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ORIGINAL ARTICLE

High sensitivity C reactive protein levels and atrial fibrillation recurrence after catheter ablation for atrial fibrillation: A systematic review and meta-analysis

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Abstract

Background: Atrial fibrillation (AF) recurrence after AF ablation is not uncommon. High sensitivity C reactive protein (hs-CRP) is a widely used inflammatory marker with a potential property to predict AF recurrence. We conducted a systematic review and a meta-analysis to find an association between hs-CRP levels and AF recurrence after ablation.

Methods: We searched PubMed, Embase, and Wiley-Cochrane Library from inception to January 2022 for studies that reported hs-CRP levels in patients who underwent AF ablation. Weighted mean difference (WMD) was used to evaluate the difference between hs-CRP levels in post-ablation AF recurrent and non-recurrent group. Also, the difference between hs-CRP levels in pre- and post-ablation was determined.

Results: We identified 10 studies, and a total of 789 patients were included (299 recurrent vs. 490 non-recurrent patients). The mean age was 57.7 years (76.4% male). There was no difference in baseline hs-CRP levels between AF recurrent and non-recurrent group (WMD = 0.05, 95% CI = −0.04 to 0.15, $p = 0.045$). However, higher hs-CRP levels post-ablation were found in AF recurrent group (WMD = 0.09, 95% CI = 0.03–0.15, $p < 0.001$).

Conclusion: There is no significant difference in baseline hs-CRP levels between AF recurrent and non-recurrent patients after AF ablation. However, higher post-ablation hs-CRP level was found in AF recurrent group. High Sensitivity C reactive protein may play a role as a predictor of AF recurrence.

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia worldwide and occurs in 19.2 per 1000 persons per year.[1] The prevalence does increase with age and in the United States, AF affects about 2.5 million people.[2,3]

Catheter ablation of AF is the procedure that aims to perform electrical isolation of pulmonary veins with possible additional

ablations to eliminate the atrial arrhythmogenic substrates. This intervention requires a trans-septal approach and may cause complications, such as peri-procedural hematomas, perforations, tamponade, stroke, and pulmonary vein stenosis.[4–7] However, AF recurrence is common and some patients may require repeated catheter ablation.[8] Thus, the identification of markers that can help patient selection is crucial.

High-sensitivity C-reactive protein (hs-CRP), an inflammatory marker, may play an essential role as a predictor of AF recurrence. Studies have shown that inflammation of the left atrium may play a role in the initiation and continuance of AF.[9] Recent studies have shown that higher baseline CRP level was associated with higher rates of post-ablation recurrence.[10]

However, previous studies[10–13] reported conflicting results on whether hs-CRP can predict AF recurrence after AF ablation. Therefore, we conducted a systematic review and a meta-analysis to find an association between hs-CRP levels and AF recurrence after ablation.

2 | METHODS

Systematic review and meta-analysis were performed under the guidance of the PRISMA guideline.[14] We used three main search engines (PubMed, Embase, and Wiley-Cochrane Library) to identify studies that evaluated the associations between CRP and AF recurrence after catheter ablation from inception to January 31, 2022. The keywords used for the search were "C-reactive protein", "Atrial fibrillation" and "Catheter ablation" (Table S1). The references of all identified publications were hand-searched for additional relevant studies.

2.1 | Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the study was a prospective observational study design, (2) Studies evaluated the association between hs-CRP level and AF recurrence before and after catheter ablation, (3) the study used AF recurrence rates as an outcome, and (4) the period of follow-up was ≥3 months. The exclusion criteria were: (1) patients undergoing electrical shock or cardioversion, surgical operation, or without any treatment (including catheter ablation); (2) baseline CRP is not available in the sufficient follow-up period; (3) non-human study; (4) abstracts, unpublished reports, and non-English language articles.

