

## Review Article

# The Predictive Role of Inflammatory Biomarkers in Atrial Fibrillation as Seen through Neutrophil-Lymphocyte Ratio Mirror

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Atrial fibrillation (AF) is the most common arrhythmia and is responsible for significant disease burden worldwide. Current evidence has suggested that systemic inflammatory response plays a crucial role in the initiation, maintenance, and progression of AF. So, recent efforts have been directed in search of measurable inflammatory biomarkers as additional tools in severity and prognosis assessment of AF. A simple, and easily obtainable, inflammatory marker is the neutrophil-lymphocyte ratio (NLR), which has shown good performance in preliminary studies as a potential prognostic biomarker in patients with AF. In this work, we performed a thorough review of clinical studies that evaluated the role of C-reactive protein (CRP), interleukin-6 (IL-6), and NLR as predictors of outcomes in AF. We gave a particular emphasis on the NLR because it is a simpler, widely available, and inexpensive biomarker.

## 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, which in 2010 was estimated to affect about 33.5 million individuals in the world [1], with a prevalence around 2.3–3.4% among adults [2], and may reach 9% in those aged over 80 years [3]. Studies point to an increase in both incidence and prevalence [1, 4, 5], as well as the attributable mortality [1, 5], so that between 1990 and 2013 AF was the factor with the greatest relative increase in the burden of cardiovascular diseases (CVDs) [5]. Future projections predict a 2-fold increase in the number of cases of AF in 2050 [3]. The AF is associated with significant morbidity and mortality, increasing the risk of stroke and death from all causes [6, 7].

Recent investigations have registered significant advances in the understanding of the pathogenic mechanisms underlying AF [8, 9]. One of the most explored mechanisms and that has gained more and more space in recent years is the inflammatory response [10, 11]. The literature has emphasized

the role of inflammation in the initiation, maintenance, and progression of AF [8, 12, 13]. Several inflammatory biomarkers, as C-reactive protein (CRP) and interleukins, have been associated with the occurrence of AF and its prognosis, including vascular events [10, 14–16]. In fact, the incidence of AF is increased in other situations that share significant systemic inflammatory response such as nonalcoholic fatty liver disease [17] and metabolic syndrome [18, 19], suggesting a role of inflammation as a mediator between atrial fibrillation and these situations.

Among the inflammatory biomarkers, the neutrophil-lymphocyte ratio (NLR), defined as the ratio of absolute counts of neutrophils and lymphocytes, has emerged recently as effective outcomes predictor in atrial fibrillation [20, 21], a role also demonstrated for ischemic heart disease and stroke [22–24]. NLR is a simple, inexpensive, and widely available biomarker and has been shown to be a good predictor of atrial arrhythmias that reflects the role of unbalanced white cells (with the predominance of activated neutrophils) in arrhythmogenesis [8, 9, 25].

Multiple inflammatory markers have been studied as predictors of outcomes in AF, from those with potential direct involvement in the pathogenesis, such as IL-6 and NLR [11, 26], and others only as a reflection of underlying immune responses, but apparently without direct participation as CRP [27]. There are those that are being more used in research contexts than in clinical practice. In this paper, we performed a thorough review of clinical studies focusing on CRP, IL-6, and NLR, as they are more reliable in clinical practice, with particular emphasis on the NLR because it is simpler, more widely available, and inexpensive.

## 2. Overview of Inflammatory Biomarkers in Atrial Fibrillation

Several studies have demonstrated the association between inflammatory markers and the incidence, severity, response to treatment, and prognosis in AF [14–16, 28]. An analysis of a large study with 17,120 participants, without prior history of arrhythmia, high-sensitivity C-reactive protein (hs-CRP), was associated with a 36% increase in the risk of developing AF (hazard ratio [HR]: 1.37,  $p$ -trend < 0.01) for each increasing tertile above baseline, with persistently high risk, comparing the highest to the lowest hs-CRP tertile, even after adjustment for potential confounders (hazard ratio [HR] 1.96;  $p$  < 0.01) [29]. In other studies in patients with AF, CRP was a significant predictor of stroke [14, 30] and peripheral embolism [31]. In treated patients who underwent electrical cardioversion, a high hs-CRP was an independent predictor of AF recurrence even after adjusting for confounders variables [32, 33]. In another study following patients after catheter ablation, a high hs-CRP was an independent predictor of recurrence ( $p$  = 0.021) during a median follow-up of 15 months [15]. The contribution of inflammation in atrial activity seems to begin early, as demonstrated in a study where a high CRP was an independent risk factor for spontaneous contrast in transesophageal echocardiography [34]. This reflects that electromechanical impairment begins before any electrocardiographic visible dysrhythmia.

Other inflammatory biomarkers associated with AF and its progression are interleukin-6 (IL-6) [35] and interleukin-18 [36]. In one of these studies, with 3,762 adults with chronic kidney disease, a high plasma IL-6 level was associated with AF at baseline (Odds Ratio [OR], 1.61;  $p$  = 0.001) and predicted new-onset AF (OR, 1.25;  $p$  = 0.03) during a mean follow-up of 3.7 years [35]. In a study with patient in oral anticoagulation for AF, a high-sensitivity interleukin-6 (hsIL6) was a predictor of long-term cardiovascular events (HR 1.97,  $p$  = 0.002) and all-cause mortality (HR 2.48,  $p$  < 0.001) [37]; and adding hsIL6 to the clinical risk scores (CHADS2 and CHA2DS2-VASc) improved the discrimination index value for prediction of long-term cardiovascular events and death [37]. In another study with rhythm control strategy, IL-6 and CRP were significantly higher in those with AF recurrence than in those maintaining sinus rhythm (mean IL-6: 1.84 versus 1.19,  $p$  < 0.005; CRP: 1.24 versus 0.59,  $p$  < 0.005) [38]. Table 1 summarizes the clinical studies that

have assessed the role of general inflammatory biomarkers in AF.

## 3. The Particular Role of Neutrophil-Lymphocyte Ratio as a Predictive Biomarker in Atrial Fibrillation

**3.1. Incidence and Prevalence.** A high NLR is associated with increased incidence of AF, as was evident in a prospective cohort, with 275 patients who underwent nonemergency coronary artery bypass grafting, where the group with postoperative AF had higher preoperative NLR (median 3.0 versus 2.4,  $p$  = 0.001) [21]. These findings were also evident in a study with patients undergoing coronary angiography, with stent placement, for acute ST-segment elevation myocardial infarction, where those who developed AF had higher post-catheterization NLRs at 48 hours (median 5.23 versus 3.00,  $p$  = 0.05) and 96 hours (median 4.67 versus 3.56,  $p$  = 0.03) [59], suggesting an inflammatory contribution to new-onset postprocedural AF. In another study with diabetic patients, NLR was significantly higher in those with AF than in the AF-free group (mean  $2.87 \pm 1.3$  versus  $2.2 \pm 1.56$ ,  $p$  = 0.019) and was an independent risk factor for AF (OR 3.486,  $p$  = 0.004) using 2.38 as cut-off [60].

**3.2. Severity and Incidence of Stroke.** A high NLR not only predicts higher incidence of AF but also is a predictor of disease severity and risk of stroke [61, 62]. In a study with 309 patients with nonvalvular AF, a high NLR (>2.59) was an independent risk factor for the presence of left atrial thrombus on transesophageal echocardiography (TEE) (OR 1.59;  $p$  < 0.02) [61]. In another study with TEE, a high NLR (>2.92) was a predictor of reduced (<10 cm/sec) left atrial appendage wall velocity (LAAWV) in patients with paroxysmal AF [63]. A large retrospective cohort including 32,912 patients with AF showed that each increase in NLR quartile above the lowest was associated with a significant increase in risk of stroke with HRs of 1.11 (0.91–1.35), 1.25 (1.03–1.51), and 1.56 (1.29–1.88) for the second, third, and highest quartiles, respectively; and adding NLR to CHA2DS2-VASc risk score improved the accuracy for prediction of stroke [62]. Even in those in oral anticoagulation, a high NLR level was a predictor of stroke [20].

