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CLINICAL REVIEW

Association between preablation and postablation neutrophil-lymphocyte ratio and atrial fibrillation recurrence: A meta-analysis

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Abstract

Atrial fibrillation (AF) recurrence has become common in patients who have undergone catheter ablation. High neutrophil lymphocyte ratios (NLR) have been linked to an increased risk of recurrent AF. The research is, however, not conclusive. This meta-analysis addressed the value of easily accessible and affordable pre- and postablation NLR levels as indicators of AF recurrence in patients who had undergone ablation. We searched PubMed, SCOPUS, and Google Scholar for pertinent studies through May 2023. Using random effects models, the aggregated odds ratio (OR) of pre- and post-NLR and AF recurrence was estimated. Inter-study heterogeneity was described using I^2 statistics and leave-one-out sensitivity analysis. A p-value $<.05$ was considered statistically significant. The literature search yielded 270 studies, seven of which were included in this meta-analysis of 1923 patients who experienced AF recurrence after undergoing ablation. There are five retrospective and two prospective studies with a mean follow-up of 20.5 months. The unadjusted odds ratio (OR) of AF recurrence for preablation NLR was 1.33 (95% CI: 1.04–1.71, $p<.01$, $I^2=95.49\%$), while the adjusted OR was 1.45 (95% CI: 0.87–2.43, $p<.01$, $I^2=95.1\%$). The unadjusted odds ratio (OR) for postablation NLR was 1.21 (95% CI: 1.09–1.36, $p<.01$, $I^2=85.9\%$), and the adjusted odds ratio (OR) was 1.28 (95% CI: 0.93–1.76), demonstrating significant heterogeneity ($I^2=95.32\%$) with a p-value $<.01$. NLR was significantly associated with AF recurrence prediction. To detect AF recurrence, we recommend that clinicians add a simple NLR blood test to their diagnostic modalities.

KEYWORDS
atrial fibrillation (AF), catheter ablation, meta-analysis, neutrophil-lymphocyte ratio (NLR), recurrence/recurrent

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and is associated with considerable morbidity and mortality.[1] The global burden of AF has increased so rapidly in the last 20 years that disability-adjusted life years (DALYs) for AF have almost linearly increased, with its incidence and prevalence rising by 63% and 66% after 30 years.[2] The most frequent AF trigger activity is extrasystoles from pulmonary veins, and catheter ablation is the most effective method for controlling rhythm since it maintains sinus rhythm better than anti-arrhythmic medications. Even though the results were favorable, the recurrence rate of AF was up to 30%–50% at the end of the 12th month.[3] Inflammatory indicators have recently been employed in numerous studies to predict the recurrence of AF following ablation in addition to clinical characteristics such as persistent AF, diabetes mellitus, heart failure, and left atrial structural abnormalities.[4] Atrial cardiomyocytes that are experiencing inflammation change the refractory period, slow conduction, enlarge the heart, and produce fibrous tissue.[1] Various markers of inflammation, including C-reactive protein (CRP) and interleukins, have been linked to the presence and prognosis of AF. Among these markers, the neutrophil-lymphocyte ratio (NLR), which gauges the relative counts of neutrophils and lymphocytes, has recently emerged as a potent predictor of outcomes in AF. NLR serves as a simple, cost-effective, and widely accessible biomarker. It effectively anticipates atrial rhythm disturbances by reflecting the role of white blood cell(WBC) dyscrasias, particularly the predominance of activated neutrophils, in arrhythmogenesis.[4] Although the NLR has been found to be a predictor of AF recurrence, after catheter-based ablation it does not hold the same significance for patients with acute AF who have undergone electrical conversion to sinus rhythm.[5] As our knowledge in this field advances, the NLR could potentially play a role in improving patient care and outcomes in managing AF. Therefore, the main goal of this systematic review and meta-analysis was to examine the correlation between pre-NLR and post-NLR with the recurrence of AF in postablation patients.

