Atrial fibrillation type modulates the clinical predictive value of neutrophil-to-lymphocyte ratio for atrial fibrillation recurrence after catheter ablation

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Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) has been proposed as an indicator of a systemic inflammatory response. There are baseline differences in the inflammation status between paroxysmal atrial fibrillation (PAF) and persistent AF (PerAF). The NLR changes and late recurrences of AF (LRAF) after ablation depending on the AF type remain unknown.

Methods: Consecutive AF patients undergoing pulmonary vein isolation (PVI) by radiofrequency catheter ablation were enrolled from September 2014 to June 2018. The peripheral blood leukocyte NLR 1 day before and 36–48 h after PVI were measured. First, the relationship between NLR changes after to before ablation (ΔNLR) and ERAFs/LRAFs in PAF and PerAF patients were investigated to exclude the baseline inflammation status and evaluate catheter ablation induced inflammation. Second, the clinical impact of the NLR for predicting LRAFs was evaluated.

Results: There hundred sixty-nine PAF and 264 PerAF patients from Osaka Rosai AF registry were enrolled. The ratio of ERAFs/LRAFs in PAF and PerAF patients were 26.8%/22.5% and 39.4%/29.9%, respectively. In PAF and PerAF patients, the ΔNLR was significantly higher with ERAF than no-ERAF (p = 0.022 and p = 0.010, respectively). In PAF patients, the ΔNLR was significantly higher with LRAF than no-LRAF (p = 0.017), while with PerAF, the ΔNLR did not significantly differ between LRAFs and no-LRAFs. In PAF, the ΔNLR was independently and significantly associated with LRAFs after PVI (p = 0.029).

Conclusion: The ΔNLR was significantly higher only in PAF patients with LRAFs than no-LRAFs, but not in PerAF patients. The ΔNLR was useful for predicting LRAFs after PVI in PAF patients.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is associated with considerable morbidity and mortality [1]. Extrasystoles from pulmonary veins are the most common AF trigger activity and pulmonary vein isolation (PVI) has been established as a standard therapy for patients with drug-refractory paroxysmal atrial fibrillation (PAF) [2–8]. The efficacy and safety of the PVI for AF have been reported in several randomized trials [9–11].

The pathophysiology of AF is very complex, and the fundamental AF-promoting mechanism and causes of arrhythmia recurrence after catheter ablation are incompletely understood. Inflammatory signaling in atrial cardiomyocytes causes an effective refractory period change, conduction slowing, hypertrophy, and fibrosis [12]. It has been reported that inflammatory cytokines are useful predictors for the prevalence and prognosis of AF and AF ablation procedures [13–16]. The complete blood count (CBC) parameters such as the neutrophil-to-lymphocyte ratio (NLR) have been proposed as reliable indicators of the immune activation and inflammation [17,18]. However, the relationship between the inflammatory status after AF ablation and AF recurrence has not been fully elucidated. A previous study showed that the difference in the inflammation status was observed in patients between those with a paroxysmal and those with a permanent condition [19]. However, no study has evaluated the relationship between the NLR and early recurrence of AF/atrial tachycardia (ERAF) and late
recurrences of AF/atrial tachycardia (LRAF) in patients with PAF and PerAF. Therefore, in the present study, we aimed to investigate the relationship between the change in the NLR during the procedure and ERAF/LRAF after PVI, to exclude the difference in the baseline inflammation status in patients with PAF and PerAF. We also aimed to evaluate the clinical impact of the change in the NLR as a prognostic factor for LRAF after the ablation.