**3.3. Treatment Response and Mortality.** A high NLR is also a predictor of poor response to treatment as shown in a study, where it predicted AF recurrence after successful cardioversion with amiodarone [64]. In another study with 251 patients with symptomatic AF who underwent cryoablation, a high preablation NLR (>3.15) was a predictor of postprocedural disease recurrence (HR 2.15, 95% CI 1.70 to 2.73,  $p$  < 0.001) [65]. Regarding mortality, no specific study relating NLR and increased mortality in patients with AF was found. However, a high NLR was an independent predictor of short- and long-term mortality in patients with stroke in general (irrespective of being cardioembolic or atherosclerotic) [24, 66, 67]. Table 2 summarizes the clinical studies that have assessed the role of NLR as a prognostic biomarker in AF.

TABLE 1: Clinical studies on the predictive value of inflammatory biomarkers (other than NLR) in atrial fibrillation (chronological order).

Study (year) [ref]	Biomarker(s)	Number of patients	Threshold	Assessment period	Results
Conway et al. (2004) [11]	IL-6 and CRP	106 patients with chronic AF and 41 healthy controls	Median comparison between groups	At baseline of the study	Patients with AF had significantly higher levels of IL-6 (median 24 versus 3 pg/mL, $p = 0.034$ ) and CRP (median 0.27 versus 0.13 mg/dL, $p = 0.003$ ), compared with controls. Plasma IL-6 levels were higher among AF patients at "high" risk of stroke using risk scores ( $p = 0.003$ )
Thambidorai et al. (2004) [31]	hs-CRP	104 patients with AF who underwent TEE	Median comparison between groups	CRP measured $\leq 1$ week after TEE	Patients with identified thromboembolic risk factors on TEE had greater CRP levels than those without (1.00 versus 0.302 mg/dL). CRP also correlated with clinical stroke risk factors
Psychari et al. (2005) [39]	CRP and IL-6	90 patients with AF (70 with persistent AF who underwent PCV and 20 with permanent AF) and 46 controls	Mean comparison between groups	6 hours after CV or in the morning hours after fasting	Compared with controls patients with AF had increased CRP (mean 5.7 versus 2.3 mg/L, $p = 0.002$ ) and IL-6 (mean 8.3 versus 2.9 pg/mL, $p < 0.001$ ). There was positive relation between LAD and inflammatory markers (CRP [ $R = 0.37$ , $p < 0.001$ ] and IL-6 [ $R = 0.46$ , $p < 0.001$ ])
Malouf et al. (2005) [33]	hs-CRP	67 patients with AF or atrial flutter who underwent successful ECV	Mean comparison between groups	Before ECV	Pre-CV hs-CRP levels were an independent predictor of arrhythmia recurrence (OR 2.19, 95% CI 1.05–4.55, $p = 0.036$ ) even after adjusting for confounders
Watanabe et al. (2006) [32]	hs-CRP	106 patients with AF who underwent ECV	$\leq 0.12$ mg/dL for CV success and $\geq 0.06$ mg/dL for recurrence	Immediately prior to ECV	A lower hs-CRP ( $\leq 0.12$ mg/dL) was an independent predictor of successful ECV (OR 0.33, 95% CI 0.21–0.51). In turn, a high hs-CRP was the only independent predictor of AF recurrence (OR 5.30, 95% CI 2.46–11.5) using a cut-off value of hs-CRP $\geq 0.06$ mg/dL, and after adjustment for coexisting cardiovascular risks
Lip et al. (2007) [40]	CRP and CD40	880 subjects with AF from SPAF III clinical trial	Multiple cut-offs (tertiles)	Within 30 days of enrollment or after 3 months in the study	Patients with moderate to high stroke risk (measured by CHADS2 score and NICE criteria) had the highest levels of CRP (Kruskal Wallis test, $p < 0.001$ ). All-cause mortality (log rank test, $p = 0.001$ ) and vascular events ( $p = 0.05$ ), but not stroke, were more common in patients with high CRP levels during a mean follow-up of 453 ( $\pm 229$ ) days. Soluble CD40 ligand was not related to prognosis

TABLE 1: Continued.

Study (year) [ref]	Biomarker(s)	Number of patients	Threshold	Assessment period	Results
Liu et al. (2007) [41]	CRP	A meta-analysis of 7 studies with 420 AF patients who underwent successful ECV	Mean difference between groups	At baseline of primary studies	Atrial fibrillation relapsed in 229 patients. Baseline CRP levels were greater in patients with AF recurrence than in those without (SMD 0.35 units, 95% CI 0.01–0.69)
Fujiki et al. (2007) [38]	IL-6 and CRP	35 patients with AF who underwent successful PCV	Mean comparison between groups	After pharmacological restoration of SR	During the 1-year follow-up period, 15 patients presented recurrence of AF. Patients with AF recurrence had significantly higher plasma levels of both IL-6 (mean $1.84 \pm 0.66$ versus $1.19 \pm 0.51$ ng/L, $p < 0.005$ ) and CRP ( $1.24 \pm 0.79$ mg/L versus $0.59 \pm 0.40$ , $p < 0.005$ ) than those without. There was a significant positive correlation between levels of IL-6 and CRP
Henningesen et al. (2009) [42]	IL-6 and hs-CRP	56 patients with persistent AF who underwent successful ECV	2.8 pg/mL for IL-6 and 3.0 mg/L for hs-CRP (analysis included median comparison)	Before CV and after 1, 30, and 180 days	After 180 days of follow-up, the recurrence rate was 68%. Patients with recurrence of AF had significantly higher hs-CRP ( $2.0$ versus $1.25$ mg/L, $p < 0.001$ ) and IL-6 ( $2.75$ versus $1.96$ pg/mL, $p < 0.001$ ) than those who maintained SR. Baseline IL-6 was the only independent predictor of recurrent AF ( $p = 0.04$ ) in a multivariate Cox analysis
Henningesen et al. (2009) [43]	IL-6 and hs-CRP	46 patients with paroxysmal or persistent AF who underwent RFCA	Median comparison between groups	Before the first ablation procedure and at follow-up visits	After 12 months of follow-up, the recurrence rate was 59%. Patients with recurrence of AF had significantly higher IL-6 ( $1.4$ versus $0.9$ pg/mL, $p = 0.007$ ) and hs-CRP ( $2.2$ versus $0.7$ mg/L, $p = 0.018$ ) at baseline than those who maintained SR. IL-6 concentration prior to ablation was an independent predictor of recurrent AF ( $p = 0.027$ )
Lin et al. (2010) [15]	hs-CRP	137 patients with AF who underwent mapping and catheter ablation	2.92 mg/L	Before the first ablation procedure	Higher hs-CRP was associated with an increased frequency of nonpulmonary vein ectopies (34.4% versus 17%, $p = 0.034$ ) and was an independent predictor of recurrence ( $p = 0.021$ ) in a multivariable regression model after adjusting for other potential covariates
Cianfrocca et al. (2010) [44]	CRP	150 patients with persistent nonvalvular AF, who underwent TEE prior to CV	3 mg/L (analysis included mean comparison between groups)	Before CV	C-reactive protein was significantly associated with thrombus and/or dense SEC (OR 3.41, 95% CI 1.2–9.8)

TABLE 1: Continued.