Two investigators (S.J. and A.P.) independently reviewed the studies and extracted data using the inclusion and exclusion criteria to minimize bias and improve reliability. A third reviewer (L.N.) checked conflicting data. The following data were extracted from each eligible study: (1) publication details: first author's last name, publication year, and origin of the studied population; (2) characteristics of the studied population: sample size, age, gender, diagnoses, and methods of CRP measurement; (3) ablation method; (4) the rate of AF recurrence, methods of AF detection, and mean follow-up time; (5) mean and standard deviation (SD) of hs-CRP in each group. The hs-CRP level after completed follow-up from each study was used for post-ablation analysis. Observational studies were assessed by the Newcastle-Ottawa Scale (NOS) for quality assessment.[15]

2.2 | Statistical analysis

This meta-analysis was performed using a random-effects model. Weight mean difference (WMD) was used to determine the difference in CRP level between the AF recurrence group and the non-recurrence group. Q-statistic and I^2 statistic was used to assess evidence of heterogeneity.[16] The I^2 statistic ranges in value from 0 to 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25\%–50\%$, moderate heterogeneity; $I^2 \geq 50\%$, substantial heterogeneity).[17] Publication bias was assessed using a funnel plot. Sensitivity analysis was also performed to assess the influence of individual studies on the overall meta-analysis, as described by Patsopoulos et al.[18] All analyses were conducted using STATA software (version 14 STATA Corp).

3 | RESULTS

We identified 401 studies after the initial search. After the initial screening title and abstract, 53 studies were identified and carefully evaluated. After the pre-analysis screening, 30 studies were excluded due to unrelated or duplication. The remaining 23 studies then underwent full-text reading, and 13 studies were excluded due to a lack of baseline or follow-up CRP levels. Finally, 10 studies met the inclusion and were included in the final analysis (Figure 1).[19–28]

A total of 789 patients were included, with 299 in the AF recurrence group and 490 in the non-recurrence group. The population was male predominance (76.37%) with a mean age of 57.1 ± 8.53 years old, and the mean AF duration before ablation was 60.84 ± 40.60 months. The ablation technique was mainly pulmonary vein isolation with radio-frequency ablation. Some studies also used additional linear line ablation, and 1 study used the cryoablation technique.[28] The mean follow-up time was 12.25 months, and the success rate ranged from 40% to 80%.

The characteristics of included studies are shown in Table 1. The NOS of the included studies are described in Table S2.

The baseline hs-CRP levels were reported in 9 studies. The mean hs-CRP pre-ablation was 0.48 ± 0.97 mg/dL in the recurrent group and 0.40 ± 0.61 mg/dL in the non-recurrent group. Our analysis showed no significant difference in baseline hs-CRP levels between the two groups

(WMD = 0.05, 95% CI −0.04 to 0.15, $p = 0.6$, $I^2 = 49.5\%$) (Figure 2).

The post-ablation mean hs-CRP levels were 0.72 ± 0.73 mg/dL in the recurrent group and 0.38 ± 0.51 mg/dL in the non-recurrent group. The results showed higher post-ablation hs-CRP levels were associated with a higher rate of AF recurrence after AF ablation (WMD = 0.09, 95% CI 0.03 to 0.15, $p < 0.001$, $I^2 = 81.9\%$) (Figure 3).