2. Methods

2.1. Study population

Consecutive AF patients who underwent a PVI by radiofrequency catheter ablation were enrolled from September 2014 to June 2018 in our hospital. The patients who underwent a PVI by cryoballoon ablation were excluded because of the different mechanism of myocardial injury and inflammation between radiofrequency catheter ablation and cryoballoon ablation [20]. In the present study, PAF was defined as AF persistence for within 1 week and PerAF was defined as AF persistence for more than 1 week. No patients had NSAIDS and/or corticosteroids prior to the ablation procedure due to non-cardiac comorbidities such as collagen disease. No patient with infectious disease prior to the procedure was included in our study. All patients received a detailed informed consent and the study protocol was approved by the hospital’s institutional review board. The procedure was in accordance with the ‘Declaration of Helsinki’ and the ethical standards of the responsible committee on human experimentation. This study was granted an exemption from requiring ethics approval by Osaka Rosai Hospital Ethics Committee because this study was a retrospective observational study and the permission for using the clinical data were obtained from all study patients on admission.

2.2. Echocardiography

All patients underwent transthoracic echocardiography before the ablation. The left atrial diameter was measured at end-systole on the M-mode image obtained from the parasternal long-axis view. Transthoracic echocardiography was performed with a 5 MHz multiplane probe and live images were interpreted by experienced physicians who were blinded to the outcome of the ablation. Transesophageal echocardiography prior to the PVI was performed to exclude any left atrial or left atrial appendage thrombi.

2.3. Ablation

All antiarrhythmic drugs (AADs) were discontinued at least 3 weeks before the ablation. No patient was on amiodarone before the ablation. In our hospital, all AADs were discontinued before the PVI because a previous study demonstrated AADs, in particular Na+ channel blockers, suppress extrasystoles from pulmonary veins [21]. Anticoagulation therapy was started at least 3 weeks before the ablation procedure. A bolus infusion of 25 mg of hydroxyzine pamoate and 15 mg of pentazocine was intravenously administered before the ablation procedure. The ablation procedure was performed under mild sedation obtained with propofol and dexmedetomidine and the patients received adaptive servoventilation. An esophagus temperature monitoring catheter via the nose was placed. A duo-decapolar catheter (BeeAT, Japan Lifeline Co., Tokyo, Japan) was placed in the coronary sinus through the right internal jugular vein. If the patient was in AF, internal atrial cardioversion was performed with biphasic energy of 15–20 J. We performed a transseptal puncture under guidance with the SOUNDSTAR™ three dimensional Ultrasound Catheter (Biosense Webster, Diamond Bar, CA, USA) from the right atrium. After the transseptal puncture, one more long sheath (8.5Fr SL0, Abbott, Chicago, IL, USA) was inserted into the LA. A 100 IU/kg body weight bolus of heparin was administered following the transseptal puncture and heparinized saline was continuously infused to maintain the activated clotting time at 300–350 s. One circular mapping catheter was deployed in the superior and inferior pulmonary veins and the left-sided then right-sided ipsilateral PVs were circumferentially ablated guided by three-dimensional LA mapping (CARTO3, Biosense-Webster, Diamond Bar, CA, USA). The PVI was performed with a 3.5 mm ablation catheter with an externally irrigated tip catheter (ThermoCool® SmartTouch™ Catheter, Biosense-Webster, Diamond Bar, CA, USA). Ablation procedures performed between September 2014 and July 2018 were contact force (CF)-guided, whereas those between August 2018 and August 2019 were ablation index (AI)-guided. In the CF-guided ablation, the lesion creation was guided by CF targets of 5–40 g. Each radiofrequency application was delivered for 25 s with a power of up to 30 W. In the AI-guided ablation, the procedure was guided by AI target values for each lesion as follows: 450 for the anterior/roof segments and 400 for the posterior/inferior segments of the LA. The esophageal temperature was monitored continuously during the ablation procedure to avoid any thermal injury, and the radiofrequency delivery was terminated immediately when the esophageal temperature reached >40 °C. The endpoint of the PVI was the achievement of bidirectional conduction block between the LA and PVs, and any dormant PV conduction revealed by adenosine triphosphate and isoproterenol (up to 20 μg/min) was eliminated. When AF persisted after the PVI or firing sites of atrial premature contraction triggers were detected, a substrate modification was sequentially performed.