Study (year) [ref]	Biomarker(s)	Number of patients	Threshold	Assessment period	Results
Maehama et al. (2010) [45]	CRP	A total of 165 patients with nonrheumatic AF	Median comparison between groups	Within 1 week before TEE	Patients in the high-risk group according to CHADS2 score had significantly greater CRP levels than those in the intermediate- and low-risk groups (0.80 mg/dL versus 0.16 mg/dL versus 0.08 mg/dL, $p < 0.01$ , resp.). And the incidence of LA SEC and LA thrombus on TEE increased with an increasing CHADS2 score
Marott et al. (2010) [27]	CRP	46,876 individuals from 2 large studies (including 2,111 with AF)	Multiple cut-offs (quintiles)	NA	The highest CRP quintile was associated with increased risk of atrial fibrillation compared with the lower quintile (OR 2.19, 95% CI 1.54–3.10). However, CRP did not fulfill the causality criterion, whereas its elevation by genetically CRP did not increase atrial fibrillation risk
You et al. (2010) [14]	CRP, IL-6, and Cystatin C	103 AF patients (28 with AF complicated by ischemic stroke) and 112 controls	Median comparison between groups	At baseline	AF patients had higher levels of hs-CRP ( $p = 0.004$ ), IL-6 ( $p = 0.000$ ), and cystatin C ( $p = 0.000$ ) than control subjects. Plasma hs-CRP level was also higher in patients with AF complicated by ischemic stroke compared with those with simple AF ( $p = 0.036$ )
Luan et al. (2010) [36]	IL-18 and MMP-9	56 patients with AF and 26 controls	Mean or median comparison between groups	At first 24 hours after admission	IL-18 was significantly higher in patients with AF than in controls ( $471.50 \pm 144.91$ versus $232.20 \pm 55.33$ pg/mL; $p < 0.0001$ ). MMP-9 (OR = 1.02, 95% CI: 1.00–1.03, $p = 0.012$ ) and IL-18 were independently associated with AF (OR = 1.02, 95% CI: 1.01–1.03, $p = 0.001$ ). Interleukin-18 levels were also higher in persistent AF patients than in those with paroxysmal AF ( $p = 0.001$ )
Celebi et al. (2011) [46]	hs-CRP	216 patients with persistent AF who underwent CV	1.85 mg/dL (the analysis included mean comparison between groups)	Prior to and 1, 2, 7, and 30 days after CV	The basal hs-CRP levels were higher in patients with an AF relapse than in those without ( $1.68 \pm 0.57$ versus $1.12 \pm 0.53$ mg/dL; $p < 0.01$ ). By multivariate Cox analysis, the independent predictors of AF relapse time points were the basal and day-2 hs-CRP levels
Liu et al. (2011) [47]	hs-CRP	121 patients with AF (paroxysmal/persistent AF: 77/44) who underwent CPVI	1.41 mg/L (the analysis included median comparison between groups)	On the morning of admission, before the procedure	The plasma hs-CRP concentration was significantly higher in the group with AF recurrence than in the nonrecurrent one (median $2.22$ mg/L versus $0.89$ mg/L, $p < 0.001$ ). A higher hsCRP was a significant predictor of AF recurrence in overall (OR 5.10, 95% CI 2.14–12.11, $p < 0.001$ ) and in subgroups of paroxysmal (OR 4.12, 95% CI 1.36–12.47, $p = 0.012$ ) and persistent AF (OR 16.37, 95% CI 2.52–56.42, $p = 0.003$ )

TABLE 1: Continued.

Study (year) [ref]	Biomarker(s)	Number of patients	Threshold	Assessment period	Results
Kim et al. (2011) [48]	TGF- $\beta$ and TIMP-1	242 patients with AF (155 paroxysmal AF, 87 persistent AF) who underwent CA	10.0 ng/mL for TGF- $\beta$ and 1.1 ng/mL for TIMP-1	Biomarker measurement, LA voltage map, and 3D-CT before CA	Patients with higher TGF- $\beta$ ( $\geq 10.0$ ng/mL) had lower mean LA voltage ( $p = 0.014$ ) and greater LA volume ( $p = 0.022$ ) than those with lower levels. Similarly, patients with higher TIMP-1 ( $\geq 1.1$ ng/mL) had lower mean LA voltage ( $p = 0.019$ ) than those with lower levels. This reflects that higher plasma concentrations of this markers are closely related with LA electroanatomical (voltage and structural) remodeling
Kimoshita et al. (2011) [49]	CRP	552 patients who underwent coronary bypass surgery, analyzed retrospectively	Multiple cut-offs (the analysis included median comparison between groups)	Preoperative	AF occurred in 21.9% of patients after surgery. The median value of CRP was higher in patients who developed AF than in those who did not (2.2 versus 1.3, $p = 0.001$ ). This association persisted after adjustment for confounders (HR 1.43, 95% CI 1.22–1.97 per 1 SD increase in CRP, and HR 2.88, 95% CI 1.67–4.97 for CRP within 3.0–10.0 versus $< 1.0$ mg/dL)
Hermida et al. (2012) [50]	hs-CRP	293 with a history of AF	Multiple cut-offs (tertiles)	At visit 4	During a median follow-up of 9.4 years, hs-CRP was associated with increased risk for all-cause mortality comparing the highest versus the lowest tertiles (HR 2.52, 95% CI 1.49–4.25, $p < 0.0001$ ) after adjusting for potential confounders
Peña et al. (2012) [29]	hs-CRP	17,120 participants without prior history of arrhythmia	Multiple cut-offs ( $< 3.2$ , 3.2–5.8, and $\geq 5.8$ mg/L)	At study baseline	Each increase in hs-CRP tertile from the lowest was associated with a 36% increase in the risk of developing AF (HR 1.37, 95% CI: 1.16–1.60, $p < 0.01$ ), with an HR of 1.96 (95% CI: 1.40–2.75, $p < 0.01$ ) when comparing the highest hs-CRP tertile with the lowest
Roldán et al. (2012) [37]	IL-6	930 patients with permanent/patoxysmal AF in chronic anticoagulation	Multiples (3.35 pg mL $^{-1}$ for CVE, 4.16 pg mL $^{-1}$ for mortality)	At baseline	During a median follow-up of 957 (784–1087) days, 107 adverse cardiovascular events occurred (3.14%/year), which included 37 stroke/TIA events (1.5%/year). On multivariate analysis, a high IL-6 was associated with adverse cardiovascular events (OR 1.97, 95% CI 1.29–3.02, $p = 0.002$ ) and all-cause mortality (HR 2.48, 9% CI 1.60–3.85, $p < 0.001$ )
Barassi et al. (2012) [51]	hs-CRP	57 patients with AF who underwent ECV	2.99	Before and 3 weeks after ECV	CRP levels ( $> 2.99$ – $3.10$ mg/L) were significantly associated with AF recurrences (OR, 14.93, 95% CI 3.90–57.19, $p < 0.001$ )

TABLE 1: Continued.

Study (year) [ref]	Biomarker(s)	Number of patients	Threshold	Assessment period	Results
Mazza et al. (2013) [52]	hs-CRP	92 patients with AF and hypertension who underwent ECV	0.30 mg/dL	Before CV	A higher hs-CRP (>0.30 mg/dL) was associated with <i>p</i> -wave alterations such as <i>P</i> maximum above 120 ms ( <i>p</i> = 0.002) and <i>P</i> dispersion above 40 ms ( <i>p</i> = 0.0006) that are useful predictors of AF recurrence
Parashar et al. (2013) [53]	hs-CRP and NT-proBNP	2,370 patients with AMI, but without AF from TRIUMPH study	Median comparison between groups	At study baseline	There was a 15% increase in the rate of AF (OR 1.15, 95% CI 1.02–1.30, <i>p</i> = 0.02), for each 2-fold increase in CRP. Similarly, for every 2-fold increase in NT-proBNP, there was an 18% increase in the rate of AF (OR 1.18, 95% CI 1.03–1.3, <i>p</i> < 0.02)
Sinner et al. (2014) [54]	CRP and BNP	18,556 Whites and African Americans from three primary studies (ARIC, CHS, and FHS)	Multiple cut-offs (each 1-SD increase)	At the index visit	1,186 new cases occurred in five years of follow-up. CRP was significantly associated with AF incidence (HR 1.18, 95% CI 1.1–1.25, <i>p</i> < 0.0001), per 1-SD increase of ln-transformed values, as was BNP (HR 1.66, 95% CI 1.56–1.76, <i>p</i> < 0.0001) During a median follow-up of 10.9 years, 721 developed incident AF. Adiponectin, CRP, IL-6, TNF- $\alpha$ , TNF- $\alpha$ SR I, and TNF- $\alpha$ SR II concentrations were each higher among Whites and independently associated with a greater risk of incident AF. Together, these inflammatory cytokines mediated 42% (95% CI 15 to 119%, <i>p</i> = 0.004) of the adjusted white race associated AF
Dewland et al. (2015) [55]	CRP IL-6, TNF- $\alpha$ , TNF- $\alpha$ SR I, and others	2,768 participants without AF (43% Black) from Health ABC Study	Multiple cut-offs (depending on the biomarker)	At the baseline study visit	In patients with AF, IL-6 was independently associated with stroke or systemic embolism ( <i>p</i> = 0.0041), major bleeding ( <i>p</i> = 0.0001), vascular death ( <i>p</i> < 0.0001), and a composite thromboembolic outcome (ischemic stroke, systemic embolism, myocardial infarction, pulmonary embolism, and vascular death) ( <i>p</i> < 0.0001), after adjusting for clinical risk factors. Similarly, CRP was independently related to myocardial infarction ( <i>p</i> = 0.0047), vascular death ( <i>p</i> = 0.0004), and the composite thromboembolic outcome ( <i>p</i> = 0.0001)
Aulin et al. (2015) [56]	IL-6 and hs-CRP	6,187 patients with nonvalvular AF from the RE-LY study	Multiple cut-offs (quartiles)	Before start of study intervention	Plasma IL-6 level was significantly associated with presence of AF at baseline (OR 1.61, 95% CI 1.21–2.14, <i>p</i> = 0.001) and was an independent predictor of NOAF (OR 1.25, 95% CI, 1.02–1.53, <i>p</i> = 0.03) during a mean follow-up of 3.7 years, after adjusting for confounders
Amdur et al. (2016) [35]	IL-6	3,762 adults with CKD enrolled in the CRIC study	Multiple cut-offs (tertiles)	At baseline	

