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Are Anti-Cyclic Citrullinated Peptide Antibodies and Hematological Inflammatory Ratios associated with Left Ventricular Dysfunction in Non-Rheumatoid Patients?

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ABSTRACT

Background: Anti-cyclic citrullinated peptide (anti-CCP) antibodies are traditionally linked to rheumatoid arthritis but may influence cardiovascular pathology through inflammatory mechanisms. Haematological inflammatory ratios, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), are inexpensive biomarkers that may reflect cardiovascular risk. This study evaluated the diagnostic value of anti-CCP and haematological ratios in predicting LV dysfunction in cardiology patients without rheumatologic disease.

Methods: We studied 130 patients attending a cardiology department (mean age: 58 ± 10 years, 52% men). Anti-CCP antibodies, CRP and IL-6 (markers of inflammation), carotid intimal-media thickness (IMT), echocardiography, and blood counts were assayed. LV dysfunction was diagnosed as an ejection fraction (LVEF) of less than 50%. Comparison of groups, analysis of correlations, and ROC curve assessment were performed.

International Journal Dental and Medical Sciences Research
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Results: Anti-CCP antibody positivity was identified in 20% of the patients. Significantly lower mean LVEF (48.6% vs. 56.0%, $p < 0.001$), higher incidence of LV dysfunction (>50%), and higher CRP, IL-6, and CIMT levels were found in anti-CCP positive compared with negative patients. Significantly elevated NLRs were also present in anti-CCP-positive individuals and in those with LV dysfunction; however, no significant associations were found with PLR and LMR. ROC curve analysis showed moderate discriminative capacity for anti-CCP (AUC = 0.72) and NLR (AUC = 0.65), whereas minimal for PLR (AUC = 0.52) and LMR (AUC = 0.45).

Conclusion: A significant association was observed betweenAnti-CCP and NLR.Their predictive accuracy has implications for further validation studies in diverse populations.Incorporating these markers could enhance screening protocols in cardiology.

Keywords: Anti-CCP antibodies, Neutrophil-to-Lymphocyte Ratio, LV dysfunction, cardiology, Inflammatory Biomarkers

I. INTRODUCTION

Anti-cyclic citrullinated peptide antibodies have long been regarded as highly specific immunological markers for rheumatoid arthritis, with established diagnostic and prognostic utility in rheumatologic practice. Beyond joint pathology, persistent immune activation in rheumatoid arthritis has been linked to accelerated atherosclerosis, myocardial remodeling, and increased cardiovascular mortality (López-Longo et al., 2009; Marasovic-Krstulovic et al., 2011; Drosos et al., 2024). Anti-CCP antibodies are thought to reflect aberrant citrullination processes that promote chronic inflammation, endothelial dysfunction, and immune-mediated vascular injury (van Venrooij&Zendman, 2008; Weber et al., 2023). These mechanisms have positioned anti-CCP positivity as a marker not only of autoimmune disease severity but also of systemic inflammatory burden with cardiovascular relevance.

Left ventricular dysfunction represents a major contributor to morbidity and mortality across a wide spectrum of cardiovascular diseases. Increasing evidence suggests that immune and inflammatory pathways play a direct role in myocardial injury, adverse ventricular remodeling, and progression to heart failure, independent of ischemic damage alone (Mann, 2015; Ridker et al., 2017). Systemic inflammation has been shown to impair myocardial contractility through cytokine-mediated effects on calcium handling, mitochondrial metabolism, and microvascular perfusion. In parallel, vascular inflammation accelerates atherosclerosis, contributing to both macrovascular and microvascular cardiac injury. These observations have prompted interest in identifying immune-inflammatory biomarkers that may aid early detection of myocardial dysfunction in clinical cardiology.

Recent investigations have begun to explore immune markers traditionally associated with autoimmune disorders in non-rheumatoid cardiovascular populations. Studies examining citrullination within cardiovascular tissues have demonstrated its involvement in valvular degeneration and vascular remodeling, particularly under oxidative and inflammatory stress (Kim et al., 2023). Shared inflammatory pathways between rheumatoid arthritis and atherosclerotic cardiovascular disease have been described at the molecular level, involving neutrophil activation, protein citrullination, and adaptive immune responses (Weber et al., 2023). These findings suggest that anti-CCP antibodies may arise in response to cardiovascular-specific inflammatory processes rather than being confined exclusively to joint pathology.

Parallel to immune antibody research, hematological inflammatory ratios derived from routine complete blood counts have gained recognition as practical markers of systemic inflammation in cardiovascular disease. The neutrophil-to-lymphocyte ratio has consistently been associated with heart failure severity, reduced left ventricular ejection fraction, and adverse outcomes across diverse populations (Uthamalingam et al., 2011; Cho et al., 2020; Angkananard et al., 2018). Platelet-to-lymphocyte and lymphocyte-to-monocyte ratios have also been investigated, though with variable associations depending on disease phenotype and study design (Azab et al., 2012; Balta et al., 2016). Despite growing interest in these markers, their interaction with immune antibodies such as anti-CCP in determining myocardial dysfunction has not been systematically evaluated.

Evidence addressing anti-CCP antibodies in non-rheumatoid cardiology patients remains limited and conflicting. Early work suggested no meaningful elevation of anti-CCP antibodies in heart failure populations without rheumatoid arthritis, raising questions regarding their cardiovascular relevance outside autoimmune disease (Iqbal et al., 2012). However, subsequent studies demonstrating immune activation, endothelial injury, and subclinical atherosclerosis in

International Journal Dental and Medical Sciences Research
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anti-CCP–positive individuals challenge this view (López-Longo et al., 2009; Giles et al., 2010). Importantly, most existing investigations focus either on rheumatoid cohorts or isolated cardiovascular outcomes, leaving a critical gap in understanding how anti-CCP antibodies, systemic inflammatory indices, myocardial function, and vascular remodeling intersect in non-rheumatoid patients.

