IJC Heart & Vasculature 47 (2023) 101228

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Association between the atrial tachyarrhythmia recurrence period and long-term major adverse clinical events following catheter ablation for atrial fibrillation

Hironori Ishiguchi [a,*], Yasuhiro Yoshiga [a], Akihiko Shimizu [b], Masakazu Fukuda [a], Masahiro Hisaoka [a], Shintaro Hashimoto [a], Takuya Omuro [c], Takayuki Okamura [a], Shigeki Kobayashi [d], Masafumi Yano [a]

[a] Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan
[b] Department of Cardiology, Ube-Kohsan Central Hospital, Ube, Japan
[c] Faculty of Health Sciences, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube, Japan
[d] Department of Therapeutic Science for Heart Failure in the Elderly, Yamaguchi University School of Medicine, Ube, Japan

ARTICLE INFO

Keywords:
Atrial fibrillation
Catheter ablation
Left ventricular ejection fraction
Heart failure, preserved ejection fraction

ABSTRACT

Background: We previously demonstrated the clinical events in patients who underwent catheter ablation (CA) for atrial fibrillation (AF). Data on the association between the period of atrial tachyarrhythmia (ATA) recurrence after CA and long-term major adverse clinical events (MACE) remain unclear. In this study, we evaluated this issue in patients with systolic impairment (left ventricular ejection fraction < 50%) and heart failure with preserved ejection fraction (HFpEF).

Methods: We retrospectively collected data from 81 patients with systolic impairment and 83 patients with HFpEF who underwent CA for AF at our institution (median follow-up: 4.9 [3.6, 6.6] years). In each group, we compared the cumulative incidence of long-term MACE (since 1 year after CA) between patients with and without ATA recurrence at three follow-up periods (3, 6 months, and 1 year after index CA). We evaluated the period of recurrence, which was the most beneficial predictor of MACE among the periods.

Results: In the systolic impairment group, the cumulative long-term MACE incidence was significantly higher in patients with ATA recurrence than in those without it within 6 months and 1 year (P = 0.04 and P = 0.01, respectively). Recurrence within 1 year showed the highest feasibility for predicting long-term MACE (area under the curve with 95% confidence interval [CI]:0.73 [0.61–0.84]). However, there was no difference in the incidence of MACE between patients with and without recurrence in a group with HFpEF in each period.

Conclusion: ATA recurrence within 1 year could predict long-term MACE in patients with systolic impairment, but not in patients with HFpEF.

1. Introduction

Catheter ablation (CA) is an established therapeutic option for atrial fibrillation (AF) [1]. Recently, several randomized controlled trials have revealed the efficacy of CA in suppressing AF burden or progression compared to medical therapy [2–4]. In addition, CA can provide prognostic benefits for patients with heart failure with reduced left ventricular ejection fraction (HFrEF) [5–7]. So far, we have evaluated the long-term prognostic events after the procedure in patients who underwent CA for AF [8,9]. We demonstrated that patients with systolic impairment (left ventricular ejection fraction [LVEF] < 50%) developed a higher incidence of major adverse clinical events (MACE) when they experienced atrial tachyarrhythmia (ATA) recurrence [8]. Although our data suggest that ATA recurrence could be a critical factor for MACE following CA for AF in patients with systolic impairment, data regarding when ATA recurrence is the most beneficial to predict the development of long-term MACE is lacking. In addition, we also reported that patients with heart failure with preserved ejection fraction (HFpEF) had a

* Corresponding author at: Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan.
E-mail address: nilebros@gmail.com (H. Ishiguchi).

https://doi.org/10.1016/j.ijcha.2023.101228
Received 27 March 2023; Received in revised form 29 April 2023; Accepted 19 May 2023

comparable incidence of MACE to patients with systolic heart failure (HF), although the proportion of non-HF-related events was significantly higher [9]. It is also imperative to ascertain whether the period of ATA recurrence, which is beneficial for predicting MACE in patients with systolic impairment, would be equally applicable to patients with HFpEF. To answer this question, we evaluated the follow-up period of recurrence, which was the most beneficial for predicting long-term MACE. We compared the long-term MACE incidence between patients with and without ATA recurrence at three follow-up periods (3, 6 months, and 1 year after CA) in a population with systolic impairment and HFpEF. We also evaluated whether the optimal follow-up point for recurrence in patients with systolic impairment remained beneficial after multivariate adjustment.