2.4. Laboratory measurement

The CBC and high sensitive C-reactive protein (hs-CRP) were measured 1 day before and 36–48 h after the ablation. The NLR before and after the ablation was calculated. The ANLR was calculated as follows: \( \Delta \text{NLR} = [\text{NLR after ablation}] - [\text{NLR before ablation}] \).

2.5. Clinical outcome

AF/AT during the first 3 months after the ablation (blanking period) was considered as an ERAF, and AF/AT of more than 3 months to 12 months after the ablation was considered as an LRAF. The clinical characteristics in the patients with PAF and PerAF were compared and the difference in the relationship between the ANLR and LRAF (from 3 months to 12 months after the PVI) was evaluated. The clinical impact of the ANLR on predicting LRAFs after the PVI was also investigated.

2.6. Follow up

After the ablation, AADs were prescribed only in ERAF patients and they were discontinued by 3 months after the ablation, regardless of any AF recurrence. The patients underwent continuous electrocardiogram (ECG) monitoring for approximately 3 days (until discharge) after the ablation. They came to our cardiology clinic 1 month after the ablation. Subsequent follow-ups were performed every 3 months at the clinic. Patients were encouraged to check their pulse rate and rhythm every day and to visit our hospital if they experienced palpitations or other symptoms. The follow-up visits included a clinical interview, ECG, blood examination, 24 h Holter monitoring or portable ECG (2 week cardiac event recording), and transthoracic echocardiography. Patients with palpitations or other chest symptoms underwent a portable ECG.
Recurrence after the ablation was defined as AF/AT documented on the ECG or AF/AT continuing longer than 30 s on the Holter or portable ECG.

2.7. Statistical analysis

JMP 15 statistical software (SAS Institute Inc., Cary, North Carolina, USA) was used for the statistical analysis. A normality test was performed for continuous variables with a Shapiro-Wilk W test. A normal distribution was not confirmed for all variables, including the age, albumin, body mass index, brain natriuretic peptide (BNP), creatinine, hs-CRP, hemoglobin, left atrial appendage flow (LAAV), left atrium diameter (LAD), left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), left ventricular ejection fraction (LVEF), pre NLR, ΔNLR, and WBC count. Continuous variables were expressed as the median [interquartile range]. Two-group comparisons were analyzed by a nonparametric test for continuous variables. Categorical data were expressed as the number (percentage) and were compared using the chi-square test or Fisher’s exact test for categorical variables. A univariate analysis with a Cox proportional hazards regression model was performed and a p-value < 0.05 was considered significant. Multivariate analyses with a Cox proportional hazards regression model for LRAFs was performed using the factors with a p-value < 0.05 as a result of the univariate analysis with a Cox proportional hazards regression model. The adjusted hazard ratios and 95% confidence intervals were calculated. A receiver operating characteristic curve (ROC) analysis was performed to compare the factors associated with LRAFs. The LRAF free ratio in the patients with PAF was estimated using Kaplan-Meier curves and statistical significance was determined using the log-rank test.

3. Results

3.1. Clinical characteristics in PAF and PerAF patients

Six hundred thirty-three AF patients who underwent a PVI by radiofrequency catheter ablation from September 2014 to June 2018 in our hospital were analyzed. One hundred forty-eight patients were excluded due to cryoballoon ablation and 96 patients were excluded due to a lack of NLR measurements pre- or post-ablation (Fig. 1). All patients were followed for 12 months after the ablation. PAF and PerAF were comprised of 369 and 264 patients, respectively. The clinical characteristics of the patients in the PAF and PerAF groups are shown in Table 1. The ratio of
females and chronic heart failure were significantly higher in the patients with PerAF than PAF. The plasma BNP level and hs-CRP were significantly higher in the patients with PerAF than PAF. In the echocardiographic parameters, the LVDd, LVDs, and LAD were significantly larger, and the LVEF and LAAV were significantly smaller in the patients with PerAF than PAF. The ratio of severe tricuspid regurgitation (TR) was significantly higher in the patients with PerAF than PAF. The incidence of additional ablation, except for cavo tricuspid isthmus block and a superior vena cava isolation, was higher in the patients with PerAF than PAF.

