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The Usefulness of RDW as a Predictor of Atrial Fibrillation Recurrence after Cryoablation

Pinar Keskin[a], Halil Lutfi Kisacik[a], Sinan Inci[b], Murat Gul[b], Ozcan Ozeke[a], Serkan Topaloglu[a], Dursun Aras[a]

[a] *Departmant of Cardiology, Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey*
[b] *Department of Cardiology, School of Medicine, Aksaray University, Aksaray, Turkey*

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SOUHRN

Cíl: Je známo, že distribuční šíře velikosti erytrocytů (red cell distribution width, RDW) souvisí se zánětem a je spojena s nepříznivým výsledným stavem pacientů s kardiovaskulárními onemocněními. Málo je však známo o úloze RDW jako prediktoru recidivy fibrilace síní (FS) po kryoablaci; naším cílem proto bylo prozkoumat vztah mezi RDW a recidivou FS po kryoablaci.
Metody: Retrospektivně jsme analyzovali zdravotní záznamy 90 pacientů po kryoablaci (průměrný věk 50,06 ± 12,36 roku) se symptomatickou paroxysmální FS, přestože měli předepsáno alespoň jedno antiarytmikum. Pacienti byli rozděleni do dvou skupin podle recidivy FS při vstupním vyšetření a na konci sledování o průměrné délce 15 měsíců.
Výsledky: Recidiva FS byla zaznamenána u 22 (24 %) pacientů. Vstupní demografické charakteristiky a průměr levé síně (3,74 ± 0,33 vs. 3,76 ± 0,31 cm; p = 0,757) byly u obou skupin podobné. Hodnoty RDW byly statisticky významně vyšší u pacientů s recidivou FS (14,17 ± 1,42 vs. 13,57 ± 0,85; p = 0,019). Hodnoty skóre CHA_2DS_2-VASc v obou skupinách se sice nelišily, avšak u pacientů se skóre CHA_2DS_2-VASc s hodnotou 3 dosáhl výskyt recidivy FS 46 %, zatímco u pacientů se skóre CHA_2DS_2-VASc s hodnotou 0 to bylo 15 %. Hodnota RDW jako prediktoru recidivy FS byla ověřována pomocí křivky operační charakteristiky a plocha pod křivkou činila 0,634 (p = 0,06) s trendem směrem ke statistické významnosti.
Závěr: Distribuční šíře velikosti erytrocytů může sloužit spolu s dalšími prediktory jako užitečný prediktor recidivy FS, ne však samostatně; tuto možnost ale ještě musejí potvrdit větší multicentrické a prospektivní studie.

ABSTRACT

Aim: Red cell distribution width (RDW) is known to be related to inflammation and has been associated with poor outcomes in patients with cardiovascular diseases. However, little is known about the role of RDW as a predictor of atrial fibrillation (AF) recurrence after cryoablation, and thus we aimed to investigate the relation between RDW and the recurrence of AF after cryoablation.
Methods: We retrospectively analyzed the case records of 90 patients after cryoablation (mean age, 50.06±12.36) with symptomatic paroxysmal AF despite being prescribed at least one anti-arrhythmic drug. The patients were divided into two groups based on the recurrence of AF and, after a mean follow-up period of 15 months.
Results: AF recurrence was detected in 22 (24%) patients. Baseline demographic characteristics and left atrial diameter (3.74±0.33 vs 3.76±0.31; p = 0.757) were similar between the two groups. RDW levels were significantly higher in patients with AF recurrence than in those without AF recurrence (14.17±1.42 vs 13.57±0.85; p = 0.019). CHA_2DS_2-VASc scores were not different between the two groups but in the patients with a CHA_2DS_2-VASc score of 3, the rate of AF recurrence was 46% while it was only 15% in patients with CHA_2DS_2-VASc score 0. The value of RDW as a predictor of a recurrence of AF was tested using the receiver operator characteristic curve and the area under the curve was 0.634 (p = 0.06) with a trend toward statistical significance.
Conclusion: RDW may be a useful predictor of AF recurrence along with other predictors but not alone, and larger multicenter and prospective studies are required to confirm this.

