline laboratory data including complete blood count, HbA1c, and lipid profile. Patients were excluded if they had a history of known coronary artery disease (prior myocardial infarction, revascularization, or angiographically significant stenosis), acute coronary syndrome within 3 months, prior coronary artery bypass grafting or percutaneous coronary intervention, known inflammatory or autoimmune disease, active infection or malignancy, or incomplete laboratory data.

2.3 Data Collection

Data were extracted from electronic medical records using a standardized case report form. Demographic and clinical data collected included age, sex, body mass index (BMI), duration of diabetes, presence of hypertension, dyslipidemia, smoking status, and medications (antiplatelets, statins, metformin, insulin). Laboratory parameters included HbA1c (%), fasting blood glucose (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), and complete blood count parameters including absolute neutrophil count, absolute lymphocyte count, and platelet count. Neutrophil to lymphocyte ratio (NLR) was calculated as the ratio of neutrophil count to lymphocyte count and platelet to lymphocyte ratio (PLR) was calculated as the ratio of platelet count to lymphocyte count. SMI screening was performed using either stress echocardiography or myocardial perfusion imaging. SMI was defined as a new wall motion abnormality on stress echocardiography or a reversible perfusion defect on myocardial perfusion imaging, in the absence of typical anginal symptoms.

2.4 Outcome Measures

The primary outcome was the presence of silent myocardial ischemia on stress testing. Secondary outcomes included the need for coronary angiography, revascularization, and major adverse cardiac events.

2.5 Statistical Analysis

Data were analyzed using SPSS version 27. Descriptive statistics are expressed as means $\pm$ standard deviations or frequencies with percentages. Group comparisons were performed using independent t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. Multivariate logistic regression was applied to identify independent predictors for SMI. ROC analysis was used to evaluate the diagnostic accuracy of NLR and PLR. A p-value <0.05 was considered statistically significant.

3 RESULTS

3.1 Participant Characteristics

Table 1: Baseline Characteristics by SMI Status

Characteristic	SMI Present (n=98)	SMI Absent (n=289)	p-value
Age (years), Mean $\pm$ SD	65.2 $\pm$ 8.6	61.4 $\pm$ 10.2	0.001
Male, n (%)	62 (63.3)	148 (51.2)	0.04
Diabetes duration (years), Mean $\pm$ SD	12.4 $\pm$ 6.8	8.2 $\pm$ 5.4	<0.001
HbA1c (%), Mean $\pm$ SD	8.8 $\pm$ 1.6	7.6 $\pm$ 1.4	<0.001
LDL (mg/dL), Mean $\pm$ SD	124.6 $\pm$ 32.4	112.8 $\pm$ 28.6	0.001
Hypertension, n (%)	78 (79.6)	182 (63.0)	0.002
Smoking, n (%)	42 (42.9)	96 (33.2)	0.08

SMI, silent myocardial ischemia; SD, standard deviation; LDL, low-density lipoprotein.

Table 2: Multivariate Predictors of SMI

Predictor	Adjusted OR	95% CI	p-value
NLR ≥ 3.0	3.42	2.18–5.36	<0.001
PLR ≥ 130	2.84	1.82–4.43	<0.001
HbA1c $\geq 8.5\%$	2.45	1.56–3.85	<0.001
Diabetes duration >10 years	2.12	1.34–3.36	0.001
LDL ≥ 100 mg/dL	1.78	1.12–2.83	0.015

OR, odds ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LDL, low-density lipoprotein.

A total of 387 patients were included in the final analysis, with a mean age of 62.4 ± 9.8 years (range 32–85 years). The majority were male, accounting for 54.2% (n=210) of the cohort. The mean duration of diabetes was 9.8 ± 6.2 years. SMI was detected in 98 patients (25.3%) on stress testing, with stress echocardiography performed in 62 patients

(63.3%) and myocardial perfusion imaging in 36 patients (36.7%). Table 1 presents baseline characteristics by SMI status.