TABLE 1: Continued.

Study (year) [ref]	Biomarker(s)	Number of patients	Threshold	Assessment period	Results
Negreva et al. (2016) [57]	hs-CRP	51 patients with AF and 52 controls	Mean comparison between groups	At hospital admission, 24 hours, and 28 days after SR restoration	hs-CRP concentrations were higher in patients with AF than in controls at baseline (mean $8.12 \pm 0.82$ versus $5.57 \pm 0.21$ mg/L, $p = 0.003$ ), and the difference persisted 24 hours after SR restoration ( $8.16 \pm 0.71$ versus $5.57 \pm 0.21$ mg/L, $p < 0.001$ )
Hijazi et al. (2016) [58]	IL-6 and CRP	14,954 patients with AF on anticoagulation from the ARISTOTLE trial	Multiple cut-offs (quartiles)	At randomisation	There was a significant association between IL-6 and CRP and all-cause mortality independent of clinical risk factors and other biomarkers (HR 1.93, 95% CI 1.57–2.37 for IL-6, and HR 1.49 95% CI 1.24–1.79 for CRP, comparing the highest with the lowest quartiles). However, there were no associations with the risk of stroke or major bleeding

3D-CT: three-dimensional computed tomography; AF: atrial fibrillation; AMI: Acute Myocardial Infarction; ARIC: Atherosclerosis Risk in Communities Study; ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CA: catheter ablation; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CHADS<sub>2</sub>: one point for congestive heart failure, hypertension, age > 75, diabetes mellitus, and two points for prior stroke or transient ischemic attack; CHS: Cardiovascular Health Study; CI: confidence interval; CKD: chronic kidney disease; CPVI: circumferential pulmonary vein isolation; CV: cardioversion; CVE: cardiovascular events; ECY: electrical cardioversion; FHS: Framingham Heart Study; Health ABC: Health, Aging, and Body Composition; HR: hazard ratio; IL-17A: interleukin-17A; IL-6: interleukin-6; LA AWW: left atrial appendage wall velocity; LAD: left atrial diameter; MACE: major adverse cardiovascular events; MMP-9: matrix metalloproteinase-9; NA: not available; NICE: National Institute for Health and Clinical Excellence; NOAF: new-onset atrial fibrillation; NT-proBNP: NT-pro-brain natriuretic peptide; OR: Odds Ratio; PCI: percutaneous coronary intervention; PCV: pharmacological cardioversion; POAF: postoperative atrial fibrillation; RE-LY study: "Randomized Evaluation of Long-term anticoagulant therapy" study; RFC: radiofrequency catheter ablation; SAFHIRE: Study of Atrial Fibrillation in High-Risk Elderly; SEC: spontaneous echo contrast; SMD: standardized mean difference; SPAF: Stroke Prevention in Atrial Fibrillation; sPsel: soluble P-selectin; SR: sinus rhythm; STEMI: ST-segment elevation myocardial infarction; TEE: transesophageal echocardiography; TGF- $\beta$ : transforming growth factor- $\beta$ ; TIMP-1: tissue inhibitor of metalloproteinase-1; TNF- $\alpha$ : tumor necrosis factor alpha; TNF- $\alpha$  SR I: tumor necrosis factor alpha soluble receptor I; TNF- $\alpha$  SR II: tumor necrosis factor alpha soluble receptor II; vWF: von Willebrand factor.



TABLE 2: Clinical studies on the predictive value of the neutrophil-lymphocyte ratio as a biomarker in atrial fibrillation.

Study [ref]	Year	Number of patients	Threshold	Assessment period	Results
Gibson et al. [21]	2010	275 patients without previous atrial arrhythmia, undergoing CABG	Median comparison between groups	Preoperatively and on postoperative day 2	The incidence of AF was greater in groups with higher preoperative NLR (median 3.0 versus 2.4, $p = 0.001$ ) and postoperative NLR (median 9.2 versus 7.2, $p < 0.001$ )
Ertaş et al. [20]	2013	126 patients with nonvalvular AF	Mean comparison among subjects with or without stroke	At admission	In patients with nonvalvular AF, mean NLR was significantly higher among subjects with stroke compared to individuals without a stroke (5.6 versus 3.1)
Canpolat et al. [65]	2013	251 patients with symptomatic AF who underwent cryoablation	3.15	Preprocedural	Patients with a high preablation NLR ( $>3.15$ ) had a 2.5-fold increased risk of AF recurrence after successful cryoablation
Im et al. [68]	2013	499 patients who underwent RFCA for paroxysmal or persistent AF	5.6	At baseline and on day 1 after RFCA	In multivariate analysis, a high post-NLR was an independent predictor for early recurrence after RFCA (HR 1.09; $p = 0.047$ ). Patients with higher NLR ( $>5.6$ ) had significantly lower AF-free survival on Kaplan-Meier (K-M) curve
Sahin et al. [60]	2013	144 diabetic patients (72 with and 72 without AF)	2.38 (analysis included mean comparison between groups)	Retrospectively recorded from patient files	The mean NLR was significantly higher in diabetic patients with AF than in those without (mean 2.87 versus 2.2, $p = 0.019$ ). Using a cut-off point of 2.38 NLR was associated with AF (OR 3.486, $p = 0.004$ )
Trivedi et al. [70]	2013	165 patients with paroxysmal AF, who underwent RFCA	3.08 (analysis included mean comparison between groups)	One day prior to ablation	Baseline NLR was high in patients with AF recurrence (mean 3.2 versus 2.5, $p < 0.001$ ). A high baseline NLR ( $>3.08$ ) was a significant predictor of postablation AF recurrence (HR 1.99, 95% CI 1.33–2.96, $p = 0.001$ )
Guo et al. [69]	2014	379 lone AF patients who underwent catheter ablation	5.15 (analysis included mean comparison between groups)	Before and after catheter ablation	The patients who developed AF recurrence had a higher postablation NLR than patients with no recurrence (5.74 versus 4.66, $p < 0.001$ ). A high postablation NLR ( $>5.15$ ) was an independent predictor of AF recurrence (HR 1.514, 95% CI 1.36–1.68, $p < 0.001$ )
Acet et al. [71]	2014	A total of 197 subjects (71 with paroxysmal, 63 with persistent/permanent AF, and 63 AF-free controls)	2.1 (analysis included mean comparison between groups)	At baseline	Higher NLR ( $>2.1$ ) had a significant relationship with nonvalvular AF (OR 11.31, $p < 0.001$ ) compared with control group; and the mean value was significantly higher in those with persistent/permanent compared to those with paroxysmal AF ( $3.4 \pm 0.6$ , versus $2.5 \pm 0.6$ , $p < 0.001$ )
Nikoo et al. [26]	2014	112 AF patients and 107 controls	Mean comparison between groups	At baseline	A significant positive correlation was observed between NLR and increased interleukin-17 (IL-17A) in AF ( $p = 0.006$ ). Elevated IL-17A, on the other hand, was significantly increased in patients with AF compared to controls ( $1.28 \pm 3.5$ versus $0.19 \pm 0.64$ pg/mL, $p = 0.001$ )

TABLE 2: Continued.