2. Methods

2.1. Study design

The present study was designed as a single-center historical cohort study. The study was approved by the institutional ethical committee. The requirement for informed consent was waived owing to the opt-out system. The tenets of the Declaration of Helsinki and ethical standards of the responsible committee on human experimentation were followed.

We retrospectively collected data of patients who had systolic impairment (defined as LVEF $<$ 50%) or a diagnosis of HFpEF from consecutive patients who underwent CA for AF between January 2009 and December 2020. Patients in whom the CA procedure was halted due to procedural complications or those who dropped out of follow-up within 1 year were excluded. The diagnosis of HFpEF was previously described [9] in patients who met both of the following criteria: (I) an LVEF of $\geq$ 50% and (II) symptoms consistent with HF, as evidenced by elevated natriuretic peptides or a history of hospitalization for HF, according to current guidelines [10]. Our study design consisted of two cohorts: (I) a group with systolic impairment and (II) a group with HFpEF. In each group, we compared the cumulative incidence of long-term MACE between patients with and without ATA recurrence at three follow-up periods (3 months, 6 months, and 1 year after CA).

2.2. Study endpoints

Our primary endpoint was to explore the period of recurrence, which was the most beneficial predictor of long-term MACE in patients with systolic impairment and HFpEF. We compared the cumulative incidence of long-term MACE (>1 year after the initial procedure) between patients who experienced ATA recurrence at three different follow-up periods (3, 6 months, and 1 year after the index procedure) and those who did not. As a secondary endpoint, we evaluated the feasibility of the most beneficial period of recurrence in patients with systolic impairment using multivariate analysis.

2.3. Definition of clinical events

As described in our previous papers [8,9], MACE were associated with all-cause death (ACD), heart failure hospitalization (HFH), and cardiovascular hospitalization (CVH). In brief, unplanned hospitalization for the treatment of decompensated HF was defined as HFH, whereas CVH referred to unexpected hospitalization for the treatment of non-iatrogenic cardiovascular diseases other than HF.

2.4. CA protocol

Our CA protocol has been previously described [8,9]. In brief, all patients underwent pulmonary vein isolation using radiofrequency energy (Navistar Thermocool^{TM}; Biosense Webster, Diamond Bar, CA, USA) or second-generation cryoballoon energy (Arctic Front Advance, Medtronic, Inc., Minneapolis, MN, USA). In patients with persistent AF, empirical superior vena cava isolation has also been performed since October 2015. Substrate modifications were not empirically performed. Patients who were clinically diagnosed or induced with atrial flutter or atrial tachycardia during the procedure also underwent ablation to target a specific arrhythmia.

2.5. Patient follow-up

Our follow-up schedule has been previously described in detail [8,9]. Briefly, ambulatory electrocardiogram (ECG) and/or 24-h Holter ECG recordings were obtained at 1, 3, 6, and 12 months after the procedure. ATA recurrence was defined as the detection of $>$ 30 s of ATA after the blanking period. All patients were followed up for at least 5 years after the initial procedure. A repeat procedure for patients who experienced ATA recurrence was scheduled, unless the patient refused. Data regarding clinical events were obtained by inquiring about the primary care physician for each patient in October 2022.

2.6. Patients with recurrence at three different follow-up points

We compared the cumulative incidence of long-term MACE between patients with and without ATA recurrence at three different follow-up