Against this background, the present study was undertaken to evaluate the association of anti-cyclic citrullinated peptide antibodies and hematological inflammatory ratios with left ventricular dysfunction in a non-rheumatoid cardiology population. The study further aimed to examine the relationship between immune-inflammatory markers and subclinical atherosclerosis assessed by carotid intima-media thickness and plaque presence. By integrating echocardiographic assessment of left ventricular function with laboratory and vascular imaging data, this investigation sought to clarify whether immune antibody positivity identifies a subset of cardiology patients with heightened inflammatory and cardiovascular risk. A retrospective observational approach was employed using routinely available clinical data, allowing assessment of real-world associations and exploration of combined predictive models incorporating immune, inflammatory, and metabolic parameters.

II. METHODOLOGY

2.1. Study Design and Setting

This study was designed as a retrospective observational analysis conducted at the Department of Medicine, Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha, India. The objective was to examine the association between anti-cyclic citrullinated peptide antibodies, hematological inflammatory ratios, and left ventricular dysfunction in adult cardiology patients without rheumatoid arthritis. A retrospective design was selected to utilize routinely collected clinical, laboratory, and imaging data available in hospital records, reflecting real-world clinical practice. The study was carried out in accordance with the principles outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research. Data were extracted from hospital records of patients evaluated for cardiac function during the study period.

2.2. Study Participants

The study population comprised adult patients aged 18 years or older who underwent evaluation for cardiac function in the cardiology services of the institution. Patients were eligible for inclusion if they were classified as non-rheumatoid based on clinical history, medical records, and laboratory documentation, and if they had complete data available for anti-CCP antibodies, complete blood count, glycemic parameters, lipid profile, and echocardiographic assessment of left ventricular ejection fraction. Patients were excluded if they had a documented diagnosis of rheumatoid arthritis or any other systemic autoimmune disease, acute or chronic infectious conditions at the time of evaluation, known malignancy, chronic kidney disease, or if they were receiving immunosuppressive or immunomodulatory therapy. These exclusions were applied to reduce potential confounding effects on inflammatory and immune markers. Records with incomplete or missing key variables were excluded from analysis. A total of 130 patients fulfilled the inclusion and exclusion criteria and were included in the final study cohort. Participants were categorized into anti-CCP–positive and anti-CCP–negative groups based on laboratory assay results.

2.3. Data Sources and Data Collection

Data were obtained retrospectively from electronic and physical medical records maintained by the hospital. Demographic information including age and sex was recorded. Clinical data included documented cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and history of ischemic heart disease, where available. Laboratory results, echocardiographic findings, and carotid ultrasonography reports were retrieved from the institutional diagnostic databases. Data extraction was performed using a predefined data collection template to ensure uniformity. To ensure accuracy, a subset of records was independently reviewed by a second investigator, and discrepancies were resolved by consensus.

2.4. Laboratory Measurements

Blood samples had been collected during routine clinical evaluation using standard venipuncture techniques. Anti-cyclic citrullinated peptide antibodies were measured using a commercially available enzyme-linked immunosorbent assay performed in the central clinical laboratory. Results were reported in standardized units, and positivity was defined

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according to the laboratory reference cut-off values routinely used for clinical reporting.

Complete blood count parameters were measured using an automated hematologyanalyzer operating under internal quality control protocols. Absolute neutrophil count, lymphocyte count, platelet count, and monocyte count were recorded. Hematological inflammatory ratios were derived from these values. The neutrophil-to-lymphocyte ratio was calculated as the ratio of absolute neutrophil count to absolute lymphocyte count. The platelet-to-lymphocyte ratio was calculated as platelet count divided by lymphocyte count. The lymphocyte-to-monocyte ratio was calculated as absolute lymphocyte count divided by monocyte count.

Glycemic control was assessed using glycated hemoglobin measurements obtained through high-performance liquid chromatography–based methods. Lipid profile parameters, including total cholesterol and other components, were measured using enzymatic colorimetric assays. All laboratory investigations followed standardized institutional protocols and quality assurance measures.

2.5. Echocardiographic Assessment

Transthoracic echocardiography was performed for all patients as part of routine cardiology evaluation. Echocardiographic examinations were conducted using standard commercially available ultrasound systems in the cardiology department. Left ventricular ejection fraction was assessed using two-dimensional echocardiography, primarily employing the modified Simpson's biplane method, in accordance with recommendations of the American Society of Echocardiography.

Echocardiographic measurements were obtained by experienced cardiologists, and finalized reports were used for analysis. Left ventricular systolic dysfunction was defined based on documented LVEF values using established clinical thresholds. Only finalized echocardiographic reports available in the medical records were included.

2.6. Assessment of Subclinical Atherosclerosis

Subclinical atherosclerosis was evaluated using carotid artery ultrasonography in patients for whom vascular imaging data were available. Carotid intima-media thickness was measured using high-resolution B-mode ultrasonography with a linear array transducer. Measurements were obtained from the common carotid artery following standard imaging protocols. Mean CIMT values were recorded, and the presence or absence of carotid plaque was noted based on ultrasonographic criteria described in the imaging reports. These vascular parameters were included to assess their association with immune markers, inflammatory ratios, and left ventricular function.

2.7. Data Management and Processing

All extracted data were entered into a secure electronic database for analysis. Continuous variables were reviewed for plausibility and completeness. Derived variables, including hematological ratios, were calculated directly from raw laboratory values to minimize rounding errors. Data distributions were assessed for normality prior to statistical testing. Outliers were examined but not excluded unless attributable to clear data entry errors. Missing data were not imputed, and analyses were performed using complete-case datasets for each specific comparison.