3.2. Relationship between the ΔNLR and clinical outcomes in the PAF and PerAF patients

The NLR before the ablation did not significantly differ between the patients with PAF and PerAF (2.174 [1.583, 2.990], 2.118 [1.576, 2.764], respectively) (Fig. 2A). The ΔNLR did not significantly differ between the patients with PAF and PerAF (0.633 [−0.029, 1.523], 0.722 [0.077, 1.504], respectively) (Fig. 2B). The ratio of ERAFs in the PAF and PerAF patients was 26.8% (99/369) and 39.4% (104/264), respectively. The NLR before the ablation did not significantly differ between the PAF patients with ERAFs and those without ERAFs (1.947 [1.608, 2.753], 2.217 [1.576, 3.047], respectively) (Fig. 2C). The ΔNLR was significantly higher in the PAF patients with LRAFs than No-LRAFs (0.547 [0.130, 1.870], 0.658 [0.097, 1.376], respectively, p = 0.017) (Fig. 2H). The NLR before the ablation did not significantly differ between the PerAF patients with LRAFs and those without LRAFs (2.029 [1.479, 2.746], 2.141 [1.625, 2.746], respectively) (Fig. 2I). In the PerAF patients, the ΔNLR did not significantly differ between the patients with ERAFs and No-ERAFs (0.790 [0.114, 1.823], 0.705 [0.064, 1.443], respectively, p = 0.610) (Fig. 2J).

The ratio of LRAFs in the PAF and PerAF patients was 22.5% (83/369) and 29.9% (79/264), respectively. The NLR before the ablation did not significantly differ between the PAF patients with LRAFs and No-LRAFs (2.091 [1.958, 2.773], 2.113 [1.576, 2.764], respectively) (Fig. 2G). The ΔNLR was significantly higher in the PAF patients with LRAFs than No-LRAFs (0.801 [0.221, 1.872], 0.640 [−0.013, 1.341], respectively, p = 0.010) (Fig. 2F).

Since the ΔNLR was shown to be significantly higher in 'PAF' patients with LRAFs than No-LRAFs as above, the clinical characteristics and predictive value of the ΔNLR in predicting LRAFs in PAF patients were evaluated. The clinical characteristics of the LRAF and No-LRAF groups for PAF are shown in Table 2. The ratio of females was significantly higher in the patients in the LRAF than No-LRAF group. The CHADS2 VASc score and LAD were significantly larger and albumin and hemoglobin lower in the patients in the LRAF than No-LRAF group. The procedural characteristics and complications stratified for the LRAF and No-LRAF groups with...
Clinical characteristics stratified LRAF and No-LRAF in PAF patients.