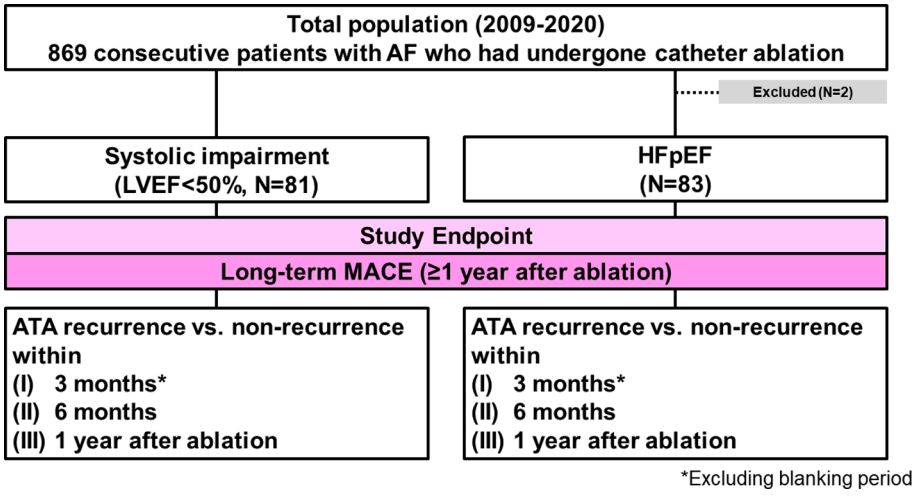

Fig. 1. Flow chart showing the study protocol AF, atrial fibrillation; ATA, atrial tachyarrhythmia; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MACE, major adverse clinical events.

Table 1
Patient demographics.

	Total (n = 164)	Systolic impairment (n = 81)	HFpEF (n = 83)	P-value
Age (years), mean ± SD	67 ± 10	65 ± 11	68 ± 9	0.07
Female sex, n (%)	56 (34)	23 (28)	33 (40)	0.12
Persistent AF, n (%)	103 (63)	51 (63)	52 (63)	0.97
History of AF, (months), median (IQR)	9 (3, 31)	9 (3, 38)	7.5 (3, 24)	0.22
NYHA class, mean ± SD	1.8 ± 0.7	1.8 ± 0.7	1.7 ± 0.6	0.76
BMI (kg/m^2), mean ± SD	24 ± 4	23 ± 4	24 ± 4	0.12
Pacemaker, n (%)	12 (7)	7 (9)	5 (6)	0.52
*ICD/CRT, n (%)	16 (10)	16 (20)	0	<0.0001
*SBP (mmHg), mean ± SD	125 ± 20	120 ± 17	130 ± 22	0.005
HR (/min), mean ± SD	75 ± 19	77 ± 18	73 ± 20	0.06
CTR, mean ± SD	51 ± 5	51 ± 5	52 ± 5	0.54
CHA_2DS_2-VASc, mean ± SD	2.8 ± 1.7	2.7 ± 1.8	3 ± 1.5	0.054
*CAD, n (%)	18 (11)	14 (17)	4 (5)	0.01
DM, n (%)	29 (18)	19 (23)	10 (12)	0.06
*DCM/DHCM, n (%)	9 (5)	9 (11)	0	0.001
HCM, n (%)	8 (5)	3 (4)	5 (6)	0.49
VHD, n (%)	6 (4)	2 (2)	4 (5)	0.42
Ablation-related parameters				
Radiofrequency-PVI, n (%)	141 (86)	68 (84)	73 (88)	0.46
Cryo-PVI, n (%)	23 (14)	13 (16)	10 (12)	0.46
CTI-ablation, n (%)	48 (29)	26 (33)	22 (27)	0.43
Posterior wall isolation, n (%)	0	0	0	>0.99
LA-linear ablation, n (%)	1 (1)	1 (1)	0	0.31
SVC isolation, n (%)	74 (45)	35 (43)	39 (47)	0.63
Echocardiographic parameters				
*LVDd (mm), mean ± SD	51 ± 7	55 ± 7	48 ± 5	<0.0001
*LVEF (%), mean ± SD	50 ± 14	39 ± 8	62 ± 9	<0.0001
LAD (mm), mean ± SD	44 ± 7	44 ± 8	43 ± 6	0.82
LAVI (ml/m^2), mean ± SD	56 ± 18	58 ± 19	55 ± 17	0.27
Therapeutic agents				
ACEI/ARB, n (%)	115 (70)	59 (73)	56 (67)	0.45
Beta-blocker, n (%)	137 (84)	71 (88)	66 (80)	0.16
MRA, n (%)	49 (30)	26 (32)	23 (28)	0.54
Diuretics, n (%)	91 (55)	40 (49)	51 (61)	0.12
*AADs, n (%)	32 (20)	21 (26)	11 (13)	0.04
*Amiodarone, n (%)	20 (12)	19 (24)	1 (1)	<0.0001
Laboratory data				
eGFR (mL/min/1.73 m^2), mean ± SD	56 ± 20	54 ± 18	58 ± 21	0.29
BNP level (pg/mL), median (IQR)	160 (87, 294)	168 (94, 357)	153 (87, 233)	0.38