2.8. Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean and standard deviation, while categorical variables were expressed as frequencies and percentages. Comparisons between anti-CCP–positive and anti-CCP–negative groups were conducted using the independent samples t-test for normally distributed continuous variables. The chi-square test was used for comparison of categorical variables. For variables not meeting normality assumptions, appropriate non-parametric tests were considered. Correlation analyses were conducted to evaluate associations between anti-CCP antibodies, hematological inflammatory ratios, carotid intima-media thickness, and left ventricular ejection fraction. Pearson correlation coefficients were used for normally distributed variables, and Spearman rank correlation coefficients were applied when distributional assumptions were not met.

Receiver operating characteristic curve analysis was used to assess the diagnostic performance of anti-CCP antibodies and hematological ratios in predicting left ventricular dysfunction. Areas under the curve were calculated with corresponding confidence intervals. A multivariable logistic regression model was constructed incorporating anti-CCP status, neutrophil-to-lymphocyte ratio, HbA1c, and selected clinical risk factors to evaluate combined predictive performance. Model discrimination was assessed using the area under the ROC curve. All

International Journal Dental and Medical Sciences Research
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statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

III. RESULTS

3.1. Population characteristics

A total of 130 adult patients evaluated for cardiac function were included in the final analysis. All participants were aged 18 years or older and had no documented history of rheumatoid arthritis or other autoimmune disorders. The cohort consisted exclusively of cardiology patients with available laboratory and imaging data, including anti-cyclic citrullinated peptide antibody status, complete blood count parameters, lipid profile, glycemic indices, and echocardiographic assessment of left ventricular ejection fraction. Patients with active or chronic infections, malignancy, renal failure, or those receiving immunosuppressive therapy were excluded to minimize confounding influences on inflammatory markers. The retrospective nature of the study allowed assessment of real-world clinical data from routine hospital practice.Anti-CCP antibodies were detected in a subset of the cohort, enabling comparison between anti-CCP–positive and anti-CCP–negative patients. Baseline demographic variables and cardiovascular risk factors were broadly comparable between groups, allowing focused evaluation of immune and inflammatory markers in relation to left ventricular function and vascular parameters.

Table 1. Demographic and clinical characteristics of the study population by anti-CCP status

Variable	Overall (N = 130)	Anti-CCP Negative (n = 104)	Anti-CCP Positive (n = 26)	p-value*
Age (years), mean ± SD	57.7 ± 8.9	56.9 ± 9.2	61.0 ± 7.4	0.03
Sex, n (%)				
Female	71 (54.6)	58 (55.8)	13 (50.0)	0.59
Male	59 (45.4)	46 (44.2)	13 (50.0)	
Body mass index (kg/m²), mean ± SD	27.0 ± 2.9	26.9 ± 2.9	27.3 ± 2.8	0.41
Hypertension, n (%)	82 (63.1)	56 (53.8)	13 (50.0)	0.74
Diabetes mellitus, n (%)	61 (46.9)	49 (47.1)	12 (46.2)	0.93
Smoking history, n (%)	33 (25.4)	27 (26.0)	6 (23.1)	0.76
Statin use, n (%)	56 (43.1)	45 (43.3)	11 (42.3)	0.92

*p-values calculated using independent samples t-test for continuous variables and chi-square test for categorical variables.

3.2. Anti-CCP positivity was associated with reduced left ventricular systolic function

Analysis of echocardiographic findings revealed a clear difference in left ventricular systolic performance between anti-CCP–positive and anti-CCP–negative patients. Individuals with anti-CCP positivity demonstrated a significantly lower mean left ventricular ejection fraction compared with those who were anti-CCP negative. The average LVEF among anti-CCP–positive patients was approximately 45 percent, indicating a

International Journal Dental and Medical Sciences Research
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greater burden of systolic dysfunction within this group (Figure 1).

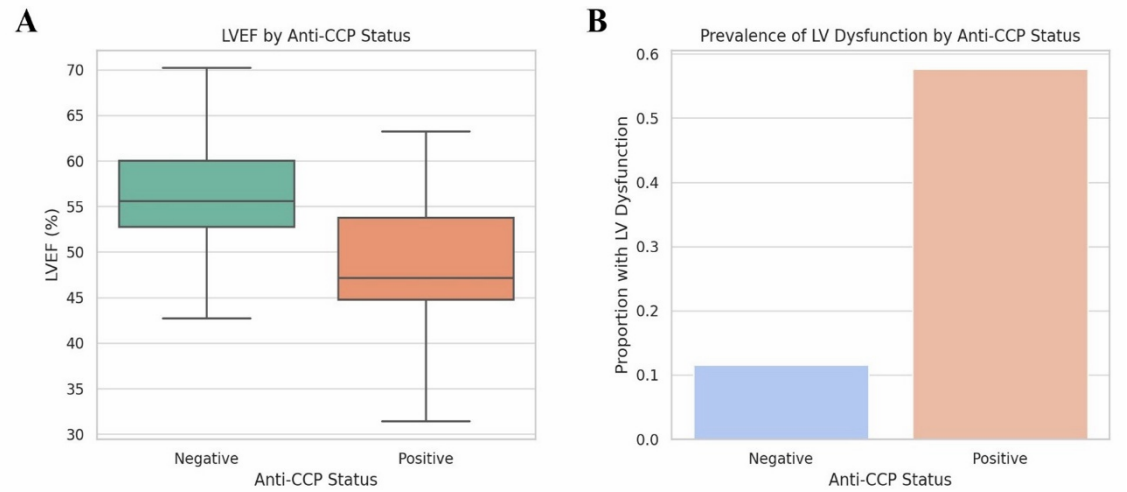

Figure 1: Association between anti-CCP status and left ventricular systolic function.**(A)** Mean LVEF between Anti-CCP-positive and negative patients.**(B)**prevalence of LV dysfunction in anti-CCP-positive and negative patients.

