



Simple hematological predictors of AF recurrence in patients undergoing atrial fibrillation ablation

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Abstract

Background Red cell distribution width (RDW) and neutrophil-to-lymphocyte ratio (NLR) are simple hematologic indices that have been used to predict adverse outcomes in different clinical settings. The aim of our study is to determine whether RDW and NLR can predict atrial fibrillation (AF) recurrence in patients undergoing AF ablation. **Methods** Consecutive patients, without known hematological disorders, who underwent AF catheter ablation between January 2014 and April 2017 were enrolled into this study. Blood samples were taken one day before and five hours after the ablation procedure. **Results** A total of 346 patients (224 males (65%), mean age: 59 ± 11 years old) were included. After a mean follow up of 26.2 ± 12.1 months, 80 (23.1%) patients experienced late AF recurrence (defined as any recurrence after the blanking period of three months), while 97 (28%) patients experienced early AF recurrence during the blanking period. Univariate analysis showed that early arrhythmia recurrence, type of AF and NLR after the procedure were significantly associated with late AF recurrence, while early arrhythmia recurrence and NLR remained significant in multivariate analysis. RDW was not associated with late AF recurrence. None of the parameters above predicted early arrhythmia recurrence. **Conclusions** Simple and inexpensive hematological indices such as NLR should be evaluated for their ability to predict AF recurrence in patients undergoing catheter ablation in larger prospective studies.

J Geriatr Cardiol 2019; 16: 671–675. doi:10.11909/j.issn.1671-5411.2019.09.008

Keywords: Atrial fibrillation; Neutrophils; Radiofrequency ablation

1 Introduction

Hematological indices such as red cell distribution width (RDW) and neutrophil-to-lymphocyte ratio (NLR) have been associated with incident atrial fibrillation (AF).^[1–6] RDW reflects variability in the size of circulating erythrocytes and is a marker of anisocytosis,^[7] while NLR is a systemic inflammatory marker with prognostic significance for cardiovascular diseases.^[8] Specifically, a high neutrophil count reflects subclinical inflammation, and a reduced lymphocyte count reflects physiologic stress and poor general health. As a result, the NLR provides information on both

the inflammatory status and the stress response.^[9] In light of the well-characterized association between inflammation and AF,^[10] a number of studies have evaluated the role of corticosteroids in preventing AF recurrence after AF catheter ablation.^[11–14] Specifically, the STEROID-AF study showed that oral corticosteroids have significant effect in lowering certain cytokines, but this was not translated to better outcomes following AF ablation.^[11] Another randomized controlled trial reported that low dose corticosteroids administered for a short period, shortly after AF ablation may have a beneficial role in prevention of immediate and mid-term follow-up AF recurrences.^[12] In addition, periprocedural short-term moderate intensity steroid therapy reduced early arrhythmia recurrence but it was not effective in preventing late AF recurrence following AF ablation.^[13] These findings highlight the possible association between inflammation and AF recurrence in patients undergo catheter ablation. Furthermore, there is an increased interest in

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Received: November 18, 2018 **Revised:** December 31, 2018

Accepted: January 30, 2019 **Published online:** September 28, 2019

finding simple predictors for identifying patients who are at higher risk of AF recurrence and who might benefit from adjunctive antiarrhythmic medications post-ablation. Therefore, we investigated the values of RDW, NLR and other simple hematological indices for predicting AF recurrence in patients undergoing AF ablation in our center.

2 Methods

2.1 Patients and ablation procedure

This retrospective cohort study included consecutive patients undergoing AF catheter ablation between January 2014 and April 2017 in our center. The exclusion criteria were those with known hematological disorders. Catheter ablation was performed under intravenous sedation with midazolam and remifentanyl by two experienced operators (Efremidis M and Letsas KP). The ablation procedure has been described in full details elsewhere.^[15] In brief, after the three-dimensional geometry of the left atrium was obtained using CARTO (Biosense Webster, Inc.), wide circumferential lesions for isolation of large atrial areas around both ipsilateral pulmonary veins (PVs) were applied using a 3.5 mm-tip ablation catheter (Thermo Cool Navi-Star and Smart Touch, Biosense Webster, Inc.). The endpoint of the ablation was the absence or dissociation of potentials in the isolated area as documented by the circular mapping catheter (Lasso, Biosense Webster, Inc.) placed within each of the PVs. In addition, exit block was confirmed by pacing around the circular mapping catheter from within each PV. Entrance and exit block of the PVs were evaluated 30 min after the initial isolation. The patients were anticoagulated using acenocoumarol with a target international normalized ratio of 2.0–3.0 or direct oral anticoagulants at least four weeks before and three months after the procedure. We routinely received blood samples from all patients who underwent AF catheter ablation one day before and about five hours after the ablation procedure. We measured a complete blood count, creatinine and troponin levels.