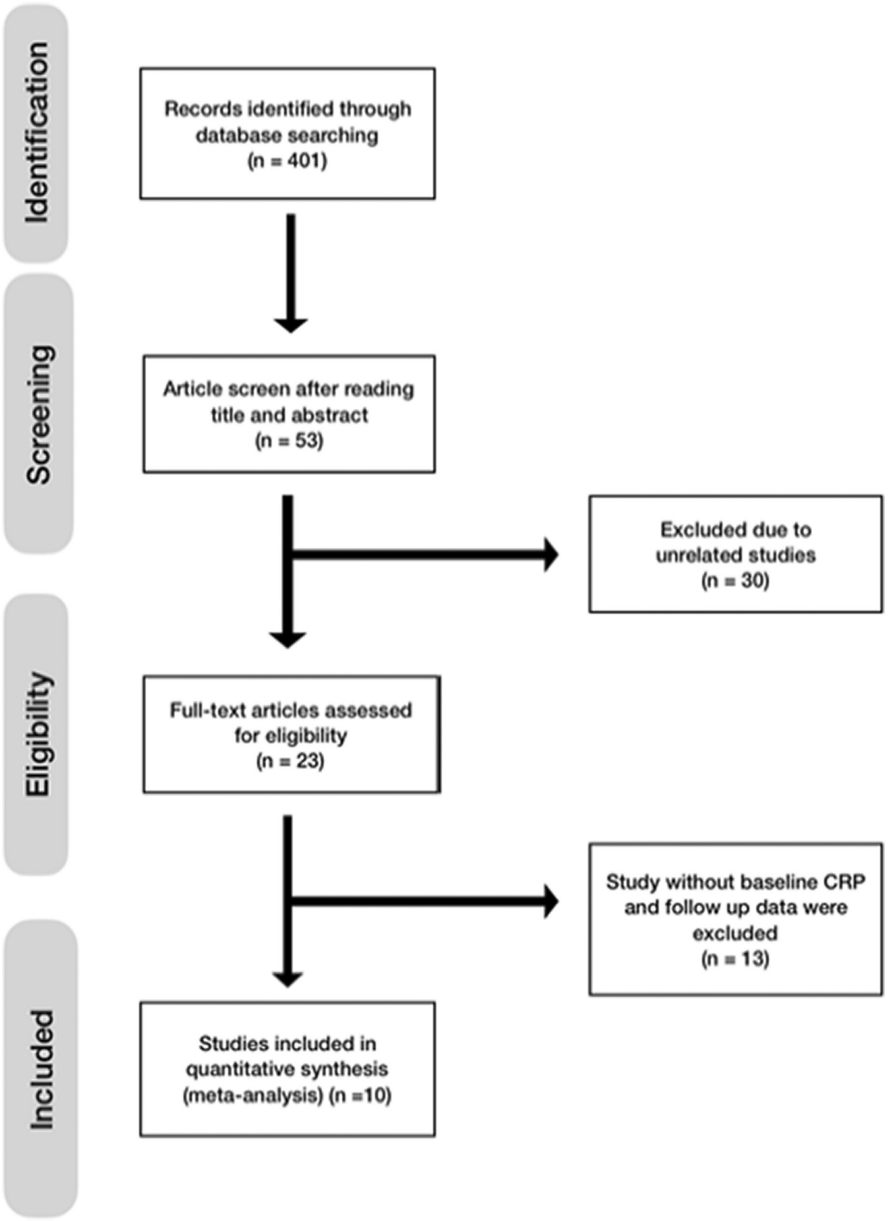

FIGURE 1 PRISMA flow diagram of study identification.

We conducted a sensitivity analysis for each outcome by excluding one study at a time to assess the stability of the results of the meta-analysis. None of the results were significantly altered for every outcome and it remained similar to the complete analysis. This indicated that our results were robust. We investigated the effect of potential publication bias by creating a funnel plot from included studies that appeared to have publication bias. No bias was observed, as the distribution of studies is symmetrical on both sides of the mean. The funnel plots are shown in Figures S1 and S2.

4 | DISCUSSION

This study is the most updated meta-analysis on the association of hs-CRP and AF recurrence after AF ablation. The main finding in our study is the association between hs-CRP levels after AF ablation and AF recurrent risk. In total 789 patients from 10 studies after AF ablation was done, mean hs-CRP level in the recurrent group was 0.72 ± 0.73 and 0.38 ± 0.51 mg/dL in the non-recurrent group. In the pooled- analysis, there was a significant difference in post-ablation hs-CRP levels between the two groups (Figure 3). However, we did not find a significant difference in baseline hs-CRP levels between the recurrence and non-recurrence group post-ablation (Figure 2).