Numerical data are expressed as mean ± SD or median (interquartile range [IQR]; first quartile, third quartile). Categorical data were expressed as percentages and numbers.
Asterisk (*) indicates statistical significance (P < 0.05).
AADs, anti-arrhythmic drugs; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; CRT, cardiac resynchronisation therapy; CTI, cavotricuspid isthmus; CTR, cardiothoracic ratio; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LA, left atrium; LAD, left atrial diameter; LAVI, left atrial volume index; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart association; PVI, pulmonary vein isolation; SBP, systolic blood pressure; SD, standard deviation; SVC, superior vena cava; VHD, valvular heart disease.

periods (3, 6 months, and 1 year after the initial procedure). Patients with recurrence diagnosed at 3 months follow-up were considered to have recurrence within 3 months, because we excluded recurrence within the blanking period. Regarding the other follow-up points, patients with recurrence diagnosed at 6 months and 1 year were considered to have recurrence within 6 months and 1 year, respectively.

2.7. Statistical analysis

Normally distributed and non-normally distributed variables are expressed as mean ± standard deviation and medians with interquartile ranges (first and third quartiles), respectively. Differences in continuous variables were evaluated using the Mann–Whitney *U* test. Categorical variables are presented as frequencies with proportions (%) and were compared using the chi-square (χ^2) test. The recurrence rate following the procedure was also compared using the χ^2 test. The incidence of each event was expressed as the incidence rate (event number/the total number of person-years × 100) and the cumulative incidence with 95% confidence intervals (CIs) was calculated at the last follow-up. The log-rank test was used to compare the cumulative incidence between patients with and without ATA recurrence. The follow-up period, which was the most beneficial among the three periods, was analyzed by comparing the area under the curve (AUC) with the 95% CI obtained from receiver operating characteristic (ROC) analysis in each group. Comparisons were performed using the Delong test. In the group with systolic impairment, the period with the highest AUC was inputted into the univariate and multivariate analyses to predict long-term MACE. Variables reported to be associated with the prognosis of patients with HF in our and other studies [8–10] were selected for the analysis. The continuous variables used in the analysis were dichotomized according to conventional cut-off points. The findings were presented as hazard ratios and 95% CI. Statistical analysis was conducted using SPSS version 19 (IBM Corp., Armonk, NY), and the results were deemed statistically significant at a P-value of<0.05.

3. Results

3.1. Study population

The flow chart of the study protocol is presented in Fig. 1. Among the consecutive 869 patients with AF in whom CA was performed, 81 and 85 were assigned to the systolic impairment and HFpEF groups, respectively. In the HFpEF group, two patients were excluded from the analysis: one patient interrupted the procedure owing to cardiac tamponade and another patient dropped out owing to death within 1 year after the procedure. Patient demographics are shown in Table 1. As previously reported, patients with systolic impairment had a significantly higher proportion of coronary artery disease, diabetes mellitus, and dilated cardiomyopathy/dilated hypertrophic cardiomyopathy. Ablation procedures were comparable between the groups.

3.2. Ablation results

All patients included in this study successfully underwent ablation. The complication rate was comparable between the groups (0% for systolic impairment and 1.2% [1/83 patients] for HFpEF). At 3 months follow-up, 20% (16/81 patients) of the systolic impairment group and 16% (13/83 patients) of the HFpEF group had ATA recurrence. Until 6 months follow-up, 33% (27/81) of patients with systolic impairment and 24% (20/83) of those with HFpEF experienced ATA recurrence. Until 1 year follow-up, 37% (30/81) of patients with systolic impairment and 31 % (26/83) of those with HFpEF experienced ATA recurrence. The rate of recurrence was comparable between the groups in each period (P = 0.49 in 3 months, 0.19 in 6 months, and 0.44 in 1 year). The rate was also comparable between the groups during the entire follow-up period (51% [41/81] of patients with systolic impairment and

Table 2A
Demographics comparison between recurrence within 1 year and non-recurrence in systolic impairment group.