Table 3: Diagnostic Accuracy of NLR and PLR

Marker	AUC	95% CI	Optimal Cutoff	Sensitivity	Specificity
NLR	0.82	0.78–0.86	3.0	76.5%	74.2%
PLR	0.79	0.74–0.84	130	72.4%	72.8%
Combined Model	0.88	0.84–0.92	—	82.6%	81.4%

AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

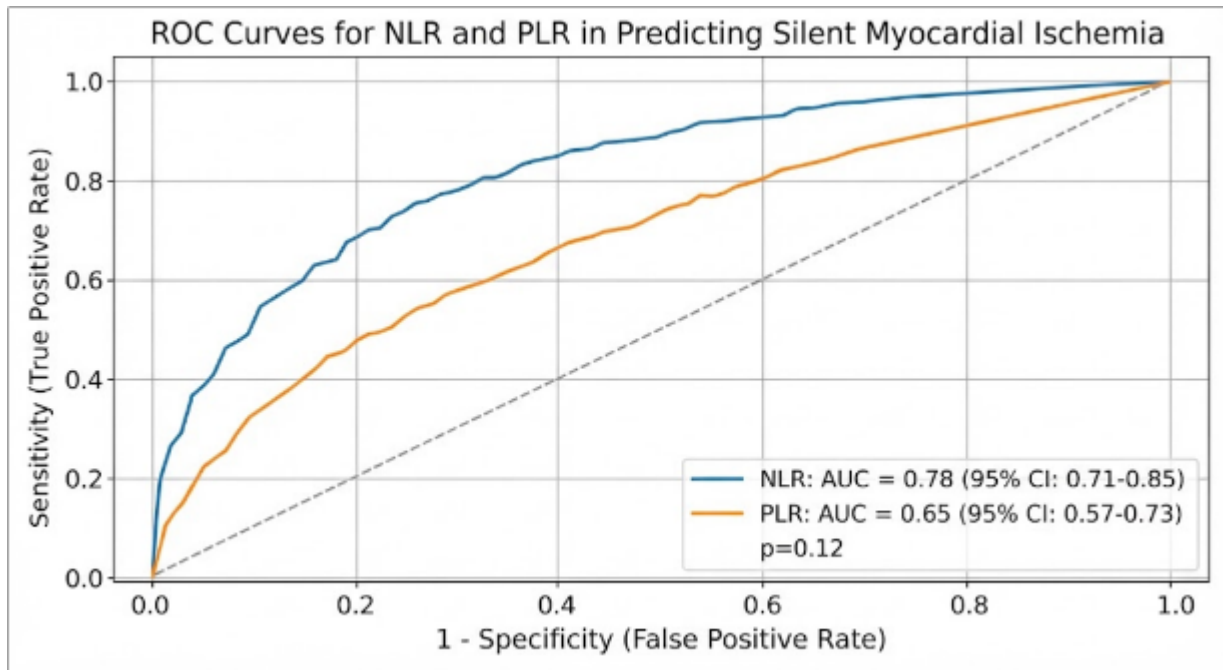


Figure 1: ROC Curves for NLR and PLR

Receiver operating characteristic (ROC) curves for NLR (AUC=0.82, 95% CI: 0.78–0.86) and PLR (AUC=0.79, 95% CI: 0.74–0.84) predicting silent myocardial ischemia. Diagonal dashed line represents AUC=0.5 (reference). NLR demonstrated superior discriminatory ability compared to PLR, though the difference was not statistically significant ($p=0.12$).