There are many studies that published the data about the relationship between the inflammatory biomarkers and AF including the past 4 meta-analysis studies.[10–13] The recent meta-analysis by Jiang et al. has studied the relationship between baseline hs-CRP level and AF recurrence rate and concluded that there were positive associations. Other meta-analysis studies done by Jiang et al. and Boyalla et al. also found the same result. Another meta-analysis by Wu et al. studied AF recurrent rate in patients undergoing coronary

TABLE 1 Baseline demographic, clinical, and laboratory characteristics of total patient, recurrent and non-recurrent groups.

First author	Year	Country of origin	Study type/Method	Ablation procedure	Ablation energy source	Total population ($n = 789$)	Recurrent ($n = 299$)	Non-recurrent ($n = 490$)	Total male population	Male (%)		Total mean age (years)	Mean age (years)	
										Recurrence	Non-recurrence		Recurrence	Non recurrence
Konstantinos P. Letsas	2008	Germany	Retrospective	PVI	RF	72	28	44	58	86	77	54.90	53.30	55.80
David Carballo	2018	Switzerland	Prospective cohort study	PVI[a]	RF	195	101	94	161	80.20	84	57.50	56.90	58.30
Jun Liu	2010	China	Retrospective	PVI[b]	RF	121	36	85	93	86.08	71.60	55.14	55.09	55.06
Kristoffer Mads Aaris Henningsen	2009	Denmark	Prospective cohort study	PVI[c]	RF	46	27	19	30	63	68	54.93	57	52
Naoko Sasaki	2013	Japan	Prospective cohort study	PVI[b]	RF	60	29	31	49	79.30	83.90	57.60	58.90	56.30
Jinqi Fan	2010	China	Prospective cohort study	PVI[c]	RF	33	10	23	21	60	73.91	56.39	55.90	56.60
Jelena Kornej	2012	Germany	Prospective cohort study	PVI[c]	RF	67	12	55	43	75	62	59.35	61	59
Takehiro Kimura	2014	Japan	Prospective cohort study	PVI[d]	RF	44	15	29	N/A	N/A	N/A	59	61	58
Veysi Can	2021	Turkey	Prospective cohort study	PVI	RF and Cryoenergy	101	20	81	76	40	44.40	61	65	60
Yasuo Okumura	2011	Japan	Prospective cohort study	PVI[b]	RF	50	21	29	38	85.70	69	61.30	63.90	59.40

First author	AF duration (months)	Follow-up time (months)	AF duration (months)		hs-CRP pre-procedure (mg/dL)	hs-CRP pre-procedure (mg/dL)		hs-CRP post-procedure (mg/dL)	
			Recurence	Non-currence		Recurrent group	Non-recurrence group	Recurrent group	Non-recurrent group
Konstantinos P. Letsas	66	12.5	68.40	63.60	0.30	0.30	0.30	0.36	0.32
David Carballo	N/A	6	N/A	N/A	1.40	2.12	1.51	1.50	1.30
Jun Liu	51.57	44	72	92.70	N/A	N/A	N/A	2.29	0.89
Kristoffer Mads Aaris Henningsen	62.40	12	60	66	0.10	0.10	0.10	0.22	0.07
Naoko Sasaki	52	12	73	37	0.07	0.09	0.04	0.07	0.03
Jinqi Fan	50.08	3	58.80	46.80	0.12	0.15	0.10	0.29	0.10
Jelena Kornej	72.10	6	68	73	0.21	0.20	0.20	0.26	0.21
Takehiro Kimura	N/A	12	N/A	N/A	0.10	0.10	0.10	0.07	0.04
Veysi Can	N/A	12	N/A	N/A	1.08	1.20	1.20	2.29	1.01
Yasuo Okumura	70.90	3	97.30	48.70	0.06	0.07	0.07	0.07	0.05