All patients in our institution underwent routine follow-up post-ablation, as per our institution's protocol. Specifically, patients were evaluated every week at the dedicated arrhythmia outpatient clinic of our institution for the first month after the procedure. Patients had follow-up visits with a 24-h Holter electrocardiogram at 1, 3, 6, 9, 12 months and for every 6 months thereafter or whenever they developed symptoms consistent with recurrent AF. Antiarrhythmic drugs, except amiodarone, were discontinued five days before the ablation procedure and were re-initiated on the next day only in patients with non-paroxysmal AF for three months after the procedure. Amiodarone was discon-

tinued for four weeks before the procedure to allow enough time for wash out while non-paroxysmal AF patients were reloaded after the procedure.^[16] The study was approved by the Hospital's Ethics Committee.

2.2 Statistical analysis

Continuous variables are presented as mean \pm SD, while categorical ones are presented as absolute and relative frequencies (percentages). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables with and without normal distribution were compared using Student's *t*-test or the Mann-Whitney *U* test, respectively. Pearson's chi-square or Fisher's exact test were used to test for any associations between two categorical variables. We examined univariate models and multivariate models with forward selection of variables per likelihood ratio criteria by using binary logistic regression analysis. Variables with a univariate *P*-value $<$ 0.2 were included in the multivariable model (Hosmer-Lemeshow). Receiving operating characteristics curve (ROC) was performed to assess the best cutoff value of significant continuous variables to predict AF recurrence. Analyses were performed with SPSS (version 17.0, SPSS Inc., Chicago, IL, USA) and all reported *P*-values are two-tailed. Double-sided *P*-values less than 0.05 were considered as indicative of statistical significance.

3 Results

A total of 346 patients (224 males (65%), mean age: 59 \pm 11 years), who were followed for a mean period of 26.2 \pm 12.1 months, were included. The indication for AF ablation was symptomatic AF (paroxysmal AF: 216 (62%), persistent AF: 121 (35%), long standing persistent AF: 9 (3%)) refractory to antiarrhythmic drugs. During follow-up, 80 (23%) patients experienced late AF recurrence (defined as any recurrence after the blanking period of three months), while 97 (28%) patients experienced early AF recurrence during the blanking period. Of the different hematological indices studied, only NLR after ablation was significantly associated with late AF recurrence during after ablation (*P* = 0.035). By contrast, RDW before or after ablation procedure was not significantly associated with late arrhythmia recurrence. Other factors significantly associated with late recurrence of AF were early arrhythmia recurrence (*P* = 0.023), type of AF (*P* = 0.0009) and procedure time (0.041) (Table 1). Multivariate analysis was performed, including variables with *P* $<$ 0.2 on univariate analysis. This revealed early arrhythmia recurrence (OR = 1.94, 95% CI: 1.11–3.41, *P* = 0.02) and NLR post-ablation (OR = 1.1, 95% CI: 1.01–1.20,

Table 1. Baseline characteristics, procedural characteristics and hematological indices between patients with and without late atrial fibrillation recurrence.