2 | METHODS

2.1 | Search strategies

Two reviewers (S.L. and S.M.) thoroughly screened PubMed, Google Scholar, and Scopus in a systematic way. We searched these databases with relevant keywords: "Neutrophil/lymphocyte ratio" and "atrial fibrillation" in PubMed and got 56 results. "NLR levels," "atrial fibrillation ablation," "ablation," "hematological predictors," and "atrial fibrillation recurrence" brought up 214 results in Google Scholar. Two reviewers (SL and SM) examined the titles, abstracts, and reference lists of all the reports that were found to see if there were any possibly relevant studies that came out after January 2013 until May 2023. Also, a thorough search was done of the professional meetings of the European Society of Cardiology, the American College of Cardiology, and the American Heart Association over the last 5 years. Detailed description of selection of studies are mentioned in PRISMA compliant flow diagram (Figure 1).

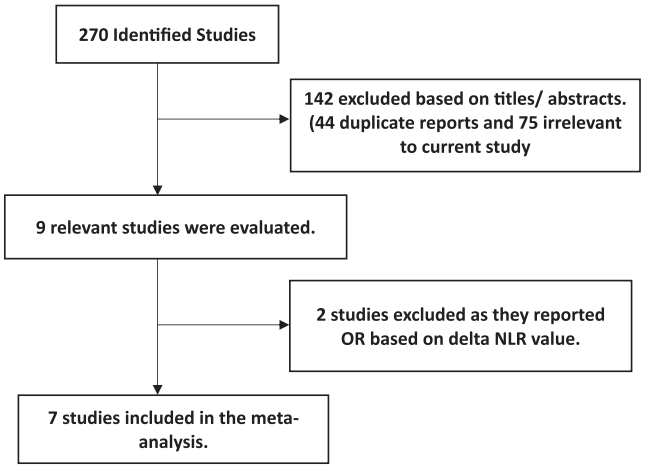

FIGURE 1 Flow diagram of the selection process. OR, odds ratio.

2.2 | Inclusion criteria

We included studies that fulfilled the criteria:

a. Either the study was a prospective cohort study or a retrospective cohort study. We excluded individual case reports, editorials, or review articles.
b. The study needed to measure the neutrophil-to-lymphocyte ratio (NLR) before or after the ablation treatment and document the outcomes during follow-up.
c. The hazard ratio (HR) or odds ratio (OR) and the 95% confidence interval (CI) for NLR and the recurrence of AF were reported.
d. Only studies that clearly diagnosed AF in accordance with guidelines were chosen. Additionally, we only included studies written in English in our analysis.

2.3 | Study selection

Two independent reviewers (SL and SM) examined the abstracts or titles of the studies identified by the electronic search in order to identify all potentially eligible studies. Then, complete manuscripts of potentially relevant reports were retrieved and evaluated for compliance with the inclusion criteria. After rechecking the source data and consulting with the third reviewer (SJ), the examiners reached a consensus regarding any ambiguities or discrepancies.

2.4 | Data extraction

Seven independent evaluators extracted data independently using a standard data extraction form to determine inclusion eligibility. To assess NLR's ability to predict the risk of AF recurrence, we extracted

and analyzed all multivariate-adjusted HR/OR and the corresponding 95% CI. The extracted data elements for this study included the first author's last name, the publication year, the country in which the study was conducted, the study design, study population, sample size, participants' age and gender, duration of follow-up, methods of AF detection and rates of AF recurrence, and cohorts were randomized and the baseline comorbidities such as hypertension, dyslipidemia, diabetes, coronary artery disease, mean body mass index, smoking, and alcohol consumption, cardiac surgeries mean N-terminal pro B-type natriuretic peptide levels (NT-proBNP levels), high-sensitivity C-reactive protein levels (Hs-CRP levels), mean red cell distribution width (mean RDW), mean white blood cell count (mean WBC count), mean lymphocyte count, mean neutrophil count, mean hemoglobin levels, mean platelet count, mean albumin levels, mean globulin levels, mean monocyte count, mean serum creatinine levels, estimated glomerular filtration rate (eGFR) levels, mean serum uric acid levels, prior history or current congestive heart failure (CHF), mean left ventricular ejection fraction (LVEF), mean left atrial dimension (LA dimension), Mean Atrial Fibrillation European Heart Rhythm Association score (AF EHRA score), mean AF duration, and CHA_2DS_2-VASc score were also taken into consideration.