Keywords:
Atrial fibrillation
Cryoablation
RDW

Address: Murat Gul, MD, Aksaray University School of Medicine, Department of Cardiology, Aksaray 68100, Turkey, e-mail: drmuratgul68@gmail.com
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Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and is present in 1–2% of the general population.[1] The incidence of AF is both age- and gender-dependent, the prevalence of AF is <0.5% between the age of 40–50 years, increases with age and is seen in 5–15% of the population at the age of 80 years.[2,3] AF is associated with death, stroke and other thromboembolic events, heart failure and increased hospitalization, and a reduction in quality of life, exercise capacity, and left ventricular function. Catheter ablation is currently being frequently used to restore sinus rhythm, especially in patients with paroxysmal AF who remain symptomatic despite optimal medical therapy.[4] Radiofrequency (RF) current is the most commonly used energy source for pulmonary vein ablation, but other energy sources have been investigated because of the possibility of serious but rarely encountered complications with RF sources. Cryothermal energy, used with the cryoballoon technique, is an example of such an alternative to RF current. Although a meta-analysis of the studies investigating rhythm control in paroxysmal AF has demonstrated that ablation is superior to antiarrhythmic drugs in restoring sinus rhythm,[5–10] the risk of AF recurrence after ablation is an important concern and numerous factors affecting AF recurrence have been investigated. Inflammatory markers have been demonstrated to be definite predictors of recurrence,[11–13] and more importantly, it was shown that red cell distribution width (RDW) was correlated with CRP level, which was in turn associated with high mortality in various studies. Further, chronic inflammation and neurohumoral activation can also result in unfavorable cardiovascular events by increasing RDW.[14–16] Although a relationship between RDW and AF incidence has been demonstrated in various studies, few studies have investigated the relationship between RDW and postprocedure AF recurrence in patients who have undergone cryoablation. Thus, this study aimed to investigate whether RDW could predict post-procedure AF recurrence and the role of inflammation in AF recurrence.

Material and methods

Patients

A total of 90 patients who had undergone cryoablation for symptomatic paroxysmal AF despite being prescribed at least one antiarrhythmic drug in Turkey Yüksek Ihtisas Education and Research Hospital between July 2010 and April 2013 were retrospectively researched. Clinical and biochemical data of the patients were obtained from patient files. Patients with systolic blood pressure greater than 140 mmHg or diastolic blood pressure over 90 mmHg or with a history of antihypertensive drug use were considered hypertensive. Patients with a fasting LDL level over 130 mg/dL, fasting triglyceride level over 200 mg/dL, or with a history of statin use were considered hyperlipemic. Patients with a fasting blood glucose greater than 126 mg/dL at two different times or receiving treatment for diabetes mellitus were considered diabetic. Smoking history was also evaluated. All patients underwent 24-hour Holter monitoring before the procedure and at the 3rd and 6th-month follow-up visits. In symptomatic patients, an ECG obtained at the moment of symptom appearance was also examined. The presence of AF/flutter/tachycardia longer than 30 seconds was considered a failure of the procedure.[17] Patients with structural heart disease, history of valve surgery, left atrial thrombosis, marked left atrial dilatation (parasternal long axis view >5 cm), coagulation problems, ejection fraction ≤55%, uncontrolled hyperthyroidism, deficiency of vitamin B12 and folic acid or being treated for these conditions, chronic kidney disease, systemic disease, and active infection were excluded. The study complied with the principles of the Declaration of Helsinki and was approved by the local ethics committee.

Preprocedural evaluation

All patients underwent transthoracic echocardiography, performed using a Vivid 7 Dimension Cardiovascular Ultrasound System, (GE Medical Systems, USA), before the cryoballoon ablation procedure and echocardiographic measurements were made according to the criteria recommended by the American Echocardiography Society.[18] All patients also underwent transesophageal echocardiography within 48 h before the procedure to exclude a left atrium thrombus that was defined as an echogenic mass in the left atrial appendage that continued into more than one plane and could be clearly distinguished from surrounding tissue; patients with thrombus in the left atrial appendage were excluded. Anticoagulants were discontinued at least 48–72 h before the procedure, and enoxaparin (1 mg/kg) was initiated if INR was <2 in the interim. The ablation was performed when INR was <1.5. The prescribed anti-arrhythmic drugs were discontinued at least five times their half-life before the procedure. Results of all biochemical parameters, thyroid function tests, hemostasis, and complete blood count, measured using standard laboratory methods, were obtained from the patient case files.