	Total (n = 81)	Recurrence within 1 year (n = 30)	Non-recurrence (n = 51)	P-value
Age (years), mean ± SD	65 ± 11	65 ± 12	65 ± 10	0.84
Female sex, n (%)	23 (28)	13 (43)	10 (20)	0.23
Persistent AF, n (%)	51 (63)	19 (63)	32 (63)	0.41
History of AF, (months), median (IQR)	9 (3, 38)	7.5 (3, 24)	9 (4, 38)	0.54
NYHA class, mean ± SD	1.8 ± 0.7	1.8 ± 0.8	1.8 ± 0.7	0.84
BMI (kg/m^2), mean ± SD	23 ± 4	23 ± 4	24 ± 4	0.48
*Pacemaker, n (%)	7 (9)	7 (23)	0	0.003
ICD/CRT, n (%)	16 (20)	6 (20)	10(20)	0.96
SBP (mmHg), mean ± SD	120 ± 17	121 ± 19	120 ± 16	0.88
HR (/min), mean ± SD	77 ± 18	78 ± 19	76 ± 17	0.58
CTR, mean ± SD	51 ± 5	51 ± 4	51 ± 5	0.81
CHA_2DS_2-VASc, mean ± SD	2.7 ± 1.8	2.6 ± 1.7	2.7 ± 1.8	0.75
*CAD, n (%)	14 (17)	1 (3)	13 (25)	0.01
DM, n (%)	19 (23)	8 (27)	11 (21)	0.6
DCM/DHCM, n (%)	9 (11)	4 (13)	5 (10)	0.62
HCM, n (%)	3 (4)	2 (7)	1 (2)	0.27
VHD, n (%)	2 (2)	0	2 (4)	0.27
Ablation-related parameters				
Radiofrequency-PVI, n (%)	68 (84)	25 (83)	43 (84)	0.91
Cryo-PVI, n (%)	13 (16)	5 (17)	8 (16)	0.91
CTI-ablation, n (%)	26 (33)	11 (37)	15 (30)	0.5
Posterior wall isolation, n (%)	0	0	0	>0.99
LA-linear ablation, n (%)	1 (1)	0	1 (0.5)	0.44
SVC isolation, n (%)	35 (43)	11 (37)	24 (49)	0.36
Echocardiographic parameters				
LVDd (mm), mean ± SD	55 ± 7	54 ± 6	55 ± 7	0.45
LVEF (%), mean ± SD	39 ± 8	40 ± 7	38 ± 8	0.44
LAD (mm), mean ± SD	44 ± 8	44 ± 7	44 ± 8	0.84
LAVI (ml/m^2), mean ± SD	58 ± 19	61 ± 21	57 ± 18	0.57
Therapeutic agents				
ACEI/ARB, n (%)	59 (73)	21 (70)	38 (75)	0.65
Beta-blocker, n (%)	71 (88)	29 (97)	42 (82)	0.06
MRA, n (%)	26 (32)	10 (33)	16 (31)	0.85
Diuretics, n (%)	40 (49)	16 (53)	24 (47)	0.58
AADs, n (%)	21 (26)	10 (33)	11 (22)	0.24
*Amiodarone, n (%)	19 (24)	8 (27)	11 (22)	0.6
Laboratory data				
eGFR (mL/min/1.73 m^2), mean ± SD	54 ± 18	51 ± 21	55 ± 16	0.35
BNP level (pg/mL), median (IQR)	168 (94, 357)	192 (82, 399)	158 (98, 291)	0.38

Numerical data are expressed as mean ± SD or median (interquartile range [IQR]; first quartile, third quartile). Categorical data were expressed as percentages and numbers.
Asterisk (*) indicates statistical significance (P < 0.05). Abbreviations are as Table 1.

Table 2B
Demographics comparison between recurrence within 1 year and non-recurrence in HFpEF group.