TABLE 1 Continued

First author	BMI	BMI		Diabetes militias (%)		Total	Hypertension (%)		Heart failure (%)		Total ischemic	Ischemic heart disease (%)	
	total	Recurrent	Non-recurrent	Total DM (%)	Recurrent	Non-recurrent	hypertension (%)	Recurrent	Non-recurrent	Total heart failure (%)	Recurrent	Non-recurrent	heart disease (%)	Recurrent	Non-recurrent
Konstantinos P. Letsas	26.10	27	25.60	22	18	25	19	32	11	N/A	N/A	N/A	3	N/A	N/A
David Carballo	30	28.80	31.40	1.50	1	2.10	N/A	N/A	N/A	N/A	N/A	N/A	6.10	4	6.60
Jun Liu	26.18	27.10	25.80	N/A	N/A	N/A	43.81	50	41.20	N/A	N/A	N/A	N/A	N/A	N/A
Kristoffer Mads Aaris Henningsen	N/A	N/A	N/A	2	N/A	N/A	28	33	21	N/A	N/A	N/A	15	22	5
Naoko Sasaki	22.90	23.20	22.60	10	10	9.60	46.70	51.70	41.90	13.30	20.70	6.50	5	3.40	6.50
Jinqi Fan	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jelena Kornej	29	29	28	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Takehiro Kimura	23.20	23.40	23.10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	6.70	20.70	N/A	N/A	N/A
Veysi Can	31.59	31.60	30.80	28	35	24.70	55.90	60	54.30	N/A	N/A	N/A	N/A	N/A	N/A
Yasuo Okumura	25.10	28	23	10	14.30	6.90	42	61.90	27.60	6	9.50	3.50	8	9.50	6.90

Abbreviations: DM, diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; N/A, not available; PVI, pulmonary vein isolation; RF, radiofrequency ablation.

[a]Linear ablation were added if necessary and CTI ablation were added if atrial flutter were present.

[b]Complex Fractionated Atrial Electrograms(CFAE) were added if necessary.

[c]Linear ablation were added if necessary.

[d]Linear ablation and CFAE were added if necessary.

artery bypass graft (CABG) and found a significant positive association with circulating inflammatory markers, including hs-CRP levels.

When sinus rhythm was restored, the inflammatory process can reverse, and the hs-CRP may decrease. This finding was observed in the study done by Kallergis et al. which found that sinus rhythm after cardioversion resulted in a gradual decrease in hs-CRP.[29] Nevertheless, caution that hs-CRP is the inflammatory marker that may be influenced by the technique for blood drawing and patient's comorbidities such as other cardiovascular diseases, diabetes mellitus, and hypertension, mostly found in patients with AF.[30]

The association between baseline hs-CRP and AF was previously reported. Nevertheless, the association between baseline hs-CRP and AF recurrence was diverse. Okumura et al. have studied the association of biomarkers, including hs-CRP and AF recurrence, in 50 patients with drugs resistant AF that undergo ablation. They found no significant differences between baseline hs-CRP in the recurrence and non-recurrence groups. However, after follow-up completion, hs-CRP gradually decreased, and the hs-CRP level in the recurrence group was higher than in the non-recurrence group. Furthermore, the decrease in hs-CRP was highly associated with the rhythm changes from AF at baseline to sinus rhythm at follow-up during the blood sampling. Thus, the maintenance of sinus rhythm by ablation may help decrease the activation of the inflammatory system.[19]

The study done by Kornej et al. had study possible association between hs-CRP as well as hs-CRP changes and rhythm outcome after AF catheter ablation in 67 patients and after a follow-up at 6 months. The hs-CRP level rose in both groups after the ablation procedure, and then the hs-CRP in the non-recurrent group declined close to the baseline level before ablation. The decline in hs-CRP may be due to the inflammatory process that is usually considered to occur early after catheter ablation and could explain recurrences. Thus, the authors concluded that they were no association between hs-CRP and the recurrence of AF. But, at 6 months after ablation, the hs-CRP level was significantly higher in the recurrence group. Furthermore, in this study, it has been found that in some patients, a high baseline hs-CRP level was associated with an abnormal left atrial electrophysiologic substrate and an increased incidence of non-pulmonary vein AF sources and, consequently, ablation success rate.[20]