Ablation procedure

Ablation was performed under conscious sedation with midazolam and invasive arterial blood pressure, oxygen saturation, and ECG were monitored during the procedure. Bilateral femoral veins and the left femoral artery were used to gain vascular access. A 6Fr steerable decapolar catheter (Biosense Webster, St. Jude, USA) was placed in the coronary sinus as a reference for atrial pacing. During the right pulmonary vein (PV) isolation, the catheter was placed within the superior vena cava to stimulate the phrenic nerve. Intracardiac and superficial electrocardiograms were recorded at a speed of 100 mm/sec (EP-Tracer, Kardiotek). Transseptal punctures were performed under fluoroscopy monitoring using a Brockenbrough (BRK) transseptal needle (St. Jude Medical, Minnetonka, MN, USA). The Sheath/dilator and the needle were drawn back when the patient was in the left anterior oblique position such that the needle would fall into the fossa ovalis from the superior vena cava and the left atrium was accessed through the needle attached to the fossa ovalis. Subsequently, the sheath was placed in the left atrium using the guidewire by the first drawing the needle back. The 8 Fr transseptal sheath was then (Biosense Webster, CA, USA) replaced by a 12 Fr transseptal sheath (FlexCath, Montreal, Canada). A 28 mm cryoballoon catheter (Arctic Front; Medtronic, Minneapolis, MN) was advanced over the guidewire (0.035 inches, 180 cm, Super Stiff G.W., St Jude Medical, St. Paul, MN, USA) towards pulmonary vein through the transseptal sheath. Anticoagulation therapy after the transseptal puncture was provided by intravenous heparin administration to achieve an activated clotting time between 300 and 350 s. Pulmonary vein potentials were determined before cryoablation using a mapping catheter (Achieve; Medtronic, Minneapolis, MN), which was passed through the internal lumen of the cryoballoon catheter guidewire. The transseptal sheath was continuously washed with heparinized saline at a rate of 3–4 mL/s. A standard 5-minute freezing cycle was initiated if the necessary catheter position, as determined by the contrast injection, had been obtained, and at least two cycles were performed for each vein. A bipolar catheter was placed in the superior vena cava and the phrenic nerve was stimulated at 1 000 ms cycles with a 20-mA pulse output to avoid possible phrenic nerve paralysis encountered during cryoablation of the right superior pulmonary vein (RSPV) and right inferior pulmonary vein (RIPV). The intensity of stimulation was monitored by abdominal palpation during the procedure. Cryoablation was discontinued when a decrease in contractions occurred. After all pulmonary veins had been ablated, the mapping catheter was placed in the pulmonary veins to verify pulmonary vein isolation. The disappearance of pulmonary vein potentials and pulmonary vein dissociation were used as procedure endpoints. The ablation was repeated with a cryoballoon if pulmonary vein isolation could not be initially achieved.

Postablation follow-up

All patients underwent transthoracic echocardiography both immediately after the procedure and before hospital discharge to check for pericardial effusion. The first dose of warfarin was administered 4–6 h after the procedure and was combined with enoxaparin (1 mg/kg, every 12 h) until an effective INR of 2.0–3.0 was achieved. Post-procedure, patients were closely monitored in the intensive care unit for haemodynamic or ECG changes. At discharge, all patients were prescribed a combination of an anticoagulant (warfarin) and an antiarrhythmic for a minimum period of three months, and further therapeutic options were decided by the attending physician depending on the results of the third-month evaluation for antiarrhythmic therapy and the CHA_2DS_2-VASc score for anticoagulation. All patients underwent a 12-lead ECG at the 3rd-, 6th-, and 12th-month evaluation, irrespective of whether they had complaints during follow-up or not. Results of the 24-hour Holter monitoring, both before the procedure and at the 3rd- and 6th-month follow-up visits were also evaluated. Recurrence was defined as episodes of AF, atrial flutter, or tachycardia, occurring after ablation and lasting for more than 30 s as documented by ECG or other recording devices.

Statistical analysis

Statistical analyses were performed using the SPSS package program (v.20,). Descriptive statistics were used for numerical variables, whereas frequency tables were created for categorical variables. Differences between categorical variables were analyzed using the chi-square test. One-way ANOVA was used to test for homogeneity and the one-sample K-S test was used for assessing normality. The independent sample T-test was used if data were normally distributed while the Mann–Whitney U test was used when data were not normally distributed. The ROC curve was generated using AF recurrence rates. *P*-values less than 0.05 were considered significant.