2.5 | Statistical analysis

The pooled effect sizes were presented as odds ratios with 95% confidence intervals. Statistical analysis of individual studies including methodologies used, how OR/HR is calculated, and factors considered for AF recurrence were summarized in Table 1. The HR value from each primary study was directly factored into the OR. To assess heterogeneity across studies, we utilized I^2 derived from the χ^2 test, which quantifies the proportion of variance in effect estimates attributable to heterogeneity as opposed to sampling error. When I^2 is greater than 50%, statistical heterogeneity is considered to be moderate. The random effects model was utilized when aggregated analysis revealed significant heterogeneity. For aggregating effect sizes, we conducted fixed-effects meta-analysis using the inverse variance method and random effects meta-analysis using the inverse variance heterogeneity method. Similarly, the sensitivity analysis was performed in a random, predefined manner. We also conducted subgroup analyses based on the study type(prospective or retrospective), country (Turkey or China), and NLR status either pre- or postablation.

3 | RESULTS

A PRISMA-compliant (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram describing the selection of studies is included in Figure 1. We found a total of 270 studies with the search criteria mentioned in the methods, including 214 results from Google Scholar and 56 results from PubMed. We excluded 142 studies based on titles or abstracts and 44 duplicate studies. The remaining 84 studies were screened further, and 75 were removed

TABLE 1 Methods of the statistical analysis of included studies.

First author	OR/HR	How was OR/HR obtained	Factors included in the model
Canoplat	HR	Multivariate Cox proportional hazard regression analysis	Age, Women, hypertension, diabetes, dyslipidemia, BMI, CAD, smoking, alcohol, nonparoxysmal AF, AF duration (years), AF EHRA score, LVEF (%), LAD, WBC count, NLR, Hs-CRP, early recurrence
Im	HR	Univariate and multivariate analysis	Persistent AF, CHF, LVESD, LVEF, LAV, post-NLR, post-Hs-CRP, CK-MB, troponin-T, BNP, ablation time, early recurrence
Guo	HR	Univariate and multivariate analysis	Age, male, BMI, nonparoxysmal AF, AF duration, LA, LVEF, pre-WBC, pre-NLR, pre-RDW, Hs-CRP, eGFR, SUA, post-WBC, post-NLR
Bazoukis	OR	Multivariate analysis	Early arrhythmia recurrence, post-NLR
Can	OR	Univariate and multivariate stepwise logistic regression analysis	NT-pro BNP, NLR, left atrial diameter, semaphoring-4D
Ding	HR	Univariate and multivariate analysis	NLR, Hs-CRP, LAD
Yiu	HR	Univariate and multivariate analysis	Age, Male, BMI, smoking, alcohol, hypertension, diabetes, CHD, use of medications, LA size, LVEF, NT-pro BNP, WBC, NLR, Hemoglobin, PLT, AGR, serum creatinine, uric acid levels, CHADS2

Note: CHADS2: Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke.

Abbreviations: AGR, Albumin-to-Globulin Ratio; BMI, Body Mass Index; BNP, B-type Natriuretic Peptide; CAD, Coronary Artery Disease; CHF, Congestive Heart Failure; CK-MB, Creatine Kinase-MB; eGFR, Estimated Glomerular Filtration Rate; EHRA, European Heart Rhythm Association; HR, Hazard Ratio; Hs-CRP, High-sensitivity C-reactive Protein; LAD, Left Atrial Diameter; LAV, Left Atrial Volume; LVEF, Left Ventricular Ejection Fraction; LVESD, Left Ventricular End-Systolic Diameter; NLR, Neutrophil-to-Lymphocyte Ratio; NT-pro BNP, N-terminal pro-B-type Natriuretic Peptide; OR, Odds Ratio; SUA, Serum Uric Acid.

because they were either irrelevant to the present study or either case reports, review articles, or editorials. Full-text manuscripts were retrieved for a detailed evaluation of nine studies. Out of them, two studies reported OR on AF recurrence based on delta NLR,[1,5] so both of them are excluded. The remaining seven studies[6–12] were included in our meta-analysis.