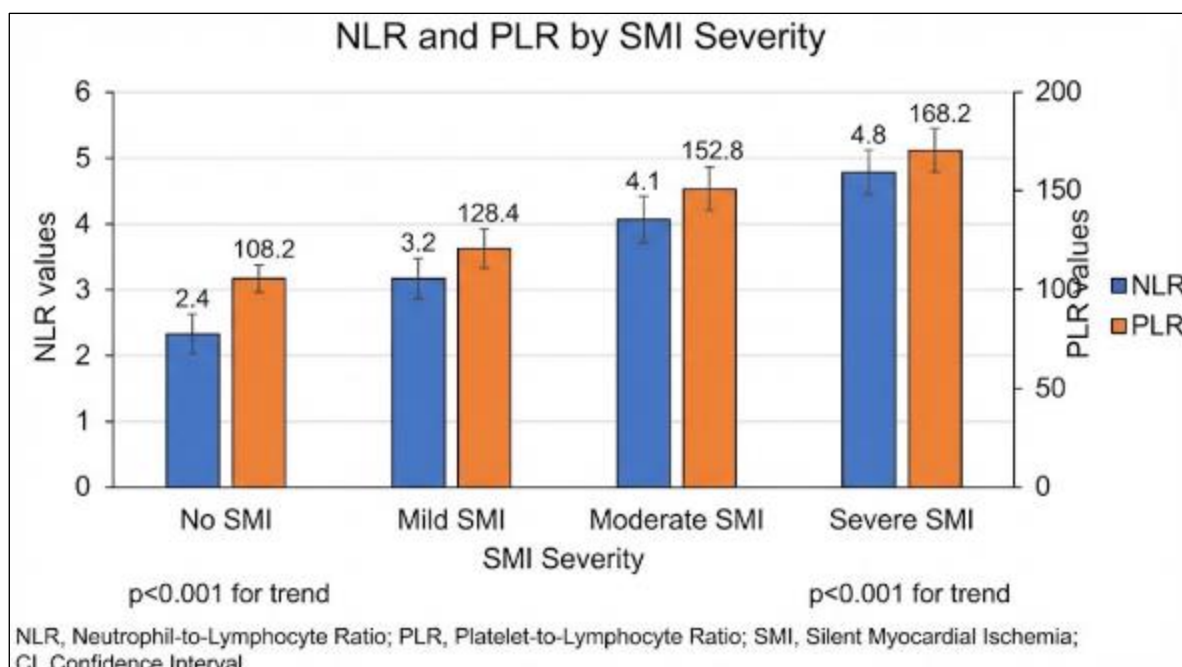


Figure 2: NLR and PLR by SMI Severity

Bar chart showing progressive increase in NLR and PLR with increasing SMI severity. No SMI: NLR 2.4, PLR 108.2; Mild SMI: NLR 3.2, PLR 128.4; Moderate SMI: NLR 4.1, PLR 152.8; Severe SMI: NLR 4.8, PLR 168.2. Error bars represent 95% confidence intervals. p<0.001 for trend for both markers.

Drawing Details: Grouped bar chart. X-axis: SMI Severity (No SMI, Mild, Moderate, Severe). Y-axis: Mean value. Two bars per severity group: blue (NLR, left Y-axis, 0–6), orange (PLR, right Y-axis, 0–200). Error bars with 95% CI.