	Total (n = 83)	Recurrence within 1 year (n = 26)	Non-recurrence (n = 57)	P-value
Age (years), mean ± SD	68 ± 9	67 ± 11	69 ± 8	0.67
Female sex, n (%)	33 (40)	11 (42)	22 (39)	0.75
Persistent AF, n (%)	52 (63)	20 (77)	32 (56)	0.07
History of AF, (months), median (IQR)	7.5 (3, 24)	9 (3, 32)	7 (3, 18)	0.44
NYHA class, mean ± SD	1.7 ± 0.6	1.8 ± 0.6	1.7 ± 0.6	0.32
BMI (kg/m^2), mean ± SD	24 ± 4	24 ± 3	24 ± 4	0.88
*Pacemaker, n (%)	5 (6)	5 (19)	0	0.0006
ICD/CRT, n (%)	0	0	0	>0.99
SBP (mmHg), mean ± SD	130 ± 22	130 ± 16	129 ± 24	0.58
HR (/min), mean ± SD	73 ± 20	75 ± 21	71 ± 20	0.39
CTR, mean ± SD	52 ± 5	51 ± 6	52 ± 5	0.62
CHA_2DS_2-VASc, mean ± SD	3 ± 1.5	2.9 ± 1.2	3.1 ± 1.6	0.84
*CAD, n (%)	4 (5)	3 (11)	1 (2)	0.054
DM, n (%)	10 (12)	3 (11)	7 (12)	0.92
DCM/DHCM, n (%)	0	0	0	>0.99
HCM, n (%)	5 (6)	1 (4)	4 (7)	0.57
VHD, n (%)	4 (5)	0	4 (7)	0.17
Ablation-related parameters				
Radiofrequency-PVI, n (%)	73 (88)	25 (96)	48 (84)	0.12
Cryo-PVI, n (%)	10 (12)	1 (4)	9 (16)	0.12
CTI-ablation, n (%)	22 (27)	10 (38)	12 (21)	0.1
Posterior wall isolation, n (%)	0	0	0	>0.99
LA-linear ablation, n (%)	0	0	0	>0.99
SVC isolation, n (%)	39 (47)	13 (50)	26 (45)	0.71
Echocardiographic parameters				
LVDd (mm), mean ± SD	48 ± 5	48 ± 5	48 ± 6	0.44
LVEF (%), mean ± SD	62 ± 9	60 ± 9	62 ± 9	0.2
LAD (mm), mean ± SD	43 ± 6	44 ± 5	43 ± 7	0.28
LAVI (ml/m^2), mean ± SD	55 ± 17	60 ± 28	56 ± 17	0.79
Therapeutic agents				
ACEI/ARB, n (%)	56 (67)	18 (69)	38 (67)	0.82
Beta-blocker, n (%)	66 (80)	22 (85)	44 (77)	0.44
MRA, n (%)	23 (28)	7 (27)	16 (28)	0.91
*Diuretics, n (%)	51 (61)	13 (50)	6 (11)	0.0007
AADs, n (%)	11 (13)	5 (19)	6 (11)	0.27
Amiodarone, n (%)	1 (1)	0	1 (2)	0.49
Laboratory data				
eGFR (mL/min/1.73 m^2), mean ± SD	58 ± 21	60 ± 28	56 ± 17	0.34
BNP level (pg/mL), median (IQR)	153 (87, 233)	127 (96, 207)	159 (82, 242)	0.91

Numerical data are expressed as mean ± SD or median (interquartile range [IQR]; first quartile, third quartile). Categorical data were expressed as percentages and numbers.
Asterisk (*) indicates statistical significance (P < 0.05). Abbreviations are as Table 1.

54% [45/83] of those with HFpEF, P = 0.64). Tables 2A and 2B shows the demographic differences between patients with recurrence within 1 year and non-recurrence in each group (Table 1A: systolic impairment, Table 2B: HFpEF). In the systolic impairment group, the proportion of coronary artery disease was significantly higher in patients with non-recurrence than those with recurrence within 1 year. In the HFpEF group, the proportion of pacemaker-implanted patients and use of diuretics were significantly higher in patients with recurrence within 1 year than those with non-reccurence.