In the study by Fan et al., included 33 patients with AF undergoing radiofrequency ablation and 30 patients in the control group. Not only that the authors found significant differences in baseline and follow-up hs-CRP levels between the AF recurrence group and non-recurrent group, but they also found a rapid rising of hs-CRP levels within 24 h after ablation which then slowly declined after 3 months. The authors suggested that these changes in hs-CRP level were directly related to inflammation from catheter ablation procedures. This study also compares the level of baseline hs-CRP in healthy individuals, patients with lone AF, and patients with AF and hypertension because authors believed that this type of underlying heart disease might be a significant confounding factor that may alter the factual relation of inflammatory

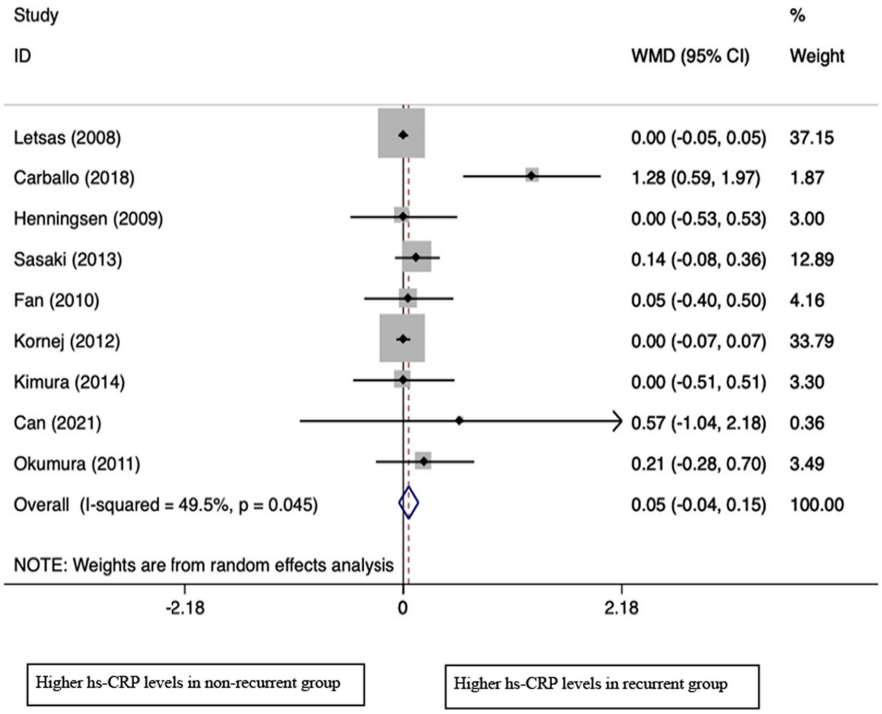

FIGURE 2 Forrest plot illustrates the pooled weighted mean difference (WMD) of the baseline hs-CRP levels between AF recurrent and non-recurrent group before atrial fibrillation catheter ablation.