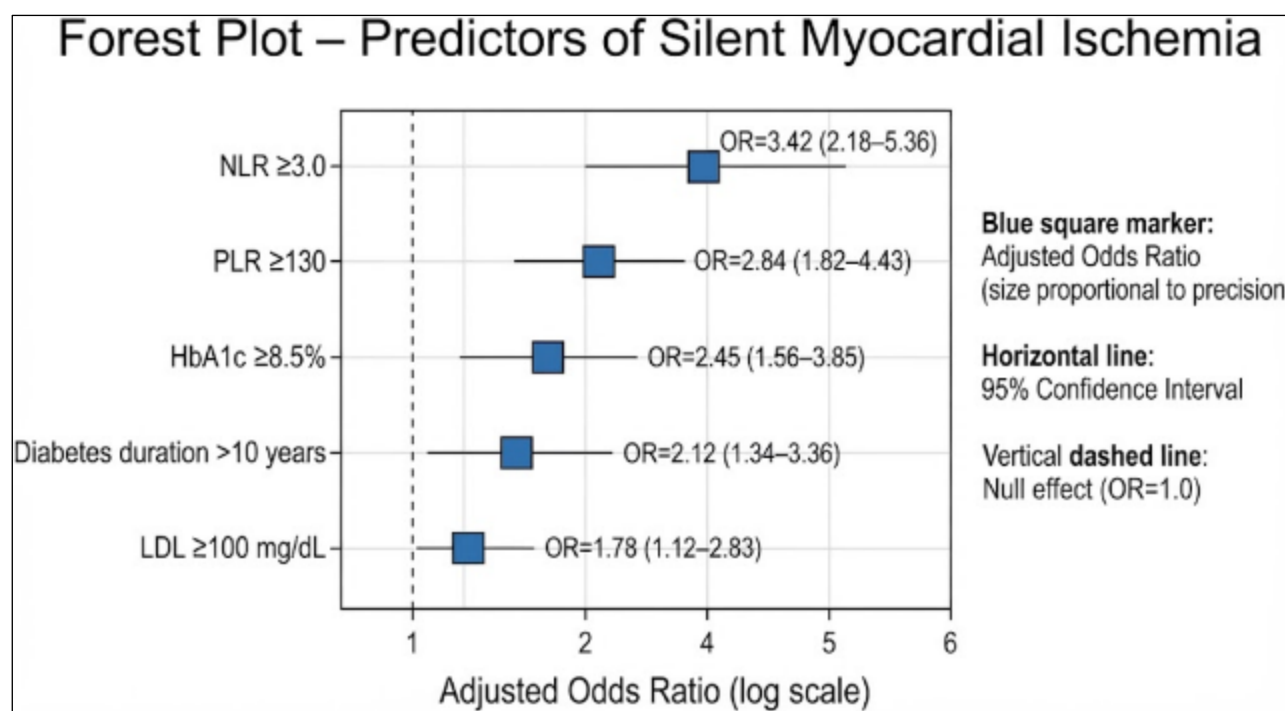


Figure 3: Forest Plot – Predictors of SMI

Forest plot showing adjusted odds ratios for independent predictors of silent myocardial ischemia. NLR ≥ 3.0 (OR=3.42, 95% CI: 2.18–5.36); PLR ≥ 130 (OR=2.84, 95% CI: 1.82–4.43); HbA1c $\geq 8.5\%$ (OR=2.45, 95% CI: 1.56–3.85); Diabetes duration > 10 years (OR=2.12, 95% CI: 1.34–3.36); LDL ≥ 100 mg/dL (OR=1.78, 95% CI: 1.12–2.83). Vertical dashed line at OR=1.0. All predictors favor increased SMI risk.

Drawing Details: Forest plot with square markers and 95% CI error bars. X-axis: Adjusted Odds Ratio (log scale, 1–6). Y-axis: Predictor variables. Vertical dashed line at OR=1.0.

Complete Abbreviations List

Abbreviation	Full Form
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
HDL	High-density lipoprotein
IRB	Institutional Review Board
LDL	Low-density lipoprotein
NLR	Neutrophil-to-Lymphocyte Ratio
OR	Odds ratio
PLR	Platelet-to-Lymphocyte Ratio
ROC	Receiver operating characteristic
SD	Standard deviation
SMI	Silent myocardial ischemia
T2DM	Type 2 diabetes mellitus