In our analysis, we included seven studies[6–12] with a total of 1923 AF patients who underwent catheter ablation. Out of 1923, 753 patients (39%) reported recurrence. Only three out of seven studies differentiated between early and late recurrence.[10–12] Among them, 242 out of 1096 patients experienced it during the first 3 months of ablation during the blanking period (early recurrence), and 511 patients out of 1923 patients reported it between 3 and 12 months after ablation (late recurrence). The main features of the study on the association between AF recurrence and NLR are presented in Table 2. Patients are in the age range of 49–69 years old. The proportion of males ranged between 35.6% and 73.4%, and the mean follow-up period varied from 3 to 30 months. Five studies are retrospective,[6,7,9,11,12] and two studies are prospective cohort studies.[8,10]

All the studies included reported AF recurrence either after radiofrequency or cryoballoon catheter ablation procedures. Four studies[6–8,10] observed an association between the recurrence of AF and preablation NLR, two studies[11,12] reported postablation NLR and one study[9] reported both pre- and postablation NLR. Among these, six studies[7–12] showed that OR of NLR and AF recurrence had a significant difference, whereas OR did not show significant results in two studies.[6,9] (Table 2).

The combined unadjusted OR of AF recurrence for preablation NLR was 1.33 (95% CI: 1.04–1.71) with significant heterogeneity across studies ($I^2 = 95.49\%$, $p < .01$), and the adjusted OR was 1.45 (95% CI: 0.87–2.43, $I^2 = 95.1\%$, $p < .01$). For postablation NLR, the unadjusted OR was 1.21 (95% CI: 1.09–1.36, $p < .01$, $I^2 = 85.9\%$), and the adjusted OR was 1.28 (95% CI: 0.93–1.76), demonstrating significant heterogeneity ($I^2 = 95.32\%$) with a p-value of <.01 (Figure 2).

3.1 | Sensitivity and subgroup analysis

We subsequently performed a leave-one-out sensitivity analysis by excluding each study at a time and recalculating the overall estimate to assess the impact of each individual study on the overall value. In our analysis, there are fluctuations in the confidence intervals, but the overall results are relatively stable and not heavily dependent on any single study (Figure 2). After removing one study[9] that had a mean age of <50 years old, the analysis did not find a significant influence on the results. After removing the study,[8] which enrolled fewer men, and also the study with the lowest quality,[7] the results did not significantly influence each other. We also performed a predefined subgroup analysis according to study design (prospective or retrospective) and geographic area(China or Turkey); there was no significant

TABLE 2 Characteristics of seven studies included in the meta-analysis.

Author	Country	Year	Study design	Sample size	Mean age (years)	Mean follow-up (months)	AF recurrence reported with either pre-ablation or postablation NLR	Unadjusted OR/HR	Adjusted OR/HR
Liu	China	2022	Retrospective	84	59	19	Pre-ablation NLR	0.99 (0.88–1.11)	
Ding	China	2022	Retrospective	263	N/A	N/A	Preablation NLR	1.57 (1.15–2.16)	1.44 (1.04–2.00)
Can	Turkey	2021	Prospective	101	60	N/A	Preablation NLR	1.01 (1.01–1.02)	1.02 (0.99–1.02)
Guo	China	2014	Retrospective	379	49	30	Pre-ablation NLR	1.12 (0.96–1.30)	
Canpolat	Turkey	2013	Prospective	251	54	19	Pre-ablation NLR	2.66 (2.15–3.29)	2.15 (1.7–2.73)
Bazoukis	China	2019	Retrospective	346	59	26	Postablation NLR	1.10 (1.01–1.20)	
Im	South Korea	2013	Retrospective	499	N/A	25	Postablation NLR	1.15 (1.07–1.24)	1.09 (1.00–1.19)
Guo	China	2014	Retrospective	379	49	30	Postablation NLR	1.48 (1.34–1.64)	1.51 (1.36–1.68)

Abbreviations: AF, atrial fibrillation; HR, hazard ratio; NLR, neutrophil lymphocyte ratio; OR, odds ratio.