| Variable                   | LRAF group in PAF (N = 83) | No-LRAF group in PAF (N = 286) | P value |
|----------------------------|-----------------------------|---------------------------------|---------|
| Age, yrs                   | 70 [65, 75]                 | 70 [63, 74]                      | 0.135   |
| Female, n (%)              | 47 (56.6)                   | 99 (34.6)                        | <0.001  |
| BMI, kg/m²                 | 23.6 [21.1, 25.9]           | 23.5 [21.4, 25.7]                | 0.745   |
| Hypertension, n (%)        | 51 (61.4)                   | 173 (60.5)                       | 0.875   |
| Diabetes mellitus, n (%)   | 14 (16.9)                   | 45 (15.7)                        | 0.804   |
| Chronic heart failure, n (%)| 9 (10.8)                    | 27 (9.4)                         | 0.705   |
| Stroke, n (%)              | 10 (12.0)                   | 20 (7.0)                         | 0.138   |
| CHADS2 VASC                |                             |                                 |         |
| 0, n (%)                   | 0 (0)                       | 28 (9.8)                         | 0.002   |
| 1, n (%)                   | 17 (20.5)                   | 50 (17.5)                        |         |
| 2, n (%)                   | 12 (14.5)                   | 69 (24.1)                        |         |
| >3, n (%)                  | 54 (65.7)                   | 139 (48.6)                       |         |
| Albumin                    | 4.0 [3.8, 4.3]              | 4.1 [4.0, 4.4]                   | 0.001   |
| Creatinine                 | 0.78 [0.60, 1.04]           | 0.80 [0.67, 0.93]                | 0.659   |
| CRP, mg/dl                 | 10.05 [0.05, 0.21]          | 0.09 [0.05, 0.18]                | 0.672   |
| WBC, /μl                   | 6200 [5300, 7200]           | 5850 [4900, 6900]                | 0.169   |
| Hemoglobin, g/dl           | 13.1 [11.3, 13.7]           | 13.7 [12.5, 14.5]                | <0.001  |
| BNP, pg/ml                 | 92.2 [56.4, 156.7]          | 57.0 [27.7, 140.1]               | 0.127   |
| NLR (pre-ablation)         | 1.947 [1.608, 2.753]        | 2.217 [1.592, 3.047]             | 0.846   |
| ANLR                       | 0.547 [0.130, 1.870]        | 0.658 [0.097, 1.376]             | 0.017   |
| Echocardiographic data     |                             |                                 |         |
| LVd, mm                    | 48 [44, 50]                 | 48 [45, 51]                      | 0.511   |
| LVds, mm                   | 28 [26, 31]                 | 29 [26, 32]                      | 0.786   |
| LAD, mm                    | 44 [40, 48]                 | 42 [39, 47]                      | 0.049   |
| LVEF, %                    | 71 [63, 75]                 | 69 [65, 73]                      | 0.933   |
| Severe MR                  | 2 (2.4)                     | 5 (1.7)                          | 0.697   |
| Severe TR                  | 3 (3.6)                     | 5 (1.7)                          | 0.304   |
| LAAV, m/s                  | 48 [35, 61]                 | 50 [36, 67]                      | 0.135   |
| Oral medications           |                             |                                 |         |
| Anticoagulant              |                             |                                 |         |
| DOAC, n (%)                | 69 (83.1)                   | 254 (88.8)                       | 0.168   |
| Warfarin, n (%)            | 14 (16.9)                   | 32 (11.2)                        | 0.168   |
| AAD, n (%)                 | 13 (15.7)                   | 71 (24.8)                        | 0.080   |
| β-blocker, n (%)           | 30 (36.4)                   | 115 (40.2)                       | 0.606   |
| ACE/IARB, n (%)            | 27 (32.5)                   | 95 (33.2)                        | 0.907   |
| Digitalis, n (%)           | 0 (0)                       | 7 (2.4)                          | 0.150   |
| Statin, n (%)              | 27 (32.5)                   | 77 (26.9)                        | 0.318   |

AAD, anti-arrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CRP, C reactive protein; DOAC, direct oral anticoagulant; LAAV, left atrial appendage flow; LAD, left atrium diameter; LRAF, late recurrence of atrial fibrillation; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; SVC-I, superior vena cava isolation.

The procedure time (from femoral puncture to venous sheath withdrawal) was significantly longer in the patients in the LRAF than No-LRAF group (203 min vs. 176 min, p = 0.002). There were no significant differences in the total number of energy applications, total ablation time for radiofrequency energy, incidence of additional ablation, and complications between the two groups. A univariate Cox proportional hazards analysis for LRAFs showed that a female sex, albumin, the NLR, neutrophil-to-lymphocyte ratio; TR, tricuspid regurgitation; WBC, white blood cell.

The present study highlighted the following results. (1) The ANLR was significantly higher in the PAF and PerAF patients with LRAFs than in those with No-ERAFs. (2) The ANLR was significantly higher in the PAF patients with LRAFs than No-LRAFs, while the ANLR did not significantly differ between the PerAF patients with LRAFs and those with No-LRAFs. (3) The ANLR was significantly and independently associated with LRAFs after the PVI in PAF patients.