The prevalence of left ventricular dysfunction was markedly higher in anti-CCP–positive patients than in their antibody-negative counterparts. This association persisted across comparisons using standard statistical testing, suggesting that anti-CCP positivity was linked to impaired myocardial performance even in the absence of clinically apparent rheumatoid disease. These findings highlight a potential relationship between immune reactivity and cardiac dysfunction that extends beyond traditional rheumatologic populations (Figure 2).

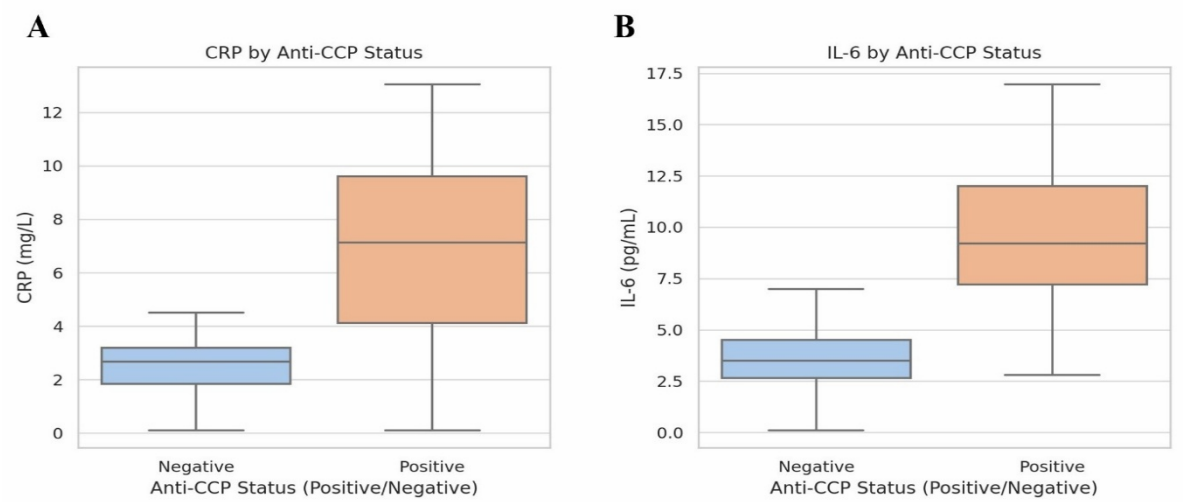

Figure 2. Comparison of systemic inflammatory markers by anti-CCP antibody status.
Box-and-whisker plot **(A)** comparing serum CRP levels between anti-CCP–negative and anti-CCP–positive patients. **(B)** depicting interleukin-6 (IL-6) levels stratified by anti-CCP status.

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 254-264 www.ijdmsrjournal.com
ISSN: 2582-6018

3.3. Inflammatory hematological ratios differed between patients with and without anti-CCP antibodies

Systemic inflammatory status was evaluated using hematological ratios derived from routine complete blood count testing. The neutrophil-to-lymphocyte ratio was notably elevated among anti-CCP–positive patients compared with anti-CCP–negative individuals. This elevation suggested a heightened inflammatory milieu in patients with immune antibody positivity (Figure 3A).In contrast, platelet-to-lymphocyte ratio and lymphocyte-to-monocyte ratio did not demonstrate consistent or clinically meaningful differences between the two groups(Figure 3B-C). Although these ratios were examined due to their established associations with cardiovascular inflammation in other settings, their discriminatory value in this cohort appeared limited. The observed pattern indicated that among commonly used hematological indices, NLR was the most responsive marker in relation to anti-CCP status and cardiac dysfunction.

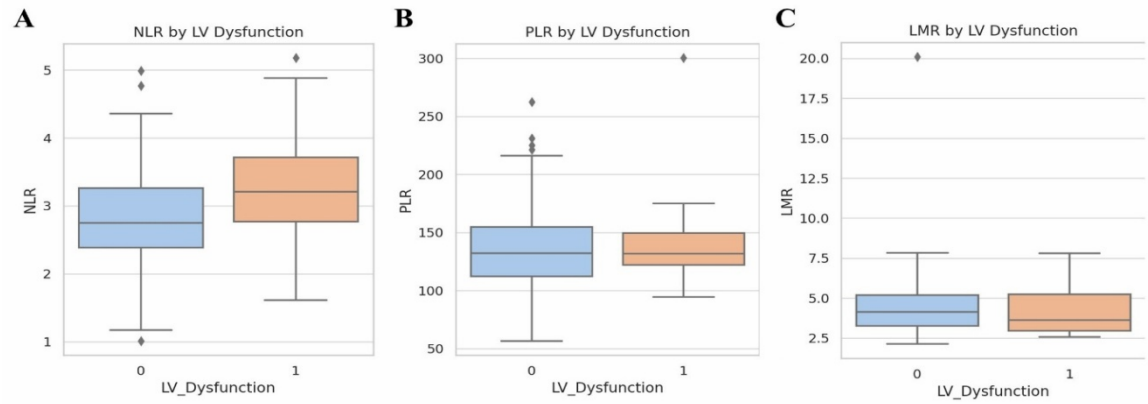

Figure 3. Hematological inflammatory ratios in relation to left ventricular dysfunction.(A) Distribution of neutrophil-to-lymphocyte ratio (NLR) among patients with and without left ventricular dysfunction. (B) Platelet-to-lymphocyte ratio (PLR) stratified by LV dysfunction status, showing overlapping distributions and limited discriminatory capacity. (C) Lymphocyte-to-monocyte ratio (LMR) according to LV dysfunction status, demonstrating no meaningful separation between groups.