Study [ref]	Year	Number of patients	Threshold	Assessment period	Results
Karavelioğlu et al. [64]	2015	218 patients restored to sinus rhythm with amiodarone	Mean comparison between groups	At admission	A high NLR was an independent predictor of AF recurrence (OR 1.584 [1.197–2.095], $p = 0.001$ ) after successful cardioversion with amiodarone
Yalcin et al. [61]	2015	309 patients with nonvalvular AF who underwent TEE	2.59	Before TEE	A high NLR (>2.59) was an independent risk factor for the presence of left atrial thrombus on TEE (OR 1.59; $p < 0.02$ ) in patients with nonvalvular AF
Saliba et al. [62]	2015	32,912 patients with AF	Multiple cut-offs in quartiles	Median NLR value of the tests performed in the year prior to study entry	Each increase in NLR quartile above the lowest was associated with a significant increase in the risk of stroke with HRs (95% CI) 1.11 (0.91–1.35), 1.25 (1.03–1.51), and 1.56 (1.29–1.88) for the second, third, and highest quartiles, respectively
Chavarria et al. [59]	2015	290 patients who underwent PCI for acute STEMI	Median comparison between groups	<6 hours preprocedural, <12, 48, and 96 hours postprocedural	Patients who developed AF ( $n = 40$ , 13.8%) had higher postcatheterization NLR at 48 hours (median 5.23 versus 3.00, $p = 0.05$ ) and 96 hours (median 4.67 versus 3.56, $p = 0.03$ )
Fukuda et al. [63]	2015	120 patients with paroxysmal AF	2.92	At baseline	A higher NLR (>2.92) was a predictor of reduced LAAWV in patients with paroxysmal AF
Wagdy et al. [72]	2016	200 patients with STEMI	4.6	At admission	A higher NLR (>4.6) was an independent predictor of NOAF, no-reflow, and in-hospital MACE (OR 3.5, $p = 0.02$ ) in patients with STEMI, after adjustment for confounding factors

AF: atrial fibrillation; NLR: neutrophil-lymphocyte ratio; OR: Odds Ratio; TEE: transesophageal echocardiography; CABG: coronary artery bypass grafting; RFCA: radiofrequency catheter ablation; NOAF: new-onset atrial fibrillation; LAAWV: left atrial appendage wall velocity; NA: not available; STEMI: ST-segment elevation myocardial infarction; CI: confidence interval; IL-17A: interleukin-17A; MACE: major adverse cardiovascular events; PCI: percutaneous coronary intervention.

#### 4. Underlying Mechanisms, Pathways, and Relationship between Biomarkers in AF

In relation to the underlying mechanisms, despite the consistency of the studies regarding the epidemiological association between inflammation and AF, there is still a substantial scarcity of data in basic sciences giving the pathophysiologic background to this link. In the case of the CRP, an acute phase protein, it seems to be more a marker of underlying immune responses than an active participant in the pathogenesis of the disease. This is reinforced by the fact that genetic polymorphisms that are associated with the double increase in CRP showed no significant association with the AF [27]. On the other hand, multiple factors interfere with CRP that would be very difficult to control in primary studies, to evaluate possible pathophysiological nexus. For this reason, we focus our description more on those related to NLR, and IL-6, which are more than simple reflectors, seeming to be actively involved in the pathogenesis of AF.

Neutrophil-lymphocyte ratio is a derived marker, expressing an imbalance in leukocytes with the dominance of neutrophils over lymphocytes, which may be only the “tip of the iceberg” of a deeper imbalance in the immunologic

response. This seems particularly true from the observation that a high NLR is associated with the excessive activation of interleukin-17 (IL-17) axis in AF [26], which is a cytokine produced mainly by T-helper 17 (Th17) a subset of T-helper cells. In fact, the differentiation of Th17 cells from naïve T cells is mediated largely by IL-6 [73–75], a cytokine produced mainly by macrophages, which are neutrophils infiltrating tissues. So, IL-6 would induce, at T-helper cells level, the polarization of the differentiation favoring the effectors Th17 cells over the regulatory T (Treg) cells [76]. Th17 cells produce IL-17 that, among other functions, is responsible for the increase in fibrosis, which is a crucial component in AF [77–80]. It is interesting that those diseases that have the IL-17 as a cornerstone of its pathophysiology, like psoriasis, or with significant increase of its levels such as nonalcoholic fatty liver disease and metabolic syndrome are associated with increased incidence of AF [17, 19, 81–83], suggesting a role of this cytokine as a mediator between AF and these clinical conditions.

The IL-17 is also associated with the upregulation of transforming growth factor beta (TGF- $\beta$ ) signaling pathways [84], another potent promoter of atrial fibrosis and consequent AF [85–87]. In addition, IL-17 stimulates the production of more

proinflammatory cytokines such as tumor necrosis factor- (TNF-)  $\alpha$  and IL-6 [88, 89] and regulates tissue infiltration by neutrophils and myocyte apoptosis, which can start and engage various other pathophysiological pathways including oxidative stress and hypercoagulability [90–92]. IL-17 induces the production of IL-6, a potent inducer of IL-17 synthesis, occurring in this way, a refeeding on the axis [73, 74].

The IL-6, as we described, plays a critical role in the regulation of IL-17 axis [73, 75]. IL-6, together with IL-23, induces the differentiation of Th17 cells from naïve T cells, at the same time that inhibits TGF-beta-induced Treg differentiation, favoring, in this way, the T17/Treg imbalance [73, 74, 76]. There is still a significant gap between the epidemiological evidence of inflammation in AF and the current understanding of underlying physiopathological basis. The clear understanding of this association is still an object of future studies from basic science to clinical practice level.

### 5. Concerns and Limitations of the Use of Inflammatory Biomarkers in AF

The main concerns and doubts that arises from the potential use of inflammatory biomarkers in AF is about the additional value of using a panel of two or more biomarkers in predicting AF outcomes than the isolated use, and if there is a superiority of a biomarker in relation to others in AF. No primary study has evaluated the additional value of two or more biomarkers in comparison with the isolated use. Even studies that studied the correlation between biomarkers [11, 14, 38] did not evaluate the additive effect of them to predict outcomes. Despite this gap, it is very likely that in clinical practice a panel of 2 biomarkers or more may be better than the isolated use of one, for predicting AF-related outcomes. So, the evaluation of the additive effect of combined use should be a subject for future studies. On the other hand, the primary studies are very controversial about the superiority of a biomarker in relation to others. So, in light of the current literature, there are no sufficient data to support such point, highlighting only that NLR is more easily accessible and inexpensive than other biomarkers as hs-CRP and IL-6.

### 6. Conclusion and Future Directions

The review of the available evidence shows that inflammatory biomarkers such as IL-6, IL-17, and NLR have a crucial role in the pathogenesis of AF. They represent an additional, noninvasive tool, with good performance, to predict new-onset disease, persistence, treatment response, recurrence, the risk of complications, and mortality in AF. The available evidence suggests that NLR, a simpler, widely available, and inexpensive biomarker, is a predictor of incidence, treatment success, recurrence, and thromboembolic complications.

Next studies should be addressed to clarify the underlying mechanisms in AF, to establish the additional value of using a panel of two or more biomarkers in predicting AF outcomes, to evaluate the superiority of a biomarker in relation to others, and to test the value of different biomarkers in different situations in the setting of AF.

### Competing Interests

The author declares no conflict of interests.