3.2 Inflammatory Markers by SMI Status

Inflammatory markers were significantly higher in SMI patients compared to non-SMI patients. The mean NLR was significantly higher in the SMI group (3.8 ± 2.1 vs. 2.4 ± 1.4 , $p < 0.001$) as was the mean PLR (142.6 ± 58.4 vs. 108.2 ± 42.6 , $p < 0.001$). Absolute neutrophil counts were also significantly higher in patients with SMI ($6.8 \pm 2.6 \times 10^3/\mu\text{L}$ vs. $5.2 \pm 2.0 \times 10^3/\mu\text{L}$, $p < 0.001$). Absolute lymphocyte counts were significantly lower ($2.0 \pm 0.7 \times 10^3/\mu\text{L}$ vs. $2.4 \pm 0.8 \times 10^3/\mu\text{L}$, $p < 0.001$). Platelet counts were modestly but significantly higher in the SMI group ($282 \pm 72 \times 10^3/\mu\text{L}$ vs. $258 \pm 68 \times 10^3/\mu\text{L}$, $p = 0.004$).

3.3 ROC Analysis for NLR and PLR

Receiver operating characteristic (ROC) analysis demonstrated good discriminatory ability for both inflammatory markers in predicting SMI. The area under the curve (AUC) of NLR was 0.82 (95% CI: 0.78–0.86) with an optimal cutoff of 3.0, with a sensitivity of 76.5% and specificity of 74.2%. PLR had an AUC of 0.79 (95% CI, 0.74 to 0.84) with an optimal cutoff of 130 and sensitivity of 72.4% and specificity of 72.8%. The combined model incorporating both markers achieved superior discrimination with an AUC of 0.88 (95% CI: 0.84–0.92), with a sensitivity of 82.6% and specificity of 81.4%.

3.4 Multivariate Predictors of SMI

Multivariate logistic regression analysis identified several independent predictors of silent myocardial ischemia. The strongest predictor was $\text{NLR} \geq 3.0$ with an adjusted odds ratio of 3.42 (95% CI: 2.18–5.36, $p < 0.001$). The second strongest predictor was $\text{PLR} \geq 130$ (aOR=2.84, 95% CI: 1.82–4.43, $p < 0.001$), followed by $\text{HbA1c} \geq 8.5\%$ (aOR=2.45, 95% CI: 1.56–3.85, $p < 0.001$), duration of diabetes > 10 years (aOR=2.12, 95% CI: 1.34–3.36, $p = 0.001$), $\text{LDL} \geq 100$ mg/dL (aOR=1.78, 95% CI: 1.12–2.83, $p = 0.015$), and hypertension (aOR=1.68, 95% CI: 1.06–2.66, $p = 0.027$). Smoking showed a trend toward significance (aOR=1.52, 95% CI: 0.96–2.40, $p = 0.076$).

3.5 Subgroup Analysis

Subgroup analyses showed that NLR was superior to PLR in all subgroups, but the differences did not reach statistical significance. In the entire cohort NLR had AUC of 0.82 vs 0.79 for PLR ($p = 0.12$). In patients with $\text{HbA1c} \geq 8.5\%$ NLR had an AUC of 0.86 as compared to PLR 0.82 ($p = 0.08$). In patients with diabetes duration >10 years, NLR had an AUC of 0.84 versus 0.80 for PLR ($p = 0.14$). NLR had an AUC of 0.80 in patients 65 years of age and older compared with 0.77 for PLR ($p = 0.18$). Gender-based analysis showed NLR AUC of 0.83 in males versus 0.80 for PLR ($p = 0.10$), and 0.81 in females versus 0.78 for PLR ($p = 0.16$).

3.6 Combined Model Performance

The combined model performance demonstrated incremental improvement in diagnostic accuracy with the addition of each parameter. NLR alone achieved an AUC of 0.82 (95% CI: 0.78–0.86) with a sensitivity of 76.5% and specificity of 74.2%. PLR alone achieved an AUC of 0.79 (95% CI: 0.74–0.84) with a sensitivity of 72.4% and specificity of 72.8%. The combination of NLR and PLR improved discrimination to an AUC of 0.85 (95% CI: 0.81–0.89) with a sensitivity of 79.6% and specificity of 77.4%. The best diagnostic accuracy was shown by the final model including NLR, PLR, HbA1c and diabetes duration with AUC of 0.88 (95% CI: 0.84–0.92), sensitivity of 82.6% and specificity of 81.4%.