3.4. Subclinical atherosclerosis was more pronounced in anti-CCP–positive patients

Assessment of vascular structure revealed significant differences in markers of subclinical atherosclerosis. Carotid intima-media thickness measurements were higher among patients who tested positive for anti-CCP antibodies compared with antibody-negative patients. The mean CIMT value in the anti-CCP–positive group approached 0.93 mm, whereas the corresponding value in the anti-CCP–negative group was approximately 0.70 mm. This difference was statistically significant and suggested greater arterial wall remodeling in patients with immune antibody positivity.

In addition to increased CIMT, carotid plaque was more frequently observed in anti-CCP–positive patients. The presence of plaque further supported the association between immune-mediated inflammation and early atherosclerotic changes. These vascular findings aligned with the

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 254-264 www.ijdmsrjournal.com
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observed reduction in left ventricular function, indicating that anti-CCP positivity may be linked to a broader cardiovascular phenotype involving both myocardial and vascular involvement.

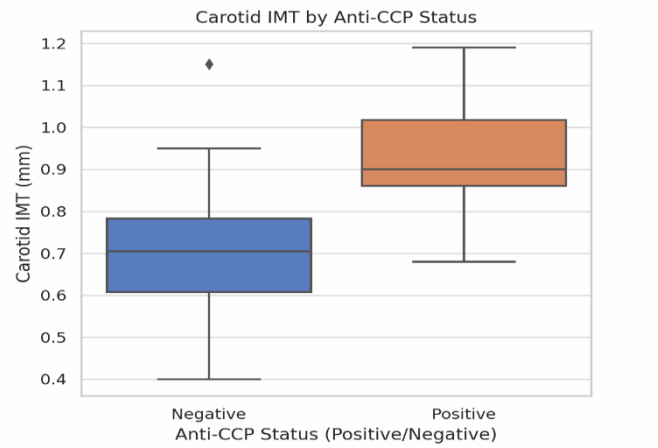

Figure 4. Comparison of CIMT between Anti CCP positive and negative patients

3.5. Correlation analysis demonstrated inverse relationships between inflammatory markers and left ventricular function

Correlation analysis was performed to explore relationships among immune markers, inflammatory indices, vascular parameters, and left ventricular systolic function(Figure 5). Anti-CCP antibody levels showed a negative correlation with left ventricular ejection fraction, indicating that higher immune reactivity was associated with poorer cardiac performance. Similarly, neutrophil-to-lymphocyte ratio demonstrated a negative correlation with LVEF, reinforcing its role as a marker of inflammation-related myocardial impairment.

Carotid intima-media thickness was also negatively correlated with LVEF, suggesting that increased vascular remodeling was associated with reduced systolic function. In contrast, inflammatory markers including anti-CCP and NLR showed positive correlations with CIMT, indicating parallel progression of immune activity and subclinical atherosclerosis. Platelet-to-lymphocyte ratio and lymphocyte-to-monocyte ratio exhibited weaker and inconsistent correlations with both LVEF and CIMT, further underscoring their limited utility in this setting.

Collectively, the correlation findings supported the presence of an interconnected relationship between immune-mediated inflammation, vascular changes, and myocardial dysfunction within the study population.

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 254-264 www.ijdmsrjournal.com
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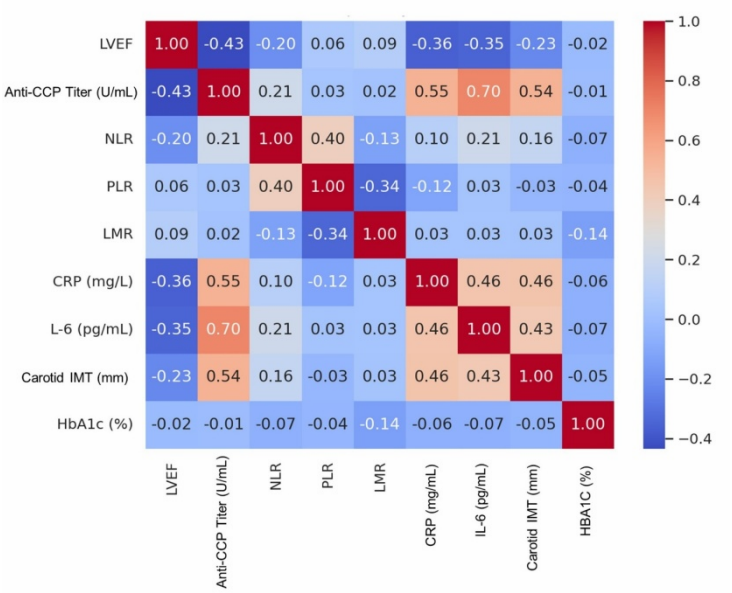

Figure 5. Correlation matrix illustrating relationships among immune, inflammatory, vascular, and cardiac parameters.

3.6. Diagnostic performance of individual markers showed moderate discrimination for left ventricular dysfunction

Receiver operating characteristic curve analysis was conducted to evaluate the diagnostic accuracy of anti-CCP antibodies and hematological ratios in identifying left ventricular dysfunction. Anti-CCP positivity demonstrated moderate discriminative ability, with an area under the curve of approximately 0.72. This finding suggested that anti-CCP antibodies alone could reasonably distinguish patients with impaired systolic function from those with preserved function.Neutrophil-to-lymphocyte ratio also exhibited modest predictive performance, with an AUC of approximately 0.65. While this level of accuracy was inferior to that of anti-CCP antibodies, it still indicated a meaningful association between systemic inflammation and cardiac dysfunction. In contrast, platelet-to-lymphocyte ratio and lymphocyte-to-monocyte ratio performed poorly, with AUC values near or below 0.55, indicating limited clinical value as standalone predictors in this cohort.These results demonstrated that not all inflammatory markers carry equal diagnostic relevance and highlighted anti-CCP and NLR as the most informative indices among those evaluated (Figure 6A).