### References

- [1] S. S. Chugh, R. Havmoeller, K. Narayanan et al., “Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study,” *Circulation*, vol. 129, no. 8, pp. 837–847, 2014.
- [2] J. Ball, M. J. Carrington, J. J. V. McMurray, and S. Stewart, “Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century,” *International Journal of Cardiology*, vol. 167, no. 5, pp. 1807–1824, 2013.
- [3] A. S. Go, E. M. Hylek, K. A. Phillips et al., “Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study,” *Journal of the American Medical Association*, vol. 285, no. 18, pp. 2370–2375, 2001.
- [4] R. B. Schnabel, X. Yin, P. Gona et al., “50 Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study,” *The Lancet*, vol. 386, no. 9989, pp. 154–162, 2015.
- [5] GBD 2013 Mortality and Causes of Death Collaborators, “Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013,” *The Lancet*, vol. 385, no. 9963, pp. 117–171, 2015.
- [6] K.-L. Chien, T.-C. Su, H.-C. Hsu et al., “Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese,” *International Journal of Cardiology*, vol. 139, no. 2, pp. 173–180, 2010.
- [7] C. Marini, F. De Santis, S. Sacco et al., “Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study,” *Stroke*, vol. 36, no. 6, pp. 1115–1119, 2005.
- [8] M. D. M. Engelmann and J. H. Svendsen, “Inflammation in the genesis and perpetuation of atrial fibrillation,” *European Heart Journal*, vol. 26, no. 20, pp. 2083–2092, 2005.
- [9] Y.-F. Hu, Y.-J. Chen, Y.-J. Lin, and S.-A. Chen, “Inflammation and the pathogenesis of atrial fibrillation,” *Nature Reviews Cardiology*, vol. 12, no. 4, pp. 230–243, 2015.
- [10] R. J. Aviles, D. O. Martin, C. Apperson-Hansen et al., “Inflammation as a risk factor for atrial fibrillation,” *Circulation*, vol. 108, no. 24, pp. 3006–3010, 2003.
- [11] D. S. G. Conway, P. Buggins, E. Hughes, and G. Y. H. Lip, “Relationship of interleukin-6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation,” *Journal of the American College of Cardiology*, vol. 43, no. 11, pp. 2075–2082, 2004.
- [12] T. T. Issac, H. Dokainish, and N. M. Lakkis, “Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data,” *Journal of the American College of Cardiology*, vol. 50, no. 21, pp. 2021–2028, 2007.
- [13] M. Harada, D. R. Van Wagoner, and S. Nattel, “Role of inflammation in atrial fibrillation pathophysiology and management,” *Circulation Journal*, vol. 79, no. 3, pp. 495–502, 2015.
- [14] L. You, P. Wang, J. Lv, K. Cianflone, D. Wang, and C. Zhao, “The role of high-sensitivity C-reactive protein, interleukin-6 and cystatin C in ischemic stroke complicating atrial fibrillation,” *Journal of Huazhong University of Science and Technology*, vol. 30, no. 5, pp. 648–651, 2010.

- [15] Y.-J. Lin, H.-M. Tsao, S.-L. Chang et al., "Prognostic implications of the high-sensitive C-reactive protein in the catheter ablation of atrial fibrillation," *The American Journal of Cardiology*, vol. 105, no. 4, pp. 495–501, 2010.
- [16] D. S. G. Conway, P. Buggins, E. Hughes, and G. Y. H. Lip, "Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation," *American Heart Journal*, vol. 148, no. 3, pp. 462–466, 2004.
- [17] G. Targher, F. Valbusa, S. Bonapace et al., "Non-alcoholic fatty liver disease is associated with an increased incidence of atrial fibrillation in patients with type 2 diabetes," *PLoS ONE*, vol. 8, no. 2, Article ID e57183, 2013.
- [18] H. Watanabe, N. Tanabe, T. Watanabe et al., "Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study," *Circulation*, vol. 117, no. 10, pp. 1255–1260, 2008.
- [19] A. M. Chamberlain, S. K. Agarwal, M. Ambrose, A. R. Folsom, E. Z. Soliman, and A. Alonso, "Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) study," *American Heart Journal*, vol. 159, no. 5, pp. 850–856, 2010.
- [20] G. Ertaş, O. Sönmez, M. Turfan et al., "Neutrophil/lymphocyte ratio is associated with thromboembolic stroke in patients with non-valvular atrial fibrillation," *Journal of the Neurological Sciences*, vol. 324, no. 1-2, pp. 49–52, 2013.
- [21] P. H. Gibson, B. H. Cuthbertson, B. L. Croal et al., "Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting," *The American Journal of Cardiology*, vol. 105, no. 2, pp. 186–191, 2010.
- [22] B. D. Horne, J. L. Anderson, J. M. John et al., "Which white blood cell subtypes predict increased cardiovascular risk?" *Journal of the American College of Cardiology*, vol. 45, no. 10, pp. 1638–1643, 2005.
- [23] Y. Arbel, A. Finkelstein, A. Halkin et al., "Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography," *Atherosclerosis*, vol. 225, no. 2, pp. 456–460, 2012.
- [24] S. Tokgoz, M. Kayrak, Z. Akpınar, A. Seyithanoğlu, F. Güney, and B. Yürüten, "Neutrophil lymphocyte ratio as a predictor of stroke," *Journal of Stroke and Cerebrovascular Diseases*, vol. 22, no. 7, pp. 1169–1174, 2013.
- [25] S. Chatterjee, P. Chandra, G. Guha et al., "Pre-procedural elevated white blood cell count and neutrophil-lymphocyte (N/L) ratio are predictors of ventricular arrhythmias during percutaneous coronary intervention," *Cardiovascular & Hematological Disorders-Drug Targets*, vol. 11, no. 2, pp. 58–60, 2011.
- [26] M. H. Nikoo, S. R. Taghavian, H. Golmoghaddam, N. Arandi, A. A. Ardekani, and M. Doroudchi, "Increased IL-17A in atrial fibrillation correlates with neutrophil to lymphocyte ratio," *Iranian Journal of Immunology*, vol. 11, no. 4, pp. 246–258, 2014.
- [27] S. C. W. Marott, B. G. Nordestgaard, J. Zacho et al., "Does elevated C-reactive protein increase atrial fibrillation risk? A mendelian randomization of 47,000 individuals from the general population," *Journal of the American College of Cardiology*, vol. 56, no. 10, pp. 789–795, 2010.
- [28] M. K. Chung, D. O. Martin, D. Sprecher et al., "C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation," *Circulation*, vol. 104, no. 24, pp. 2886–2891, 2001.
- [29] J. M. Peña, J. MacFadyen, R. J. Glynn, and P. M. Ridker, "High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial," *European Heart Journal*, vol. 33, no. 4, pp. 531–537, 2012.
- [30] W. T. O'Neal, E. Z. Soliman, G. Howard et al., "Inflammation and hemostasis in atrial fibrillation and coronary heart disease: the REasons for Geographic And Racial Differences in Stroke study," *Atherosclerosis*, vol. 243, no. 1, pp. 192–197, 2015.
- [31] S. K. Thambidorai, K. Parakh, D. O. Martin et al., "Relation of C-reactive protein correlates with risk of thromboembolism in patients with atrial fibrillation," *The American Journal of Cardiology*, vol. 94, no. 6, pp. 805–807, 2004.
- [32] E. Watanabe, T. Arakawa, T. Uchiyama, I. Kodama, and H. Hishida, "High-sensitivity C-reactive protein is predictive of successful cardioversion for atrial fibrillation and maintenance of sinus rhythm after conversion," *International Journal of Cardiology*, vol. 108, no. 3, pp. 346–353, 2006.
- [33] J. F. Malouf, R. Kanagala, F. O. Al Atawi et al., "High sensitivity C-reactive protein: a novel predictor for recurrence of atrial fibrillation after successful cardioversion," *Journal of the American College of Cardiology*, vol. 46, no. 7, pp. 1284–1287, 2005.
- [34] D. S. G. Conway, P. Buggins, E. Hughes, and G. Y. H. Lip, "Relation of interleukin-6, C-reactive protein, and the prothrombotic state to transesophageal echocardiographic findings in atrial fibrillation," *The American Journal of Cardiology*, vol. 93, no. 11, pp. 1368–1373, 2004.
- [35] R. L. Amdur, M. Mukherjee, A. Go et al., "Interleukin-6 is a risk factor for atrial fibrillation in chronic kidney disease: findings from the CRIC study," *PLoS ONE*, vol. 11, no. 2, Article ID e0148189, 2016.
- [36] Y. Luan, Y. Guo, S. Li et al., "Interleukin-18 among atrial fibrillation patients in the absence of structural heart disease," *Europace*, vol. 12, no. 12, pp. 1713–1718, 2010.
- [37] V. Roldán, F. Marín, J. Díaz et al., "High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation," *Journal of Thrombosis and Haemostasis*, vol. 10, no. 8, pp. 1500–1507, 2012.
- [38] A. Fujiki, T. Sakamoto, K. Nishida, K. Mizumaki, and H. Inoue, "Relation of interleukin-6 and C-reactive protein levels to sinus maintenance after pharmacological cardioversion in persistent atrial fibrillation," *Journal of Cardiovascular Pharmacology*, vol. 50, no. 3, pp. 264–266, 2007.
- [39] S. N. Psychari, T. S. Apostolou, L. Sinos, E. Hamodraka, G. Liakos, and D. T. Kremastinos, "Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation," *The American Journal of Cardiology*, vol. 95, no. 6, pp. 764–767, 2005.
- [40] G. Y. H. Lip, J. V. Patel, E. Hughes, and R. G. Hart, "High-sensitivity C-reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors, stroke risk stratification schema, and prognosis," *Stroke*, vol. 38, no. 4, pp. 1229–1237, 2007.
- [41] T. Liu, G. Li, L. Li, and P. Korantzopoulos, "Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion. a meta-analysis," *Journal of the American College of Cardiology*, vol. 49, no. 15, pp. 1642–1648, 2007.
- [42] K. M. A. Henningsen, S. K. Therkelsen, H. Bruunsgaard, K. S. Krabbe, B. K. Pedersen, and J. H. Svendsen, "Prognostic impact of hs-CRP and IL-6 in patients with persistent atrial fibrillation treated with electrical cardioversion," *Scandinavian Journal of*