	Late atrial fibrillation recurrence		P-value
	Yes (n = 80, 23.1%)	No (n = 266, 76.9%)	
Follow-up, months	28.3 ± 11.9	25.5 ± 12.1	0.05
Hematological indices before ablation			
NLR	2.04 ± 0.74	2.12 ± 1.36	0.43
WBC, cells/ μ L	7179 ± 1930	7454 ± 2110	0.30
Platelets, $\times 10^9$ /L	234 ± 55	234 ± 63	0.57
RBC, $\times 10^6$ / μ L	4.93 ± 0.50	4.93 ± 0.55	0.99
RDW-SD, fL	42.8 ± 3.20	42.4 ± 4.40	0.28
RDW-CV	13.7% ± 1.00%	13.8% ± 1.68%	0.85
RDW-SD/PDW	3.12 ± 0.49	3.10 ± 0.53	0.53
Troponin, ng/L	7.55 ± 6.40	10.1 ± 33.4	0.89
Creatinine, mg/dL	0.85 ± 0.19	0.85 ± 0.25	0.44
Hematological indices after ablation			
NLR	6.27 ± 3.64	5.25 ± 2.83	0.04
WBC cells/ μ L	9821 ± 3077	9493 ± 2689	0.41
Platelets, $\times 10^9$ /L	195 ± 47	201 ± 54	0.67
RBC, $\times 10^6$ / μ L	4.42 ± 0.45	4.52 ± 0.53	0.21
RDW-SD fL	42.1 ± 3.22	41.8 ± 4.80	0.63
RDW-CV	13.5% ± 0.95%	13.7% ± 1.67%	1.00
RDW-SD/PDW	3.17 ± 0.54	3.16 ± 0.55	0.57
Troponin, mg/dL	808.5 ± 447	960.7 ± 635	0.09
Baseline characteristics			
Male sex	53 (66.3%)	171 (64.3%)	0.75
Age, yrs	59.6 ± 10.3	58.6 ± 11.2	0.57
Paroxysmal AF	40 (50%)	176 (66.2%)	0.01
Hypertension	46 (57.5%)	129 (48.5%)	0.19
Diabetes	6 (7.5%)	27 (10.2%)	0.47
Dyslipidemia	31 (38.8%)	101 (38%)	0.94
Coronary artery disease	6 (7.5%)	11 (4.1%)	0.23
Antiarrhythmic drugs			
β -blockers	58 (72.5%)	183 (68.8%)	0.74
Class Ic (flecainide, propafenone)	46 (57.5%)	139 (52.3%)	0.53
Sotalol	20 (25%)	63 (23.7%)	0.90
Amiodarone	19 (23.8%)	58 (21.8%)	0.80
Procedure characteristics			
Fluoroscopy time, min	15.7 ± 8.3	16.5 ± 8.2	0.42
Procedure time, min	186.9 ± 56.7	174.4 ± 53	0.04
Radio-frequency time, min	30.15 ± 1.47	29.96 ± 2.45	0.08
Complications			
Stroke	4 (5%)	3 (1.1%)	0.03
Tamponade	0	1 (0.4%)	0.59
Early arrhythmia recurrence	31 (38.8%)	66 (24.8%)	0.02

Data are presented as mean \pm SD or n (%). AF: atrial fibrillation; NLR: neutrophil to lymphocyte ratio; PDW: platelet distribution width; RBC: red blood cells; RDW-CV: red cell distribution width-coefficient variation; RDW-SD: red cell distribution width-standard deviation; WBC: white blood cells.

$P = 0.03$) were significantly associated with late AF recurrence. No significant association between hematological indices and early arrhythmia recurrence was found (Table 2).

Table 2. Baseline characteristics, procedural characteristics and hematological indices between patients with and without early atrial fibrillation recurrence.

	Early atrial fibrillation recurrence		P-value
	Yes (n = 97, 28%)	No (n = 249, 72%)	
Follow-up, months	25.6 ± 12.5	26.4 ± 11.9	0.51
Hematological indices before ablation			
NLR	1.94 ± 0.79	2.16 ± 1.37	0.31
WBC, cells/ μ L	7396 ± 2118	7376 ± 1954	0.97
Platelets, $\times 10^9$ /L	237 ± 74	233 ± 56	0.90
RBC, $\times 10^6$ / μ L	4.93 ± 0.54	4.93 ± 0.54	0.89
RDW-SD, fL	42.8 ± 4.3	42.3 ± 4.1	0.67
RDW-CV	13.9% ± 1.8%	13.7% ± 1.4%	0.23
RDW-SD/PDW	3.1 ± 0.53	3.1 ± 0.52	0.91
Troponin, ng/L	6.98 ± 5.59	10.5 ± 34.7	0.84
Creatinine, mg/dL	0.85 ± 0.25	0.84 ± 0.2	0.99
Hematological indices after ablation			
NLR	5.62 ± 3.27	5.43 ± 2.99	0.88
WBC cells/ μ L	9545 ± 2666	9579 ± 2832	0.89
Platelets, $\times 10^9$ /L	202 ± 62.3	198 ± 48.6	0.96
RBC, $\times 10^6$ / μ L	4.47 ± 0.51	4.5 ± 0.52	0.58
RDW-SD, fL	42.4 ± 4.4	41.7 ± 4.52	0.36
RDW-CV	13.8% ± 1.8%	13.6% ± 1.4%	0.22
RDW-SD/PDW	3.15 ± 0.56	3.17 ± 0.54	0.77
Troponin, mg/dL	968 ± 626	909 ± 589	0.57
Baseline characteristics			
Male sex	62 (63.9%)	162 (65.1%)	0.84
Age, yrs	59.6 ± 10.3	58.6 ± 11.2	0.92
Paroxysmal AF	54 (55.7%)	162 (65.1%)	0.11
Hypertension	50 (51.5%)	125 (50.8%)	0.90
Diabetes	11 (11.3%)	22 (8.9%)	0.49
Dyslipidemia	33 (34%)	99 (40.1%)	0.3
Coronary artery disease	4 (4.1%)	13 (5.3%)	0.66
Antiarrhythmic drugs			
Class Ic	55 (58.5%)	130 (54.9%)	0.55
β -blockers	75 (78.1%)	166 (69.5%)	0.11
Sotalol	28 (29.2%)	55 (23%)	0.24
Amiodarone	26 (27.1%)	51 (21.3%)	0.26
Procedure characteristics			
Fluoroscopy time, min	15.7 ± 8.3	16.5 ± 8.2	0.67
Procedure time, min	230.5 ± 403	174.4 ± 53	0.004
Complications			
Stroke	2 (2.1%)	5 (2%)	0.99
Tamponade	0	1 (0.4%)	0.53