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 254-264 www.ijdmsrjournal.com
ISSN: 2582-6018

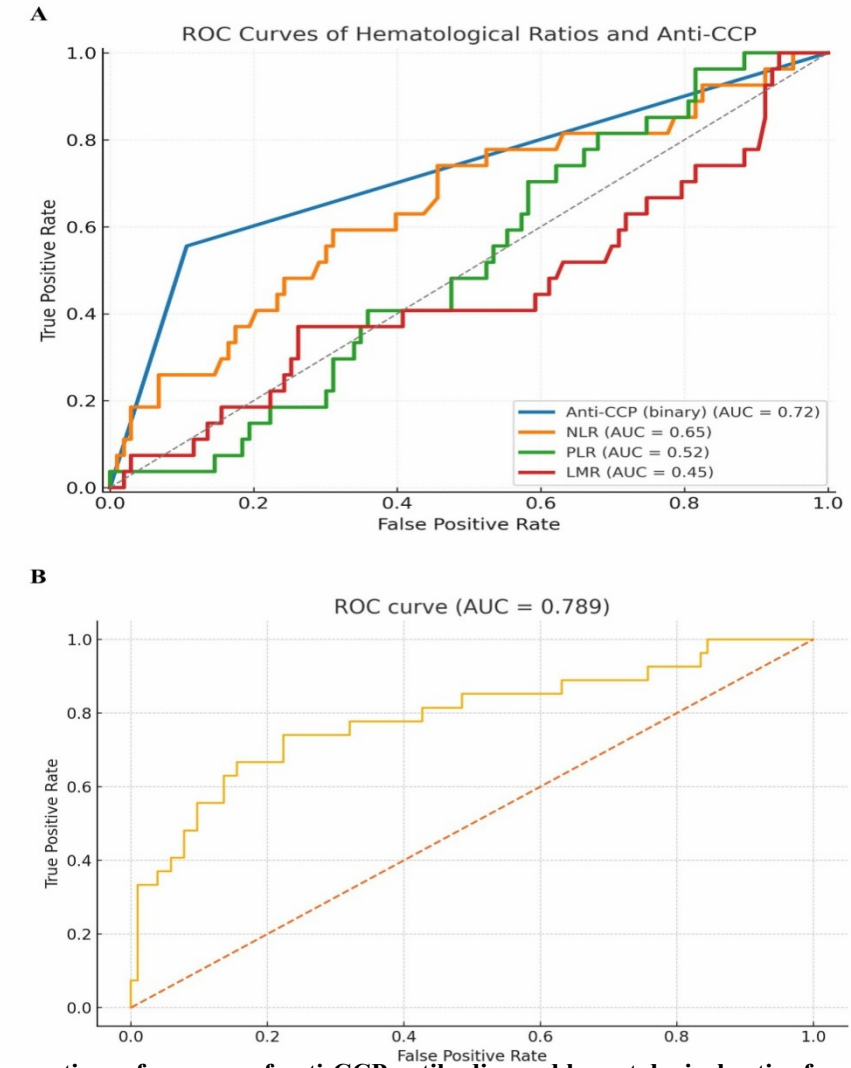

Figure 6. Diagnostic performance of anti-CCP antibodies and hematological ratios for predicting left ventricular dysfunction.(A) Receiver operating characteristic (ROC) curves comparing the discriminatory ability of anti-CCP status, NLR, PLR, and LMR for identifying left ventricular dysfunction. (B) ROC curve of the combined multivariable model incorporating anti-CCP status, NLR, HbA1c, and clinical risk factors, demonstrating improved diagnostic accuracy with an area under the curve of 0.789.

3.7. A combined multivariable model improved prediction of left ventricular dysfunction

To assess whether integrating immune, inflammatory, and metabolic parameters could enhance predictive accuracy, a combined logistic regression model was constructed. This model incorporated anti-CCP status, neutrophil-to-lymphocyte ratio, HbA1c, and relevant clinical risk factors. The combined model achieved an area under the ROC curve of approximately 0.789, representing a clear improvement over individual markers alone.The enhanced performance of the combined model suggested that left ventricular dysfunction in this population is multifactorial, with immune activation, systemic inflammation, and metabolic dysregulation contributing simultaneously. The results supported the concept that integrated risk assessment using readily available laboratory parameters may offer superior screening capability compared with reliance on single biomarkers (Figure 6B).

IV. DISCUSSION

The present study examines the association of anti-cyclic citrullinated peptide antibodies and hematological inflammatory ratios with left ventricular dysfunction in a non-rheumatoid cardiology population, an area that has

International Journal Dental and Medical Sciences Research
Volume 7, Issue 6, Nov – Dec 2025 pp 254-264 www.ijdmsrjournal.com
ISSN: 2582-6018

received limited and often conflicting attention in cardiovascular research. Unlike investigations centered on established autoimmune disease, this work focuses on patients without rheumatoid arthritis, allowing evaluation of immune-linked cardiovascular alterations outside the classical rheumatologic setting. The findings demonstrate that anti-CCP positivity and elevated neutrophil-to-lymphocyte ratio are associated with reduced left ventricular ejection fraction, increased carotid intima-media thickness, and higher prevalence of carotid plaque, supporting a role for immune-inflammatory mechanisms in myocardial and vascular dysfunction even in the absence of overt autoimmune disease.

Anti-CCP antibodies are traditionally regarded as highly specific markers for rheumatoid arthritis and have been extensively studied in relation to joint destruction and systemic inflammation (van Venrooij&Zendman, 2008; Aletaha et al., 2010). In rheumatoid cohorts, anti-CCP positivity has repeatedly been associated with increased cardiovascular morbidity and mortality, independent of traditional risk factors (López-Longo et al., 2009; Marasovic-Krstulovic et al., 2011; Drosos et al., 2024). These associations have been attributed to chronic immune activation, endothelial dysfunction, and accelerated atherosclerosis driven by citrullination-related immune responses (Weber et al., 2023). The current study extends this concept beyond rheumatoid arthritis, suggesting that anti-CCP antibodies may reflect a broader immune phenotype with cardiovascular relevance.