Results

The present study retrospectively analyzed the case data of 90 patients who had undergone cryoablation for symptomatic paroxysmal AF despite being treated with at least one antiarrhythmic. Of the 90 patients, 34 (38%) were female and 56 (62%) were male, and the mean age of the patients was 50.06±12.36 years. The average follow-up time was 15 months (range 6–30 months). During the follow-up period, AF recurred in 22 (24%) patients, while no evidence of recurrence was observed in the remaining 68 (76%) patients; thus, cases were grouped as recurrence or no recurrence. Complications because of the cryoablation procedure were observed in seven patients, three developed phrenic nerve paralysis and four developed a hematoma at the intervention site; two of these patients were from the recurrence group and five from the no-recurrence group. The demographic characteristics of the patients from both groups are listed and compared in Table 1. No statistically significant differen-

Table 1 – Baseline characteristics of the patients

Variables	Recurrence (Group I) n = 22	No-recurrence (Group II) n = 68	*p*-value
Age (years)	50.86±11.54	49.79±12.7	0.727
Gender			0.802
Male	13 (59%)	43 (63%)	
Female	9 (41%)	25 (37%)	
CAD	7 (32%)	15 (23%)	0.406
HT	11 (50%)	27 (41%)	0.469
DM	4 (18%)	4 (6%)	0.103
HL	7 (32%)	25 (38%)	0.799
Smoking	5 (23%)	20 (30%)	0.592
PCI	3 (14%)	3 (5%)	0.162
CABG	1 (5%)	0 (0%)	-
CHA_2DS_2-VASc			
CHA_2DS_2-VASc 0	5 (23%)	27 (40%)	0.051
CHA_2DS_2-VASc 1	5 (23%)	16 (24%)	
CHA_2DS_2-VASc 2	6 (27%)	18 (26%)	
CHA_2DS_2-VASc ≥3	6 (27%)	7 (10%)	

CABG – coronary artery bypass graft; CAD – coronary artery disease; CHA_2DS_2-VASc – CHA_2DS_2-VASc score; DM – diabetes mellitus; HL – hyperlipidemia; HT – hypertension; PCI – percutaneous coronary intervention.

Table 2 – Laboratory results of the patients

Variables	Recurrence (Group I) n = 22	No-recurrence (Group II) n = 68	*p*-value
RDW (%)	14.17±1.42	13.57±0.85	**0.019**
Glucose (mg/dL)	96.32±14.15	96.87±14.99	0.892
Creatinine (mg/dL)	0.90±0.22	0.87±0.17	0.557
Triglyceride (mg/dL)	148.90±58.02	147±66.61	0.907
Total cholesterol (mg/dL)	179.15±43.20	192.12±39.96	0.215
LDL (mg/dL)	110.20±36.52	116.85±36.67	0.469
HDL (mg/dL)	38.90±9.50	45.60±12.35	**0.028**
WBC (10^3/mm^3)	7.97±2.16	7.29±1.98	0.174
Platelet (10^3/mm^3)	253 ±67	254 ±60	0.937

RDW – red cell distribution width.

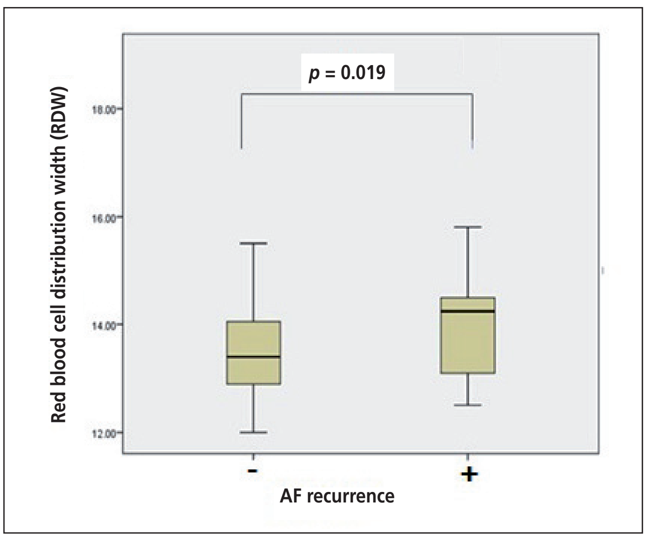

Fig. 1 – Distribution of RDW according to AF recurrence status. The transverse line in the middle of each box indicates the median value (50th percentage), whereas the bottom and top margins of the boxes indicate the 25th and 75th percentages, respectively. The minimum and maximum values are shown with the extending bars on the bottom and top of the boxes, respectively.

ces were detected between these two groups in terms of age, prevalence of hypertension, diabetes, hyperlipidemia, smoking history, coronary artery disease, and CHA$_2$DS$_2$-VASc score.