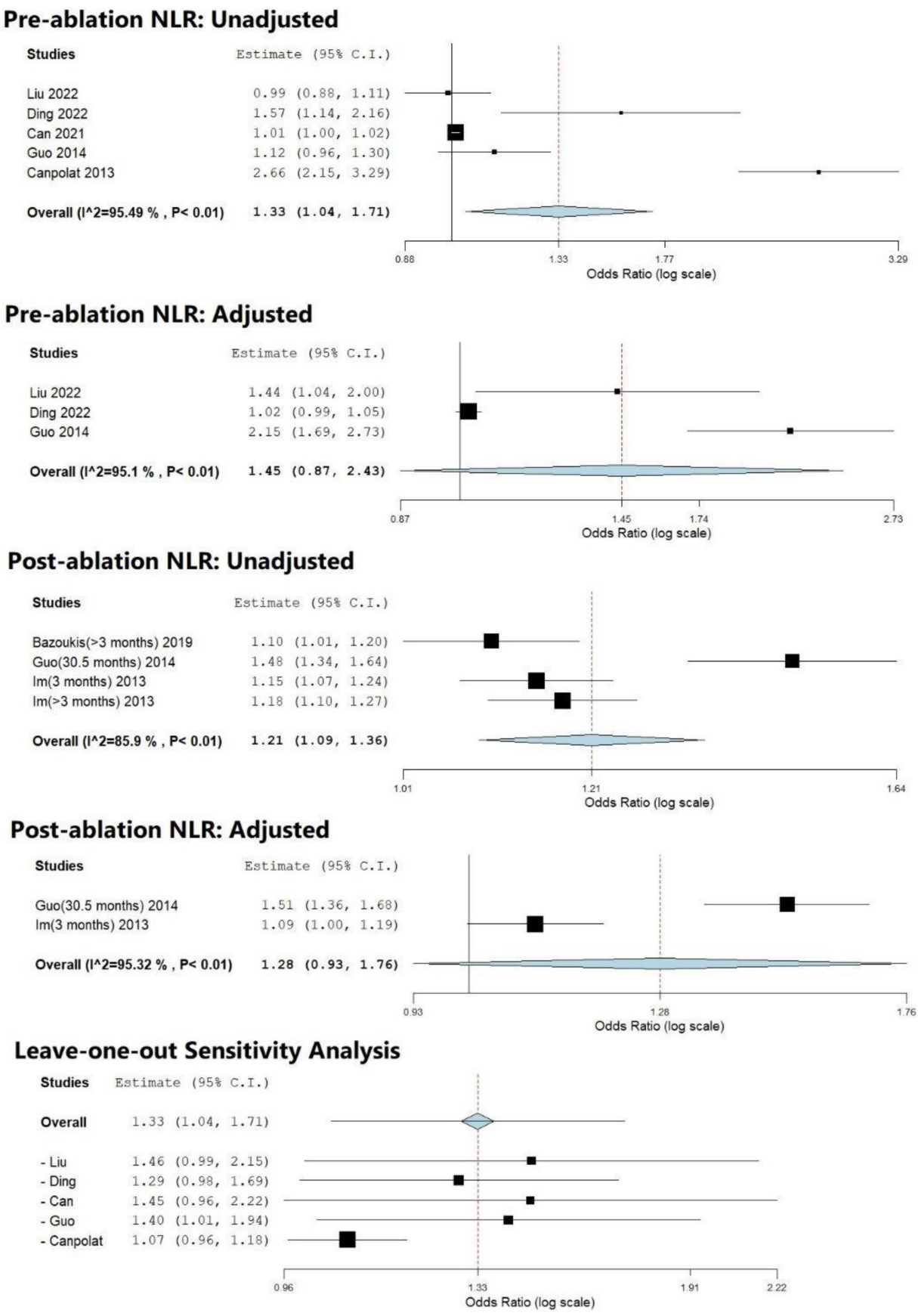

FIGURE 2 Association between preablation and postablation neutrophil lymphocyte ratios (NLR) and atrial fibrillation (AF) recurrence.

heterogeneity between studies. Therefore, this analysis confirmed the robustness of the findings.