Evidence regarding anti-CCP antibodies in non-rheumatoid populations has been inconsistent. Earlier work by Iqbal et al. (2012) reported no elevation of anti-CCP antibodies in a heart failure population without rheumatoid arthritis, leading to the view that anti-CCP positivity may be epiphenomenal and confined largely to rheumatologic disease. However, subsequent mechanistic and translational studies have suggested that citrullination processes are not limited to autoimmune arthritis but also occur in vascular and valvular tissues, particularly under conditions of oxidative stress and inflammation (Cho et al., 2009; Kim et al., 2023). The present findings align more closely with this emerging literature, indicating that anti-CCP antibodies may identify a subset of cardiology patients with heightened immune-mediated cardiovascular vulnerability.

The observed reduction in left ventricular ejection fraction among anti-CCP–positive patients is clinically relevant. Myocardial dysfunction in inflammatory states has been linked to cytokine-mediated alterations in myocardial metabolism, impaired calcium handling, and microvascular dysfunction (Mann, 2015; Ridker et al., 2017). In rheumatoid arthritis, anti-CCP positivity has been associated with subclinical myocardial involvement and altered ventricular geometry, even in patients without overt cardiovascular disease (Marasovic-Krstulovic et al., 2011; Giles et al., 2010). The present study suggests that similar processes may operate in non-rheumatoid patients, where immune activation reflected by anti-CCP positivity may contribute to myocardial remodeling and systolic impairment.

The relationship between anti-CCP antibodies and subclinical atherosclerosis observed in this study further supports a vascular component to the immune-cardiac interaction. Increased carotid intima-media thickness and higher prevalence of carotid plaque among anti-CCP–positive patients mirror findings reported in rheumatoid cohorts, where anti-CCP status correlates with accelerated atherosclerosis and endothelial dysfunction (López-Longo et al., 2009; Giles et al., 2010). Importantly, the current study demonstrates similar vascular changes in patients without diagnosed autoimmune disease, indicating that immune-mediated vascular injury may precede or occur independently of clinically apparent rheumatologic pathology.

Hematological inflammatory ratios, particularly the neutrophil-to-lymphocyte ratio, have gained prominence as accessible markers of systemic inflammation in cardiovascular disease (Li et al., 2024; Angkananard et al., 2018). Elevated NLR has been associated with heart failure severity, adverse remodeling, and increased mortality (Uthamalingam et al., 2011; Cho et al., 2020). The present study corroborates these findings by demonstrating a negative correlation between NLR and left ventricular ejection fraction, as well as moderate diagnostic performance of NLR in identifying left ventricular dysfunction. This supports the role of NLR as a low-cost inflammatory marker that reflects immune-cardiac interactions.

In contrast, platelet-to-lymphocyte ratio and lymphocyte-to-monocyte ratio showed limited discriminatory value in the present analysis. Prior studies have reported variable associations of PLR and LMR with cardiovascular outcomes, often influenced by population characteristics and disease context (Azab et al., 2012; Balta et al., 2016). The lack of strong associations in this cohort

suggests that these ratios may be less sensitive to the specific immune pathways linked to anti-CCP positivity and myocardial dysfunction. This distinction is important, as it underscores that not all inflammatory indices are interchangeable and that marker selection should be guided by biological relevance rather than availability alone.

One of the notable findings of the present study is the improved diagnostic performance achieved through a combined model incorporating anti-CCP antibodies, NLR, HbA1c, and clinical risk factors. The increase in area under the ROC curve compared with individual markers reflects the multifactorial nature of left ventricular dysfunction, where immune activation, systemic inflammation, and metabolic dysregulation converge. Similar integrative approaches have been advocated in cardiovascular risk stratification, particularly in inflammatory and immune-mediated conditions (Ridker et al., 2017; Libby, 2021). The present results support the utility of combined biomarker models in identifying patients at risk for myocardial dysfunction, particularly in settings where advanced imaging or biomarker panels are not readily available.

The novelty of this study lies in its focus on anti-CCP antibodies as cardiovascular markers in a non-rheumatoid cardiology population. While previous studies have largely confined anti-CCP–related cardiovascular risk to rheumatoid arthritis, the present findings suggest that anti-CCP positivity may capture a broader immune phenotype with implications for myocardial and vascular health. This challenges the traditional view of anti-CCP antibodies as disease-specific markers and raises the possibility that they may reflect systemic citrullination processes relevant to cardiovascular pathology (Weber et al., 2023; Kim et al., 2023). The parallel associations observed with left ventricular dysfunction and subclinical atherosclerosis further strengthen this interpretation.

V. LIMITATIONS AND CONCLUSION

Nevertheless, the findings should be interpreted in light of several limitations. The retrospective design restricts causal inference and is susceptible to selection bias. The single-center nature of the study limits generalizability to other populations and healthcare settings. The sample size, while sufficient to demonstrate associations, may not support extensive subgroup analyses or robust external validation of predictive models. Residual confounding by unmeasured variables, including inflammatory cytokines or medication use, cannot be excluded. Additionally, anti-CCP titers were analyzed categorically rather than quantitatively, which may have limited assessment of dose–response relationships.Despite these limitations, the study provides meaningful insights into immune-inflammatory contributions to cardiac dysfunction outside the setting of overt autoimmune disease. The consistent associations across echocardiographic, hematological, and vascular parameters suggest biological coherence rather than random correlation. These findings support the hypothesis that immune activation reflected by anti-CCP positivity may participate in cardiovascular remodeling processes that extend beyond rheumatoid arthritis.