Pre-ablation laboratory analyses revealed no differences between the two groups in terms of biochemical and hematological parameters except for HDL-cholesterol and RDW values (Table 2); HDL-cholesterol levels were significantly lower in the recurrence group compared to the no-recurrence group (38.90±9.50 vs. 45.60±12.35, p = 0.028) while the mean RDW value was significantly higher in the recurrence group (14.17±1.42 vs. 13.57±0.85, p = 0.019) (Fig. 1). The baseline mean left atrium diameter was similar in both groups at less than 4 cm.

The ROC (receiver operating characteristic) curve analysis for RDW as a predictor of AF recurrence revealed an area under the curve (AUC) of 0.634 with p = 0.06 (Fig. 2).

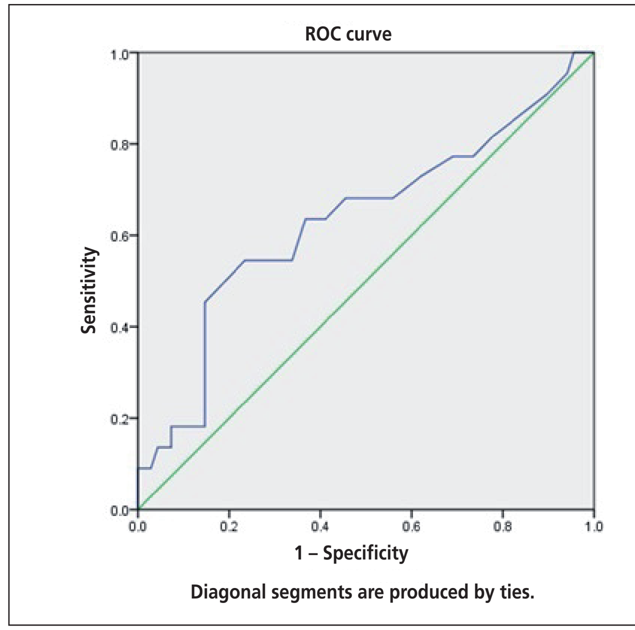

Fig. 2 – ROC curve analysis for RDW and AF recurrence.

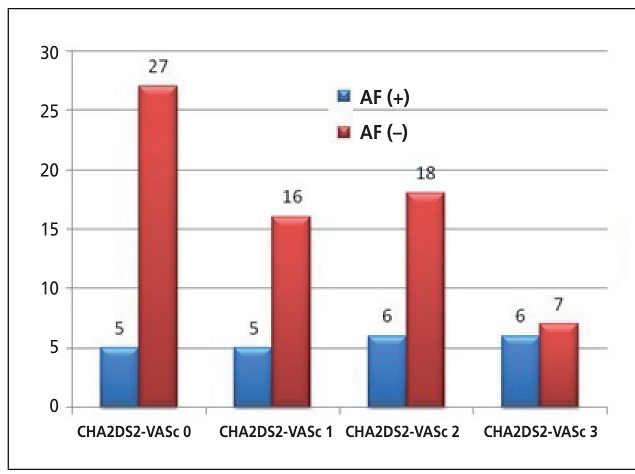

Fig. 3 – The rate of AF recurrence according to the subgroups of CHA$_2$DS$_2$-VASc.

The CHA$_2$DS$_2$-VASc score was used to stratify the patients and to explore a possible relationship between the CHA$_2$DS$_2$-VASc score and AF recurrence. While 32 of the patients had CHA$_2$DS$_2$-VASc score of 0, AF recurrence rates according to the CHA$_2$DS$_2$-VASc scores 0, 1, 2, and 3 were 15% (5), 23% (5), 25% (6) and 46% (6), respectively (Fig. 3), implying that the likelihood of AF recurrence increases as the CHA$_2$DS$_2$-VASc score increases; however, these incidence rates were not significantly different among the four score groups (p = 0.051).

Discussion

The use of ablation techniques to successfully treat atrial fibrillation has been enabled by a better understanding of its pathophysiology, and ablation is performed in patients who are symptomatic despite optimal medical therapy. The RF is currently the most common source of energy for pulmonary vein ablation, and cryothermal energy, which is used with the cryoballoon technique, is a new alternative to RF sources. Although the success rate of cryoablation is increasing along with its expanding clinical use and experience, AF recurrence rates, particularly late recurrence, remain an important problem. Therefore, factors capable of predicting post-procedure AF recurrence have been investigated.