### 4.2. Atrial fibrillation and inflammation

Atrial remodeling, which is an important cause of ectopic firing and microreentrant circuits by promoting heterogeneous conduction, is associated with the involvement of inflammatory signaling, particularly in atrial cardiomyocytes [12]. Inflammatory cytokines are well-recognized biomarkers that can predict the prevalence and prognosis of AF and AF ablation procedures [13]. TNF-α, nuclear factor κB, and NLRP3 inflammasome are the best-characterized innate inflammatory signaling pathways [1,12]. Radiofrequency catheter ablation of atrial arrhythmias is known to cause an increase in various markers of inflammation and myocardial injury [22]. Infiltration of inflammatory cytokines (IL-1, IL-8, TNF-α) into myocardial injury sites induces hematopoietic factors [23,24]. These factors stimulate hematopoiesis of neutrophils in bone marrow and a rapid supply of neutrophils from the bone marrow pool. Although segmented cells are the main neutrophils in peripheral blood, an inflammatory status, the number of stab cells and metamyelocytes increases. Neutrophils suggest nonspecific inflammation and the decrease in the number of lymphocytes reflects the inflammation [25]. Low lymphocyte counts have been reported to be related to inflammation [26]. The NLR, therefore, more effectively reveal inflammation more...
than the neutrophil count [27]. In the present study, we showed that the DNLRLR was significantly higher in PAF and PerAF patients with ERAFs than in those with No-ERAFs, and the DNLRLR was significantly and independently associated with LRAFs after the PVI in PAF patients. Further, the DNLRLR was shown to be useful in predicting LRAFs in PAF patients.

4.3. Difference in the inflammatory status during ablation between PAF and PerAF

The relationship between the inflammation status and AF has not been well elucidated, according to the different categories of AF. A previous study showed that a difference in the CRP level between patients with a paroxysmal and permanent condition was observed [19]. Liuba I et al. demonstrated that patients with PerAF had higher plasma levels of IL-8 as compared to the controls and patients with PAF [28]. They suggested a link between a low-grade inflammatory reaction and long-lasting AF and a possible source of its inflammation was observed in the systemic circulation since there were elevated IL-8 levels in the peripheral blood, right atrium, and coronary sinus but not in the pulmonary veins. Several studies have identified the importance of inflammation in the development and progression of HF, and inflammation and HF are strongly interconnected and mutually reinforce each other [29,30]. In the present study, the baseline NLR did not significantly differ between the patients with PAF and PerAF, but the hs-CRP level in the patients with PerAF was significantly higher than that in those with PAF (0.28 mg/dl vs 0.19 mg/dl, p = 0.033), and the plasma BNP level and echocardiographic parameters (LVDd, LVDs, LAD, LVEF, severe TR and LAAV) were worse in the patients with PerAF than that in those with PAF. The PerAF patients might have had advanced atrial remodeling and a higher inflammatory status than the PAF patients in our registry.

The DNLRLR was significantly higher in the PAF and PerAF patients with ERAFs than those with No-ERAFs (Fig. 2C and 2D), while the DNLRLR was significantly higher in only the PAF patients with LRAFs than in those with No-LRAFs (Fig. 2E and 2F). The mechanism of ERAFs remains to be fully elucidated. Several group-

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**Table 4**

Multivariate Cox proportional hazard analysis for LRAF in PAF patients.

|                | Univariate |     |     |     | Multivariate |     |     |     |
|----------------|------------|-----|-----|-----|--------------|-----|-----|-----|
| Age            | 1.02       | 0.99–1.04 | 0.159 |
| Female         | 2.18       | 1.41–3.38 | <0.001 |
| Hypertension   | 1.04       | 0.67–1.63 | 0.866 |
| Diabetes mellitus | 1.12   | 0.60–1.92 | 0.706 |
| Chronic heart failure | 1.12 | 0.52–2.11 | 0.753 |
| Stroke         | 1.75       | 0.85–3.23 | 0.007 |
| Albumin        | 0.48       | 0.31–0.77 | 0.001 |
| Creatinine     | 1.03       | 0.90–1.12 | 0.594 |
| Hemoglobin     | 0.79       | 0.69–0.90 | <0.001 |
| ALNLRLR (DNLRLR) | 1.15     | 1.03–1.28 | 0.009 |
| BNP            | 1.00       | 0.99–1.00 | 0.168 |
| LVId           | 0.99       | 0.94–1.03 | 0.534 |
| LAD            | 1.04       | 0.99–1.07 | 0.058 |
| LVEF           | 1.00       | 0.98–1.03 | 0.980 |
| Procedure time | 1.00       | 1.00–1.01 | 0.001 |