In conclusion, the present study demonstrates that anti-CCP antibodies and neutrophil-to-lymphocyte ratio are associated with left ventricular dysfunction and subclinical atherosclerosis in non-rheumatoid cardiology patients. The findings highlight a potential role for immune-mediated mechanisms in myocardial impairment and suggest that anti-CCP antibodies may serve as markers of cardiovascular risk beyond their traditional rheumatologic context. Future prospective multicenter studies with larger sample sizes are needed to validate these associations, explore mechanistic pathways, and determine whether the incorporation of immune markers into cardiovascular risk assessment can improve early detection and prevention strategies.

REFERENCES

[1]. Aletaha, D., Neogi, T., Silman, A. J., Funovits, J., Felson, D. T., Bingham, C. O., 3rd, Birnbaum, N. S., Burmester, G. R., Bykerk, V. P., Cohen, M. D., Combe, B., Costenbader, K. H., Dougados, M., Emery, P., Ferraccioli, G., Hazes, J. M., Hobbs, K., Huizinga, T. W., Kavanaugh, A., Kay, J., … Hawker, G. (2010). 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and rheumatism, 62(9), 2569–2581. https://doi.org/10.1002/art.27584

[2]. Angkananard, T., Anothaisintawee, T., McEvoy, M., Attia, J., &Thakkinstian, A. (2018). Neutrophil lymphocyte ratio and cardiovascular disease risk: a systematic review and meta analysis. BioMed research international, 2018(1), 2703518.

[3]. Azab, B., Shah, N., Akerman, M., & McGinn Jr, J. T. (2012). Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. Journal of thrombosis and thrombolysis, 34(3), 326-334.

[4]. Balta, S., Celik, T., Mikhailidis, D. P., Ozturk, C., Demirkol, S., Aparci, M., &Iyisoy, A. (2016). The relation between atherosclerosis and the neutrophil–lymphocyte ratio. Clinical and applied thrombosis/hemostasis, 22(5), 405-411.

[5]. Cho, J. H., Cho, H. J., Lee, H. Y., Ki, Y. J., Jeon, E. S., Hwang, K. K., ... & Oh, B. H. (2020). Neutrophil-lymphocyte ratio in patients with acute heart failure predicts in-hospital and long-term mortality. Journal of clinical medicine, 9(2), 557.

[6]. Cho, S. H., Jeong, M. H., Park, I. H., Choi, J. S., Yoon, H. J., Kim, K. H., ... & Kang, J. C. (2009). Endothelial dysfunction, increased carotid artery intima-media thickness and pulse wave velocity, and increased level of inflammatory markers are associated with variant angina. Journal of cardiology, 54(2), 183-191.

[7]. Drosos, A. A., Venetsanopoulou, A. A., Pelechas, E., & Voulgari, P. V. (2024). Exploring cardiovascular risk factors and atherosclerosis in rheumatoid arthritis. European Journal of Internal Medicine, 128, 1-9.

[8]. Giles, J. T., Malayeri, A. A., Fernandes, V., Post, W., Blumenthal, R. S., Bluemke, D., ... & Bathon, J. M. (2010). Left ventricular structure and function in patients with rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. Arthritis & Rheumatism, 62(4), 940-951.

[9]. Iqbal, N. S., Wu, Y., Hazen, S., & Tang, W. W. (2012). Anti-Cyclic Citrullinated Peptide Antibodies are Not Elevated in a Heart Failure Population without Rheumatoid Arthritis. Journal of Cardiac Failure, 18(8), S29.

[10]. Kim, A. R., Ji, E., Lee, S., Hong, S., Kim, D. H., Song, J. M., ... & Song, J. K. (2023). Association of citrullination with the progression of aortic stenosis. Scientific Reports, 13(1), 8919.

[11]. Li, X., Liu, M., & Wang, G. (2024). The neutrophil–lymphocyte ratio is associated with all-cause and cardiovascular mortality in cardiovascular patients. Scientific Reports, 14(1), 26692.

[12]. Libby, P. (2021). Inflammation in atherosclerosis. Nature Reviews Cardiology, 18(8), 531–545.

[13]. López Longo, F. J., Oliver Miñarro, D., de la Torre, I., González Díaz de Rábago, E., Sánchez Ramón, S., Rodríguez Mahou, M., ... & Carreño, L. (2009). Association between anti–cyclic citrullinated peptide antibodies and ischemic heart disease in patients with rheumatoid arthritis. Arthritis Care & Research: Official Journal of the American College of Rheumatology, 61(4), 419-424.

[14]. Mann, D. L. (2015). Innate immunity and the failing heart: the cytokine hypothesis revisited. Circulation research, 116(7), 1254-1268.

[15]. Marasovic-Krstulovic, D., Martinovic-Kaliterna, D., Fabijanic, D., &Morovic-Vergles, J. (2011). Are the anti-cyclic citrullinated peptide antibodies independent predictors of myocardial involvement in patients with active rheumatoid arthritis?. Rheumatology, 50(8), 1505-1512.

[16]. Ridker, P. M., Everett, B. M., Thuren, T., MacFadyen, J. G., Chang, W. H., Ballantyne, C., ... & Glynn, R. J. (2017). Antiinflammatory therapy with canakinumab for atherosclerotic disease. New England journal of medicine, 377(12), 1119-1131.

[17]. Uthamalingam, S., Patvardhan, E. A., Subramanian, S., Ahmed, W., Martin, W., Daley, M., & Capodilupo, R. (2011). Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. The American journal of cardiology, 107(3), 433-438.

[18]. Van Venrooij, W. J., Van Beers, J. J., &Pruijn, G. J. (2008). Anti CCP antibody, a marker for the early detection of rheumatoid arthritis. Annals of the New York Academy of Sciences, 1143(1), 268-285.

[19]. Weber, B. N., Giles, J. T., & Liao, K. P. (2023). Shared inflammatory

pathways of rheumatoid arthritis and atherosclerotic cardiovascular disease. Nature Reviews Rheumatology, 19(7), 417–428.