- Clinical and Laboratory Investigation*, vol. 69, no. 3, pp. 425–432, 2009.
- [43] K. M. A. Henningsen, B. Nilsson, H. Bruunsgaard, X. Chen, B. K. Pedersen, and J. H. Svendsen, “Prognostic impact of hs-CRP and IL-6 in patients undergoing radiofrequency catheter ablation for atrial fibrillation,” *Scandinavian Cardiovascular Journal*, vol. 43, no. 5, pp. 285–291, 2009.
- [44] C. Cianfrocca, M. L. Loricchio, F. Pelliccia et al., “C-reactive protein and left atrial appendage velocity are independent determinants of the risk of thrombogenesis in patients with atrial fibrillation,” *International Journal of Cardiology*, vol. 142, no. 1, pp. 22–28, 2010.
- [45] T. Maehama, H. Okura, K. Imai et al., “Usefulness of CHADS2 score to predict C-reactive protein, left atrial blood stasis, and prognosis in patients with nonrheumatic atrial fibrillation,” *American Journal of Cardiology*, vol. 106, no. 4, pp. 535–538, 2010.
- [46] O. O. Celebi, S. Celebi, A. Canbay, G. Ergun, S. Aydogdu, and E. Diker, “The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion,” *Cardiology*, vol. 118, no. 3, pp. 168–174, 2011.
- [47] J. Liu, P.-H. Fang, S. Dibs, Y. Hou, X.-F. Li, and S. Zhang, “High-sensitivity C-reactive protein as a predictor of atrial fibrillation recurrence after primary circumferential pulmonary vein isolation,” *Pacing and Clinical Electrophysiology*, vol. 34, no. 4, pp. 398–406, 2011.
- [48] S. K. Kim, J. H. Park, J. Y. Kim et al., “High plasma concentrations of transforming growth factor- $\beta$  and tissue inhibitor of metalloproteinase-1: potential non-invasive predictors for electroanatomical remodeling of atrium in patients with non-valvular atrial fibrillation,” *Circulation Journal*, vol. 75, no. 3, pp. 557–564, 2011.
- [49] T. Kinoshita, T. Asai, N. Takashima et al., “Preoperative C-reactive protein and atrial fibrillation after off-pump coronary bypass surgery,” *European Journal of Cardio-Thoracic Surgery*, vol. 40, no. 6, pp. 1298–1303, 2011.
- [50] J. Hermida, F. L. Lopez, R. Montes, K. Matsushita, B. C. Astor, and A. Alonso, “Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study),” *The American Journal of Cardiology*, vol. 109, no. 1, pp. 95–99, 2012.
- [51] A. Barassi, R. Pezzilli, A. M. Morselli-Labate et al., “Serum amyloid a and C-reactive protein independently predict the recurrences of atrial fibrillation after cardioversion in patients with preserved left ventricular function,” *Canadian Journal of Cardiology*, vol. 28, no. 5, pp. 537–541, 2012.
- [52] A. Mazza, M. G. Bendini, M. Cristofori et al., “C-reactive protein and P-wave in hypertensive patients after conversion of atrial fibrillation,” *Journal of Cardiovascular Medicine*, vol. 14, no. 7, pp. 520–527, 2013.
- [53] S. Parashar, D. Kella, K. J. Reid et al., “New-onset atrial fibrillation after acute myocardial infarction and its relation to admission biomarkers (from the TRIUMPH Registry),” *American Journal of Cardiology*, vol. 112, no. 9, pp. 1390–1395, 2013.
- [54] M. F. Sinner, K. A. Stepas, C. B. Moser et al., “B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies,” *Europace*, vol. 16, no. 10, pp. 1426–1433, 2014.
- [55] T. A. Dewland, E. Vittinghoff, T. B. Harris et al., “Inflammation as a mediator of the association between race and atrial fibrillation: results from the health ABC study (Health, Aging, and Body Composition),” *JACC: Clinical Electrophysiology*, vol. 1, no. 4, pp. 248–255, 2015.
- [56] J. Aulin, A. Siegbahn, Z. Hijazi et al., “Interleukin-6 and C-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation,” *American Heart Journal*, vol. 170, no. 6, pp. 1151–1160, 2015.
- [57] M. Negreva, S. Georgiev, and K. Prodanova, “Significant Increase in C-Reactive Protein and Serum Amyloid A in the Early Hours of Paroxysmal Atrial Fibrillation,” 2016, <http://www.cardiologyres.org/index.php/Cardiologyres/article/view/455/487>.
- [58] Z. Hijazi, J. Aulin, U. Andersson et al., “Biomarkers of inflammation and risk of cardiovascular events in anticoagulated patients with atrial fibrillation,” *Heart*, vol. 102, no. 7, pp. 508–517, 2016.
- [59] N. Chavarria, C. Wong, H. Hussain, H. U. L. Joiya, S. Goldberg, and A. Buda, “Persistent elevation of neutrophil/lymphocyte ratio associated with new onset atrial fibrillation following percutaneous coronary intervention for acute st segment,” *Journal of Ayub Medical College, Abbottabad*, vol. 27, no. 2, pp. 441–447, 2015.
- [60] S. Sahin, S. Sarikaya, A. Alcelik et al., “Neutrophil to lymphocyte ratio is a useful predictor of atrial fibrillation in patients with diabetes mellitus,” *Acta Medica Mediterranea*, vol. 29, no. 4, pp. 847–851, 2013.
- [61] M. Yalcin, M. Aparci, O. Uz et al., “Neutrophil-lymphocyte ratio may predict left atrial thrombus in patients with nonvalvular atrial fibrillation,” *Clinical and Applied Thrombosis/Hemostasis*, vol. 21, no. 2, pp. 166–171, 2015.
- [62] W. Saliba, O. Barnett-Griness, M. Elias, and G. Rennert, “Neutrophil to lymphocyte ratio and risk of a first episode of stroke in patients with atrial fibrillation: a cohort study,” *Journal of Thrombosis and Haemostasis*, vol. 13, no. 11, pp. 1971–1979, 2015.
- [63] Y. Fukuda, Y. Nakano, S. Tomomori et al., “Neutrophil to lymphocyte ratio predicts reduced left atrial appendage wall velocity in patients with paroxysmal atrial fibrillation,” *Journal of Cardiac Failure*, vol. 21, no. 10, p. S178, 2015.
- [64] Y. Karavelioğlu, H. Karapınar, M. Yüksel et al., “Neutrophil to lymphocyte ratio is predictor of atrial fibrillation recurrence after cardioversion with amiodarone,” *Clinical and Applied Thrombosis/Hemostasis*, vol. 21, no. 1, pp. 5–9, 2015.
- [65] U. Canpolat, K. Aytemir, H. Yorgun et al., “Role of preablation neutrophil/lymphocyte ratio on outcomes of cryoballoon-based atrial fibrillation ablation,” *American Journal of Cardiology*, vol. 112, no. 4, pp. 513–519, 2013.
- [66] S. D. Brooks, C. Spears, C. Cummings et al., “Admission neutrophil-lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy,” *Journal of NeuroInterventional Surgery*, vol. 6, no. 8, pp. 578–583, 2014.
- [67] S. Gökhan, A. Özhasenekler, H. Mansur Durgun, E. Akil, M. Üstündag, and M. Orak, “Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack,” *European Review for Medical and Pharmacological Sciences*, vol. 17, no. 5, pp. 653–657, 2013.
- [68] S. I. Im, S. Y. Shin, J. O. Na et al., “Usefulness of neutrophil/lymphocyte ratio in predicting early recurrence after