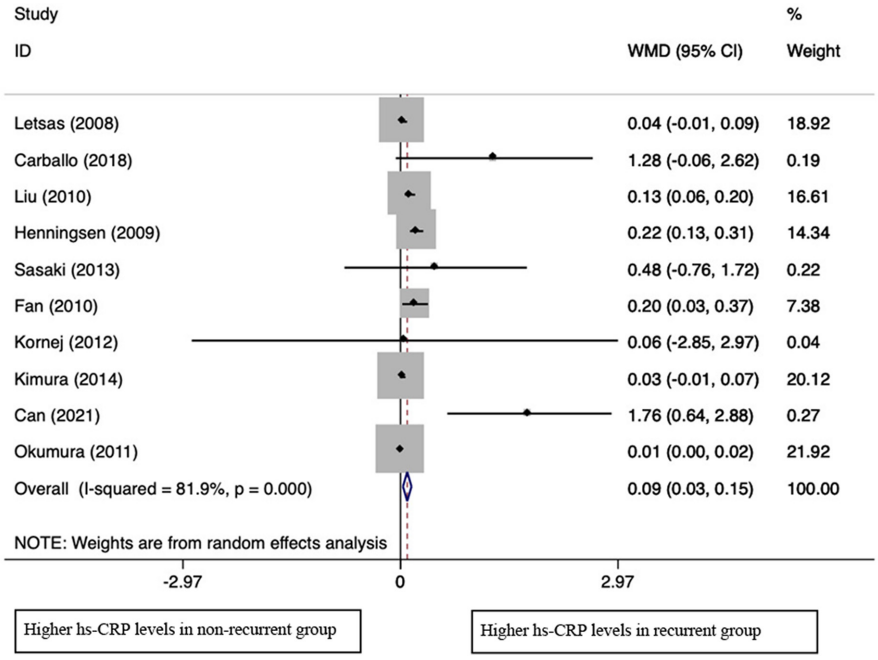

FIGURE 3 Forrest plot illustrates the pooled weighted mean difference (WMD) of the hs-CRP levels after atrial fibrillation catheter ablation between the AF recurrent and non-recurrent group.

markers with AF incidence and its recurrence. However, the results show that there were no significant differences in hs-CRP levels among these groups.[21]

Lastly, the study done by Sasaki et al. found similar results of rising and falling of hs-CRP after ablation at 6 months which eventually returned to baseline after 12 months in patients with no AF recurrence. They also report the association of hs-CRP changing and LA volume and LV ejection fraction. They found a significant reduction in the LA volume and an increase in the LV ejection fraction 6 months after ablation. These changes were most prominent in the non-recurrence group.[22]

The pathophysiology of AF is still not well understood, and the inflammatory process likely plays an important role. AF starts with rapid atrial activation that mainly originates from automatic foci in the pulmonary veins that can induce injury and apoptosis of atrial cardiomyocytes. This can lead to ischemia, microscopic structural changes, and atrial myopathy.

Cardiac adaptations to AF, such as metabolic, electrical, contractile, and anatomic remodeling, are known to be present. Also, local activation of the complement system, mediated by the binding of C reactive protein(CRP) to phospholipid components of the damaged atrial cardiomyocytes, would amplify local inflammation. These

adaptations can lead to an inflammatory response that may cause structural remodeling and favor the maintenance of AF.

CRP is a non-disease-specific acute-phase reactant that has traditionally been used to detect acute lesions, infections, and inflammation, as well as to assess the activity of inflammatory diseases, and is a good systemic marker of inflammation and tissue damage.

In the pre-ablation population, the hs-CRP levels in both recurrent and non-recurrent groups are elevated due to the inflammatory process associated with AF. This may be due to the longstanding time of atrial fibrillation in the included population that make a chronic change in atrial cardiomyocytes. This change activated the inflammatory response in the population. After the ablation procedure was done, the hs-CRP in the recurrent population was significantly increased compared to the non-recurrent population. We hypothesized that in patients with AF recurrence after ablation, there may be ongoing processes of hemodynamic, metabolic, and oxidative change that are due to inflammatory processes and lead to atrial remodeling, thus promoting AF recurrence.

Further studies are necessary to improve patient selection for ablation and avoid exposing patients to unnecessary procedures and complications. Furthermore, we should evaluate other inflammatory markers as well.

5 | LIMITATION

This study has a few potential limitations. First, most studies were observational studies with limited sample sizes due to inclusion criteria that includes the studies which have both baseline and post-ablation hs-CRP value. This could lead to the increased potential of type II errors. Thus, we could not demonstrate the association between baseline hs-CRP and post-ablation AF recurrence. Second, there was significant heterogeneity of baseline characteristics across the included studies, such as gender, type of AF, and the duration before ablation. These may be possible confounding factors that alter the outcome of our study. Finally, some trials studied the cut-off values of baseline and post-ablation hs-CRP to predict AF recurrence, but there was no consensus for the best cut-off value.

6 | CONCLUSION

This meta-analysis demonstrated a significant association between post-ablation hs-CRP and AF recurrence after catheter ablation but not pre-ablation hs-CRP. Our results add to the current literature regarding the inflammatory process involvement in AF pathogenesis. Further larger studies with long-term follow-up are needed to confirm our findings.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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