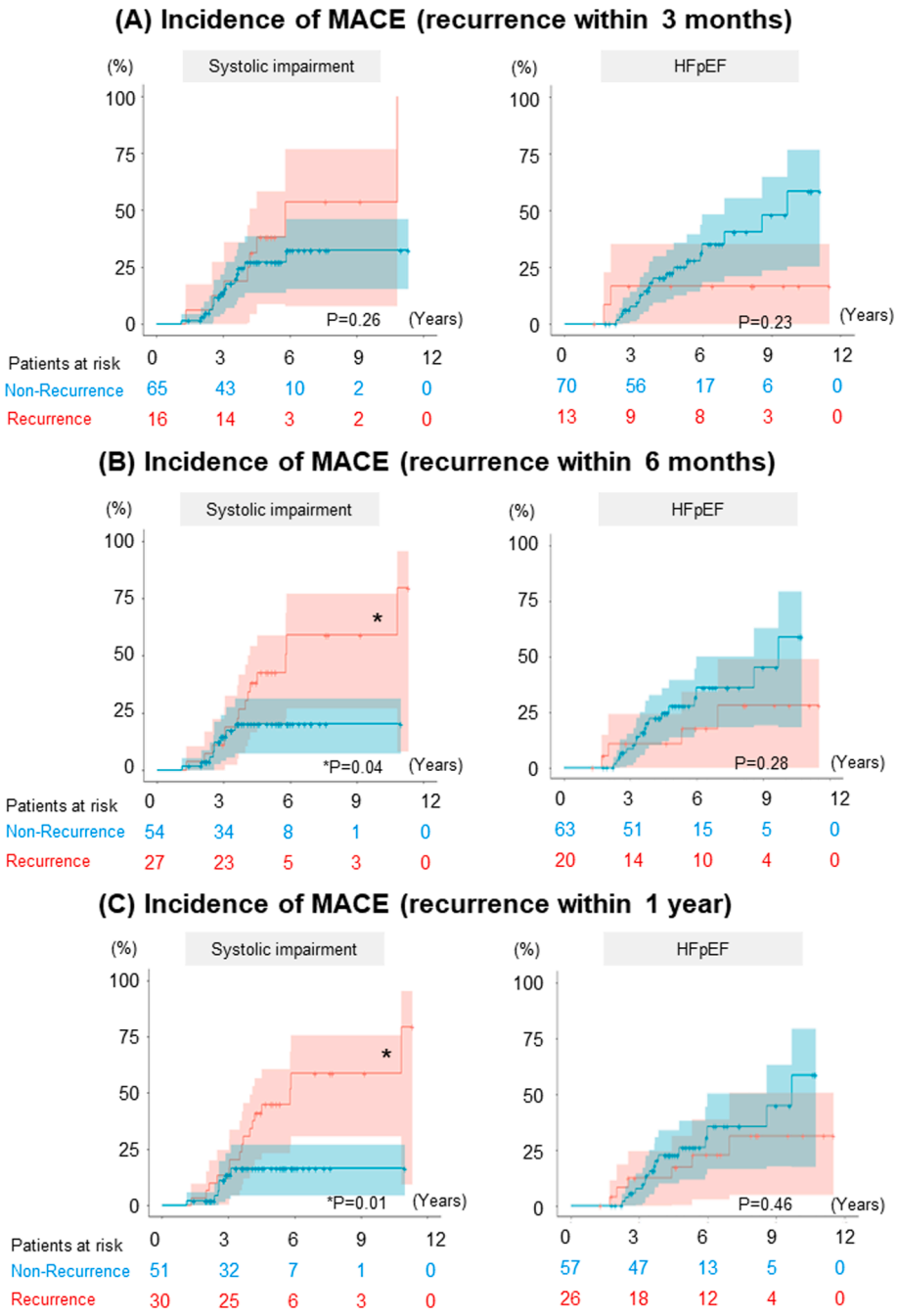

Fig. 2. Cumulative incidence of MACE in each period A. The Kaplan–Meier curve illustrating cumulative incidence with 95% CI in systolic impairment (left) and HFpEF (right) groups. In each group, the incidence was compared between patients with (red) and without (blue) ATA recurrence at 3 months. B. The Kaplan–Meier curve illustrating cumulative incidence with 95% CI in systolic impairment (left) and HFpEF (right) groups. In each group, the incidence was compared between patients with (red) and without (blue) ATA recurrence within 6 months. C. The Kaplan–Meier curve illustrating cumulative incidence with 95% CI in systolic impairment (left) and HFpEF (right) groups. In each group, the incidence was compared between patients with (red) and without (blue) ATA recurrence within 1 year. CI, confidence interval; MACE, major adverse clinical events; HFpEF, heart failure with preserved ejection fraction * $P < 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Cumulative MACE incidence in each period