4 | DISCUSSION

AF is the most common arrhythmia in clinical settings, and it is associated with increased risk of stroke, heart failure, sudden cardiac arrest, and mortality.[13,14] AF is caused by spontaneous depolarizations outside the sinoatrial node and occurs faster than sinus rhythm.[14] These ectopic activities are eliminated by scarring the atrial tissue either by heat (radiofrequency) or freezing (cryoablation). Even after ablation, AF can recur due to the reconduction of the scarred tissue or other arrhythmogenic substrates in the atria.[14] This mechanism of AF is complex, and it is mostly multifactorial. These include fibrosis, oxidative stress, inflammation, prothrombotic state, and genetic factors.[13,15] Inflammation is linked to both atrial fibrillation onset and maintenance, contributing to structural and electrophysiological alterations in atrial remodeling.[13] Inflammation plays a crucial role in substrate formation, contributing to both electrical and structural remodeling of the atria.[16] Ablation during pulmonary vein isolation (PVI) triggers the acute inflammatory response, which links inflammation to AF recurrence. Ablation causes tissue damage, leading to a severe inflammatory response. Researchers suggest that this acute inflammation on the arrhythmic substrate contributes to the recurrence of AF.[17] Previous studies with increased inflammatory markers like post-NLR, IL-6, IL-8, C-reactive protein, and tumor necrosis factor-α in recurrence patients support that inflammation plays a role in the recurrence of AF after PVI.[9,11,12,18] This is evidenced by increased infiltration of lymphomononuclear cells in atrial pathology and higher levels of inflammatory markers like in AF patients compared to people in sinus rhythm.[19,20]

The white blood cell (WBC) count and its different subtypes are determinants of inflammation. Among the different subtypes of WBC, neutrophils represent nonspecific inflammation, and decreased lymphocytes indicate physiological stress and poor health. Thus, NLR reflects the balance between both neutrophils and lymphocytes and provides information on both the stress response and inflammatory status in the body.[20] Though NLR is a novel inflammatory marker and its impact is studied in different cardiovascular diseases, its role in predicting the recurrence of AF after catheter ablation is limited.

Out of 7 studies included, only 5[6,8,10–12] clearly reported the type of AF. The majority of the patients who underwent ablation had a history of paroxysmal AF, and the second most common type is persistent AF. Previous literature reported that persistent AF is more commonly associated with AF recurrence than paroxysmal AF.[21,22] However, there are no clear data in our study about the type of AF before ablation and its influence on AF recurrence postablation.

Four studies[7,8,11,12] used radiofrequency ablation, and two studies[6,10] used cryoballoon ablation of pulmonary vein isolation. Studies in our analysis reported that procedural time was longer in patients with recurrence than in nonrecurrence patients.[10–12] A longer operation time is associated with extensive RF ablation, which causes tissue damage and a severe inflammatory response. Both the acute inflammatory response triggered by ablation and the delayed effects of ablation on the arrhythmic substrate may contribute to the early recurrence.[17] Lellouche et al. reported that 91% of the patients with early recurrences of atrial arrhythmias following AF ablation will experience late recurrences.[23] Even the studies included in our analysis reported that early recurrence and ablation time are independent predictors of late recurrence.[12] Patients in the recurrence group had increased left atrial diameter, decreased left ventricular ejection fraction, and increased comorbidities such as diabetes and hypertension.[6–8,10,12,17]

Though catheter ablation is superior to medical treatment, its efficacy is questioned because of the recurrence of AF after the procedure. Many recent studies[6–12] have suggested that an elevated NLR has a predictive role in AF recurrence postablation. But till now, no meta-analysis specifically focused on both baseline and postablation NLR and recurrence; therefore, this meta-analysis was conducted, including 1923 participants from five prospective and two retrospective observational studies, and there is a significant positive association between NLR and AF recurrence. However, there was significant heterogeneity across the studies, possibly due to variations in patient characteristics, study methodologies, or sample sizes. The inconsistency between unadjusted and adjusted odds ratios may also stem from variations in how the included studies controlled for confounding factors. This highlights the need for standardized reporting and the inclusion of confounding variables in future studies to improve the comparability and reliability of results.