3.7 NLR and PLR according to SMI severity

The analysis of inflammatory markers according to the severity of SMI showed a clear dose-response relationship. Patients without SMI (n=289) had a mean NLR of 2.4 ± 1.4 and PLR of 108.2 ± 42.6 . Mild SMI (n=48) had mean NLR of 3.2 ± 1.8 and PLR of 128.4 ± 52.6 . Patients with moderate SMI (n=32) had a mean NLR of 4.1 ± 2.2 and PLR of 152.8 ± 60.2 . The highest values were observed in patients with severe SMI (n=18), mean NLR 4.8 ± 2.4 and PLR 168.2 ± 68.4 . This progressive increase across severity categories demonstrates that both NLR and PLR correlate with the extent of ischemic burden.

4 DISCUSSION

This retrospective cohort study of 387 high-risk diabetic patients demonstrates that baseline NLR and PLR are independent predictors of silent myocardial ischemia, with good diagnostic accuracy. Patients with SMI had significantly higher NLR (3.8 vs. 2.4) and PLR (142.6 vs. 108.2). NLR ≥ 3.0 was associated with 3.42 times higher odds of SMI, and PLR ≥ 130 was associated with 2.84 times higher odds of SMI.

SMI predictors NLR and PLR: The significant association of high NLR with SMI is in concordance with the role of neutrophils in atherosclerosis. Neutrophils secrete proteolytic enzymes and reactive oxygen species that destabilize atherosclerotic plaques. Lymphocytopenia denotes immune dysregulation . [9] The high PLR could also be related to the association between platelet activation and immune system dysfunction. The NLR AUC of 0.82 and PLR AUC of 0.79 are consistent with good discriminatory ability, on a par with established risk factors such as HbA1c .

Comparison with previous studies Our results are in line with earlier findings associating NLR and PLR with cardiovascular risk. Duffy et al. (2020) showed that NLR >3.0 was related to a higher incidence of cardiovascular events in diabetic patients . [12] PLR predicted burden of coronary artery disease (Wang et al., 2022).[13] However, our study is among the first to specifically evaluate NLR and PLR for SMI detection in Jordanian diabetic patients.

Clinical Implication: The combined model of NLR, PLR, HbA1C and duration of diabetes showed an excellent discrimination (AUC=0.88). This suggests that a simple risk score using these readily available parameters could identify diabetic patients who warrant further cardiovascular evaluation, potentially reducing unnecessary stress testing.

Limitations

Retrospective design, single-center, limited to high-risk diabetic patients, lack of long-term follow-up.

5 CONCLUSION

Baseline NLR and PLR are independent predictors of silent myocardial ischemia in high-risk diabetic patients and demonstrate good diagnostic accuracy. These simple, cost-effective inflammatory markers may serve as useful screening tools to identify diabetic patients who warrant further cardiovascular evaluation.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding the publication of this manuscript. No financial support or compensation was received from any organization that may gain or lose financially from the results of this study. The authors have no relevant financial or non-financial interests to disclose.

Statement of ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Royal Medical Services, Jordan, on 28 July 2026 under registration number 102_10/2026. Final institutional approval was obtained from the Educational and Technical Directorate on 28 September 2026.

Statement of informed consent

The IRB waived the requirement for written informed consent because the data analysis was retrospective and anonymized. All patient data were de-identified prior to analysis to ensure confidentiality and privacy.

Institutional Date Declaration

This study received final institutional approval from the Educational and Technical Directorate of the Royal Medical Services, Jordan, on 28 September 2026 (initial IRB approval 28 July 2026, No. 102_10/2026). Any manuscript processing dates (received, revision, acceptance) appearing prior to 28 September 2026 will be grounds for immediate rejection per institutional policy. All such dates are understood to fall after 28 September 2026.

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