- radiofrequency catheter ablation in patients with atrial fibrillation," *International Journal of Cardiology*, vol. 168, no. 4, pp. 4398–4400, 2013.
- [69] X. Y. Guo, S. Zhang, X. L. Yan et al., "Postablation neutrophil/lymphocyte ratio correlates with arrhythmia recurrence after catheter ablation of lone atrial fibrillation," *Chinese Medical Journal*, vol. 127, no. 6, pp. 1033–1038, 2014.
- [70] C. Trivedi, L. Di Biase, S. Mohanty, and P. Mohanty, "Baseline neutrophil/lymphocyte ratio predicts recurrences after radiofrequency catheter ablation: results from prospective study on paroxysmal atrial fibrillation," *Circulation*, vol. 128, Article ID A18588, 2013.
- [71] H. Acet, F. Ertaş, M. A. Akil et al., "New inflammatory predictors for non-valvular atrial fibrillation: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio," *International Journal of Cardiovascular Imaging*, vol. 30, no. 1, pp. 81–89, 2014.
- [72] S. Wagdy, M. Sobhy, and M. Louitfi, "Neutrophil/lymphocyte ratio as a predictor of in-hospital major adverse cardiac events, new-onset atrial fibrillation, and no-reflow phenomenon in patients with ST elevation myocardial infarction," *Clinical Medicine Insights: Cardiology*, vol. 10, pp. 19–22, 2016.
- [73] L. Zhou, I. I. Ivanov, R. Spolski et al., "IL-6 programs T<sub>H</sub>-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways," *Nature Immunology*, vol. 8, no. 9, pp. 967–974, 2007.
- [74] M. J. McGeachy, K. S. Bak-Jensen, Y. Chen et al., "TGF- $\beta$  and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T<sub>H</sub>-17 cell-mediated pathology," *Nature Immunology*, vol. 8, no. 12, pp. 1390–1397, 2007.
- [75] P. R. Taylor, S. Roy, S. M. Leal et al., "Activation of neutrophils by autocrine IL-17A–IL-17RC interactions during fungal infection is regulated by IL-6, IL-23, ROR $\gamma$ t and dectin-2," *Nature Immunology*, vol. 15, no. 2, pp. 143–151, 2014.
- [76] A. Kimura and T. Kishimoto, "IL-6: regulator of Treg/Th17 balance," *European Journal of Immunology*, vol. 40, no. 7, pp. 1830–1835, 2010.
- [77] M. S. Dzeshka, G. Y. H. Lip, V. Snezhitskiy, and E. Shantsila, "Cardiac fibrosis in patients with atrial fibrillation: mechanisms and clinical implications," *Journal of the American College of Cardiology*, vol. 66, no. 8, pp. 943–959, 2015.
- [78] B. Burstein and S. Nattel, "Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation," *Journal of the American College of Cardiology*, vol. 51, no. 8, pp. 802–809, 2008.
- [79] X.-X. Fu, N. Zhao, Q. Dong et al., "Interleukin-17A contributes to the development of post-operative atrial fibrillation by regulating inflammation and fibrosis in rats with sterile pericarditis," *International Journal of Molecular Medicine*, vol. 36, no. 1, pp. 83–92, 2015.
- [80] W. Feng, W. Li, W. Liu, F. Wang, Y. Li, and W. Yan, "IL-17 induces myocardial fibrosis and enhances RANKL/OPG and MMP/TIMP signaling in isoproterenol-induced heart failure," *Experimental and Molecular Pathology*, vol. 87, no. 3, pp. 212–218, 2009.
- [81] O. Ahlehoff, G. H. Gislason, C. H. Jørgensen et al., "Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study," *European Heart Journal*, vol. 33, no. 16, pp. 2054–2064, 2012.
- [82] O. Ahlehoff, G. Gislason, M. Lamberts et al., "Risk of thromboembolism and fatal stroke in patients with psoriasis and nonvalvular atrial fibrillation: a Danish nationwide cohort study," *Journal of Internal Medicine*, vol. 277, no. 4, pp. 447–455, 2015.
- [83] D. A. Giles, M. E. Moreno-Fernandez, T. E. Stankiewicz et al., "Regulation of inflammation by IL-17A and IL-17F modulates non-alcoholic fatty liver disease pathogenesis," *PLoS ONE*, vol. 11, no. 2, Article ID e0149783, 2016.
- [84] T. Fabre, H. Kared, S. L. Friedman, and N. H. Shoukry, "IL-17A enhances the expression of profibrotic genes through upregulation of the TGF- $\beta$  receptor on hepatic stellate cells in a JNK-dependent manner," *The Journal of Immunology*, vol. 193, no. 8, pp. 3925–3933, 2014.
- [85] F. Gramley, J. Lorenzen, E. Koellensperger, K. Kettering, C. Weiss, and T. Munzel, "Atrial fibrosis and atrial fibrillation: the role of the TGF- $\beta$ 1 signaling pathway," *International Journal of Cardiology*, vol. 143, no. 3, pp. 405–413, 2010.
- [86] U. Canpolat, A. Oto, T. Hazirolan et al., "A prospective demri study evaluating the role of tgf- $\beta$ 1 in left atrial fibrosis and implications for outcomes of cryoballoon-based catheter ablation: new insights into primary fibrotic atriacardiomyopathy," *Journal of Cardiovascular Electrophysiology*, vol. 26, no. 3, pp. 251–259, 2015.
- [87] J. Li, Y. Yang, C. Y. Ng et al., "Association of plasma transforming growth factor- $\beta$ 1 levels and the risk of atrial fibrillation: a meta-analysis," *PLoS ONE*, vol. 11, no. 5, Article ID e0155275, 2016.
- [88] J. Chen, M.-Y. Liao, X.-L. Gao et al., "IL-17A induces pro-inflammatory cytokines production in macrophages via MAP-Kinases, NF- $\kappa$ B and AP-1," *Cellular Physiology and Biochemistry*, vol. 32, no. 5, pp. 1265–1274, 2013.
- [89] M. Shibata, Y. Shintaku, K. Matsuzaki, and S. Uematsu, "The effect of IL-17 on the production of proinflammatory cytokines and matrix metalloproteinase-1 by human periodontal ligament fibroblasts," *Orthodontics and Craniofacial Research*, vol. 17, no. 1, pp. 60–68, 2014.
- [90] P. Dhillon, K. Wallace, F. Herse et al., "IL-17-mediated oxidative stress is an important stimulator of AT1-AA and hypertension during pregnancy," *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 303, no. 4, pp. R353–R358, 2012.
- [91] A. Hot, V. Lenief, and P. Miossec, "Combination of IL-17 and TNF $\alpha$  induces a pro-inflammatory, pro-coagulant and pro-thrombotic phenotype in human endothelial cells," *Annals of the Rheumatic Diseases*, vol. 71, no. 5, pp. 768–776, 2012.
- [92] Y.-H. Liao, N. Xia, S.-F. Zhou et al., "Interleukin-17A contributes to myocardial ischemia/reperfusion injury by regulating cardiomyocyte apoptosis and neutrophil infiltration," *Journal of the American College of Cardiology*, vol. 59, no. 4, pp. 420–429, 2012.