Data are presented as mean \pm SD or n (%). AF: atrial fibrillation; NLR: neutrophil to lymphocyte ratio; PDW: platelet distribution width; RBC: red blood cells; RDW-CV: red cell distribution width-coefficient variation; RDW-SD: red cell distribution width-standard deviation; WBC: white blood cells.

In ROC analysis, a NLR after ablation > 3.9 had a 70% sensitivity and 38% specificity for predicting late AF recurrence (AUC = 0.58, 95% CI: 0.51–0.65, $P = 0.035$). We subsequently performed subgroup analysis regarding the type of AF (paroxysmal AF: 216 patients, non-paroxysmal AF: 130 patients). In paroxysmal AF patients, we did not find any statistically significant differences in either baseline characteristics or hematological indices (before or after ablation procedure) between patients with or without late AF recurrence. On the other hand, in non-paroxysmal AF patients, univariate analysis showed that lower platelet distribution width (PDW) levels after ablation ($P = 0.03$) and higher RDW-SD/PDW ($P = 0.01$) and troponin levels ($P = 0.04$) after the ablation procedure were significantly associated with late AF recurrence. However, the statistical significance was lost for these hematological indices in multivariate analysis.

4 Discussion

The main findings of our study are that NLR after ablation procedure and early arrhythmia recurrence were significantly associated with late AF recurrence in patients undergoing AF catheter ablation while we did not find a significant association between RDW and late AF recurrence.

Several studies have investigated the possible associations between simple electrocardiographic^[17] and hematological markers, such as RDW and NLR, and AF ablation outcomes.^[9,18–21] Elevated RDW and pre-ablation NLR have been found to be predictors of AF recurrence following cryoballoon-based AF ablation,^[9,18] while pre-ablation white blood cell count was also found to be significantly associated with AF recurrence after catheter ablation.^[19] Consistent with our results, Guo and colleagues found that post-ablation NLR was associated with higher AF recurrence rates after the ablation procedure.^[22] Similarly, a meta-analysis showed that high NLR, whether baseline or post-surgery/procedure, is associated with an increased risk of AF recurrence/occurrence after CABG, catheter ablation or cardioversion.^[2] Additionally, post-ablation NLR has been found to be an independent predictor for early arrhythmia recurrence,^[20] which is an important finding because early arrhythmia recurrence is significantly associated with late arrhythmia recurrence as revealed from the present study. However, our study did not show significant association between pre- or post-ablation NLR and early arrhythmia recurrence.

Regarding the pathophysiology of the revealed association between NLR with late arrhythmia recurrence, the NLR provides information on both the inflammatory status and

the stress response while the accumulating neutrophils contribute to atrial remodeling through the release of pro-inflammatory mediators.^[23] The findings of previous studies indicating that pre-ablation NLR levels were significantly associated with adverse ablation outcomes support the notion that pre-ablation inflammatory environment may have a role in AF recurrence and thus could be a pharmacological target to improve post-procedure outcomes. For example, previous studies investigated the role of corticosteroids in preventing AF recurrence after AF catheter ablation.^[11–13] Future prospective studies are needed on this area and they will need to take into account other contributing factors towards AF recurrence, such as the ablation technique used,^[24] heart failure status,^[25] and electrophysiological substrates present at baseline and revealed during ablation by adenosine testing.^[26]

4.1 Conclusions

In conclusion, NLR after ablation procedure was found to be significantly associated with late AF recurrence in patients undergoing AF catheter ablation. Whether post-ablation NLR levels can be used as a risk stratification tool to identify patients at higher risk of AF recurrence remains to be determined. This has the potential to change common practice as this subgroup may benefit from adjunct antiarrhythmic medications after the procedures.

4.2 Limitations

Our study is a retrospective small sized single-center observational study. Importantly, the follow-up monitoring for the detection of arrhythmia recurrence was performed via 24-h or 48-h Holter recordings and 12-lead electrocardiograms. More thorough methods of monitoring, such as loop recorders, 7-day Holter monitoring, can be used in the future to improve AF detection rates.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors have no conflicts of interest to declare.

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