The role of inflammation and oxidative stress in the pathophysiology of AF has been demonstrated in various studies.[10,19–21] The leukocytes, which are the indicators of inflammation, are present in the atrial myocardium of patients with AF alone and those with AF and structural heart disease.[22,23] Chronic inflammation is considered as important factor in the initiation and continuation of AF as it can lead to structural remodeling, such as myocyte degeneration and interstitial fibrosis.[24] A meta-analysis of 47 studies investigated the role of inflammatory factors in the development and recurrence of AF and found that an elevation in circulating inflammatory markers such as CRP and IL-6 is associated not only with a higher incidence of AF both in the general population and in by-pass patients but also with AF recurrence after electrical cardioversion and ablation.[11,25,26] Another study, which investigated the incidence of very late AF recurrence after radiofrequency catheter ablation, found that pre-procedure CRP value was an independent predictor of very late recurrence (HR 4.9, 95% CI 2.3–10.7, $p < 0.0001$).[12]

Chronic inflammation and neurohumoral activation are known to increase RDW and result in unfavorable cardiovascular events.[27–29] A study found that RDW was associated with AF, independent of cardiovascular, nutritional, and hematological parameters.[30] Given that inflammation has a known role in the pathogenesis of AF and that RDW is an inflammatory marker, the current study investigated whether RDW can predict AF recurrence after cryoablation by retrospectively analyzing data from 90 case reports. AF recurrence was documented in 22 of the 90 patients after an average 15-month follow-up period and pre-procedure RDW was significantly higher in the recurrence group compared with the no-recurrence group. In our study, we found a small but significant difference between the groups. Actually, it was demonstrated that increased RDW values were associated with adverse cardiac events even in subjects with RDW values within reference levels.[31] These results are compatible with previous reports of RDW as an inflammatory marker that is associated with unfavorable clinical outcomes in various cardiovascular diseases such as heart failure, myocardial infarction, stable coronary artery disease, and AF. To establish if RDW is indeed a predictor of AF recurrence, a ROC curve analysis was performed and the AUC was found to be 0.634 with a *p*-value of 0.06. We hypothesize that the absence of significance, in spite of an AUC of 0.634, is due to the small sample size and that a larger sample size would have yielded statistical significance. Thus, future studies with a larger sample size will be required to assess the usefulness of RDW as a predictor of AF recurrence.

Importantly, we found that the AF recurrence rate was highest in the patients with a CHA_2DS_2-VASc score of 3, probably because greater inflammation is expected to be present in patients with a higher CHA_2DS_2-VASc score, which, in turn, increases AF recurrence rates. Although data from this study were insufficient to establish a relationship between the CHA_2DS_2-VASc score and AF recurrence; nonetheless, the $CHADS_2$ score has been shown to be associated with left atrium fibrosis and inflammation.[32] Furthermore, a study of 126 patients who underwent RF catheter ablation for symptomatic paroxysmal AF also demonstrated a relationship between AF recurrence and $CHADS_2$ score (HR: 1.91, 95% CI 1.09–3.36, $p = 0.023$) and CHA_2DS_2-VASc score (HR: 1.97, 95% CI 1.16–3.33, $p = 0.012$). They also showed that a $CHADS_2$ or CHA_2DS_2-VASc score ≥ 2 has the greatest predictive value for AF recurrence.[33]

A major limitation of the present study is its relatively low patient number, apart from the fact that it is a single-center retrospective study. There was also a significant difference between the two groups in terms of patient numbers. AF recurrence was determined based on 24-hour Holter monitoring and ECG obtained when the patients were symptomatic, and thus, it is possible that AF recurrence during asymptomatic periods or when not on Holter monitoring, might have been missed. More intense heart rhythm monitoring has been related to better detection of both symptomatic and asymptomatic AF after catheter ablation.[34] Unfortunately, we did not have the opportunity to use long-term heart recordings, as they are not routinely used in our clinical practice.

In conclusion, the results of this study show that because inflammation plays a role in AF pathogenesis and AF recurrence, it is possible that RDW, in conjunction with other recurrence markers, can be used as a predictor of AF recurrence after ablation. RDW may also help screen and select patients who would be more responsive to ablation therapy and identify those who would benefit most from anti-inflammatory therapy to prevent AF recurrence. However, larger prospective studies are required to support these preliminary results.

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Conflict of interest
None.

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