BNP, brain natriuretic peptide; LAD, left atrium diameter; LRAF, late recurrence of atrial fibrillation/atrial tachycardia after pulmonary vein isolation; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NLR, neutrophil-lymphocyte ratio; PAF, paroxysmal atrial fibrillation.

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Fig. 3. ROC analysis of the DNLRLR in predicting LRAFs after the PVI in PAF patients. AUC, area under the curve; LRAF, late recurrence of atrial fibrillation/atrial tachycardia after pulmonary vein isolation; PVI, pulmonary vein isolation; ROC, receiver operating characteristics.

Fig. 4. Kaplan-Meier analysis of the LRAFs after the PVI between the DNLRLR ≥ 1.578 and DNLRLR < 1.578 groups with PAF. LRAF, late recurrence of atrial fibrillation/atrial tachycardia; NLR, neutrophil-to-lymphocyte ratio; PAF, paroxysmal atrial fibrillation; PVI, pulmonary vein isolation.
s have investigated the role of inflammation during the acute phase post-AF ablation, and the results strongly support inflammation playing a prominent role in the etiology of atrial arrhythmia recurrences within a few days post-AF ablation only in ‘PAF’ patients [31,32]. The effect of ERAFs on LRAFs is incompletely understood in PerAF patients. In PAF patients, PV reconnections are one of the most important mechanisms of LRAFs. PV reconnections are frequently the result of catheter instability and tissue edema, probably caused by a greater number of energy applications [33]. In our data, the PAF patients with a high ΔNLR (more than median value) had a greater number of applications and total application time than those with a low ΔNLR (less than the median value) (2412 sec vs. 2109 sec, p = 0.005, 97 times vs. 83 times, p < 0.001, respectively), however, the frequency of additional ablation did not significantly differ, and a high ΔNLR was independently and significantly associated with LRAFs (Table 3). On the other hand, in the PerAF patients, progressive atrial remodeling including ectopic firing and substrate abnormalities contributed to the occurrence and/or maintenance of AF after the PVI, in addition to PV reconnections [12]. Inflammation induced catheter ablation might be only a part of the cause of LRAFs in PerAF patients. We speculated that several PerAF patients did not develop LRAFs despite a high ΔNLR due to the above mentioned mechanism including non-PV AF triggers and an abnormal substrate.

4.4. Relationship between the ΔNLR and LRAF

Previous studies demonstrated the association between the NLR and clinical outcomes after the PVI. Im et al. showed the relationship between ERAFs and the postablation NLR [34]. Guo et al. showed the relationship between the postablation NLR and LRAFs [35]. A large variation was confirmed in the NLR before ablation because non-PAF patients, presenting with a high plasma BNP level, were included in the above studies and they were considered to have heart failure and persistent inflammation. We evaluated the ΔNLR to assess the effect of inflammation associated with the ablation procedure. Canpolat et al. showed the role of a preablation inflammatory environment evaluated by the NLR in the development of AF recurrence after ablation therapy in cryoballoon ablation [36]. The novelty of the present study was that it demonstrated the difference in the inflammatory status during the catheter ablation between patients with PAF and PerAF, and the ΔNLR was an independent and significant associated factor with LRAFs in only the PAF patients that underwent a PVI with radiofrequency catheter ablation. In our study we investigated the relationship between inflammation and LRAFs stratified according to PAF and PerAF patients. There were more cases than the previous reports and pre-existing inflammation could be excluded, and the inflammation caused by the ablation procedure could be purely evaluated.