NLR is used as a predictive biomarker for different cardiovascular diseases. It serves as an early marker for hypertension and diabetes.[24] In our analysis, 6 of 7 studies reported traditional cardiovascular comorbidities like diabetes and hypertension. Diabetes prevalence ranged from 8% to 35%, and it was higher in the recurrence group than in the nonrecurrence AF group. Similarly, the recurrence group reported older participants and a high incidence of hypertension. Two studies in our analysis reported high pro-BNP levels. A meta-analysis by Wang et al. reported that high NLR values are associated with increased hospital mortality in heart failure patients.[25] Additionally, all the included studies reported high Hs-CRP levels. In a study by Im et al., the Hs-CRP before radiofrequency catheter ablation (RFCA) was 0.7 mg/dL, and after RFCA was 12.8 mg/dL. This study also reported the odds of developing AF recurrence with postablation NLR as 1.18 (1.09–1.27).[12] This indicates that inflammatory mechanisms are more active in patients with AF recurrence. Therefore, considering inflammatory markers as a beneficial tool to detect the risk of recurrence would be of great assistance in terms of timely AF recurrence diagnosis.

4.1 | Limitations

Although we found a significant association between NLR and A fib recurrence, a few limitations and potential biases should be addressed.

First, there is heterogeneity among the included studies. Variations in the study design, duration, geographic regions, and baseline patient characteristics might be responsible for this heterogeneity. Second, meta-analyses may result in ecological fallacies as conclusions drawn at the study level may not accurately reflect specific individuals. Third, though our analysis showed a significant association between postablation NLR and AF recurrence, we included only three studies[9,11,12] that reported postablation NLR. However, the notable heterogeneity in the adjusted postablation NLR analysis underscores the need for further research to elucidate potential sources of variability.

5 | CONCLUSIONS

Though there have been previous meta-analyses on different hematological markers in predicting AF recurrence, our meta-analysis specifically focused on studies with NLR either pre- or postablation in predicting the recurrence of AF after an ablation procedure. Considering the results of our study, the significance of NLR as a predictive marker for AF recurrence suggests its potential clinical utility. Despite being a common laboratory test, it should not be overlooked and taken into consideration along with patient history and ECG findings when diagnosing the recurrence of atrial fibrillation. The simplicity, cost-effectiveness, and wide availability of the NLR test make it an attractive addition to the diagnostic toolkit for clinicians managing postablation patients. Incorporating NLR assessment into routine follow-up protocols could aid in the early identification of patients at higher risk of AF recurrence, enabling timely intervention and personalized management strategies.

AUTHOR CONTRIBUTIONS

Rupak Desai: Conceptualization, Methodology, Software, Formal Analysis, Resources, Data Curation, Writing-Original Draft, Writing – Review & Editing, Project administration; Sai Prasanna Lekkala, Sai Priyanka Mellacheruvu: Writing-Original Draft, Writing – Review & Editing, Visualization; Project administration; Karanvir Singh Gill, Puneeteshwar Singh Khela: Writing-Original Draft, Writing – Review & Editing; Gurjot Singh: Writing-Original Draft, Writing – Review & Editing, Data Curation; Sahas Reddy Jitta; Manali Patel, Mohmed Junaid Hingora: Writing-Original Draft, Writing – Review & Editing.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

ETHICS STATEMENTS

Since the data included in this review were deidentified and already available in publicly accessible databases, the IRB review was not mandatory. This review was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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