4.5. Clinical implication

In the present study, we showed the difference in catheter ablation induced inflammation between PAF and PerAF patients. Our results suggested that anti-inflammation could potentially be a therapeutic target for preventing LRAFs in PAF patients after the PVI. It is clearly evident that the greatest benefit from anti-inflammatory interventions such as steroids, colchicine, statins, aldosterone antagonists, and n-3 fatty acids, is observed in settings associated with a considerable inflammatory status due to tissue damage during catheter ablation [37–42]. Additionally, it might also be useful to use anti-inflammatory drugs in PAF patients with a high ΔNLR considering the comorbidities such as dyslipidemia and heart failure.

4.6. Study limitations

This study had some limitations. First, we did not measure the other inflammation markers such as the IL–1, IL–6, and IL–8. Second, the detail pathophysiology in patients with PAF and PerAF was not investigated. Third, only one measurement of the inflammation markers after the PVI was performed in this study. The different mechanisms of inflammation between PAF and PerAF might result in a different time course of the rise in the ΔNLR. Our data showed that the inflammation marker, ΔNLR, was significantly associated with arrhythmia recurrence in PAF patients after ablation. Infiltration of innate immune cells in the atrial myocardium has been observed in patients with AF, including leukocytes, TNF-α, nuclear factor kB, and NLRP3 [12]. These pathways play a pivotal role in the pathogenesis of AF, but the effect of ablation-induced inflammation remains unclear. Such translational research may facilitate the development of cardiac-specific, possibly even atrial-specific targets of key molecular pathways in AF. Fourth, in the present study, the AUC in the ROC analysis for predicting a recurrence with a cut-off of 1.578 for the ΔNLR was not a high value. This data did not strongly suggest that the ΔNLR was a predictor of AF recurrence as an inflammation marker, but we believe our present results may be hypothesis generating and deserve further investigation.

5. Conclusions

The ΔNLR was significantly higher in the PAF and PerAF patients with ERAFs than no-ERAFs. The ΔNLR was significantly higher in the PAF patients with LRAFs than no-LRAFs, while the ΔNLR did not significantly differ between the PerAF patients with LRAFs and no-LRAFs. The ΔNLR was independently and significantly associated with LRAFs after the PVI.

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CRediT authorship contribution statement

Masamichi Yano: Conceptualization, Methodology, Investigation, Writing - original draft. Yasuyuki Egami: Supervision. Kohei Ukita: Investigation. Akito Kawamura: Investigation. Hitoshi Nakamura: Investigation. Yutaka Matsushita: Visualization. Koji Yasumoto: Methodology. Masaki Tsuda: Visualization. Naotaka Okamoto: Investigation. Akihiro Tanaka: Investigation. Yasuharu Matsunaga-Lee: Conceptualization. Ryu Shutta: Methodology. Masami Nishino: Supervision. Jun Tanouchi: Supervision.

Declaration of Competing Interest

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References

[1] J. Andrade, P. Khairy, D. Dobrev, S. Nattel, The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms, Circ. Res. 114 (2014) 1453–1468.
[2] M. Haissaguerre, D.C. Shah, P. Jais, Mélecce Hocini, T. Yamane, I. Deisenhofer, M. Chauvin, Stéphane Garrigue, J. Clémenty, Electrophysiological breakthroughs
[40] T. Liu, L. Li, P. Korantzopoulos, E. Liu, G. Li, Statin use and development of atrial fibrillation: a systematic review and meta-analysis of randomized clinical trials and observational studies, Int. J. Cardiol. 126 (2008) 160–170.

[41] P. Korantzopoulos, J.A. Goudevenos, Aldosterone signaling in atrial fibrillation, J. Am. Coll. Cardiol. 55 (8) (2010) 771–773.

[42] G. Christou, K. Christou, P. Korantzopoulos, E. Rizos, D. Nikas, J. Goudevenos, The current role of omega-3 fatty acids in the management of atrial fibrillation, IJMS 16 (9) (2015) 22870–22887, https://doi.org/10.3390/ijms160922870.