During the entire follow-up period of a median of 4.9 [3.6, 6.6] years, 23 patients in the systolic impairment group and 22 patients in the HFpEF group developed long-term MACE. The cumulative incidence of MACEs in each group is presented in Fig. 2. The cumulative MACE incidence in each period in the systolic impairment group is shown in Table 3A. Notably, although the figure was comparable between patients with and without ATA recurrence at 3 months, the incidence in patients with recurrence was significantly higher than that in those without recurrence at other periods (10.2 / 100 person-years, 78 [2, 95] % vs. 4.1 / 100 persons-years, 20 [7, 31] %, Pa = 0.04 in 6 months, 10.7 / 100 person-years, 78 [4, 95] % vs. 3.4 / 100 persons-years, 16 [4, 27] %, P = 0.01 in 1 year). The analysis of recurrence during the entire follow-up period showed a trend similar to that of the 1-year cut-off. In contrast, the incidence in the HFpEF group was similar between patients with and without recurrence in each period (Table 3B). Although the incidence of CVH in patients with recurrence was significantly lower than that in those without recurrence within 1 year, the rate became comparable between recurrence and non-recurrence during the entire period.

3.4. Clinical events that comprised MACE

Regarding clinical events that comprised MACE, 40 clinical events in the systolic impairment group and 30 events in the HFpEF group were documented (Supplementary Table 1). Fig. 3 shows the histogram at a semi-annual scale, demonstrating the incidence of events in each group (A: systolic impairment, B: HFpEF). In both groups, the majority of events were HFH (systolic impairment, 83% [33/40 events]; HFpEF,

Table 3A
The incidence of each event in patients with systolic impairment.

	Recurrence		Non-recurrence		P-value
	Incidence rate, events/100 person-years	Cumulative incidence, % (95% CI)	Incidence rate, events/100 person-years	Cumulative incidence, % (95% CI)	
Recurrence at 3 months					
MACE	9.6	49 (1, 74)	5.5	32 (15, 46)	0.26
ACD	2.0	20 (0, 47)	0.9	11 (0, 20)	0.7
HFH	23	33 (9, 57)	3.9	26 (11, 41)	0.27
CVH	0	0	0.7	3 (0, 8)	0.46
Recurrence within 6 months					
*MACE	10.2	78 (2, 95)	4.1	20 (7, 31)	0.04
ACD	2.4	21 (0, 49)	0.8	8 (0, 20)	0.21
*HFH	8.0	74 (35, 100)	2.6	14 (3, 24)	0.034
CVH	0	0	0.8	4 (0, 10)	0.29
Recurrence within 1 year					
*MACE	10.7	78 (4, 95)	3.4	16 (4, 27)	0.01
ACD	2.2	18 (0, 36)	0.9	11 (0, 22)	0.34
*HFH	7.9	73 (31, 100)	2.4	12 (2, 21)	0.02
CVH	0.56	2 (0, 7)	0.45	3 (0, 10)	0.74
Recurrence during whole period					
*MACE	10.7	77 (45, 100)	1.2	6 (0, 15)	0.0006
ACD	2.1	15 (2, 27)	0	0	0.09
*HFH	8.5	72 (33, 100)	0	0	0.0002
CVH	0.4	2 (0, 7)	0.6	3 (0, 9)	0.92

Asterisk (*) indicates statistical significance ($P < 0.05$).
CI, confidence interval; ACD, all-cause death; CVH, cardiovascular hospitalization; HFH, heart failure hospitalization; MACE, major adverse clinical events. P-values express results of log-rank analysis for cumulative incidence.

Table 3B
The incidence of each event in patients with HFpEF.

	Recurrence		Non-recurrence		P-value
	Incidence rate, events/100 person-years	Cumulative incidence, % (95% CI)	Incidence rate, events/100 person-years	Cumulative incidence, % (95% CI)	
Recurrence at 3 months					
MACE	2.5	17 (0, 35)	5.7	58 (24, 76)	0.23
ACD	1.2	8 (0, 24)	1.3	32 (4, 60)	0.71
HFH	1.2	9 (0, 26)	3.3	31 (10, 51)	0.38
CVH	0	0	2.5	18 (4, 31)	0.12
Recurrence within 6 months					
MACE	3.3	28 (0, 49)	5.8	58 (17, 79)	0.28
ACD	2.4	24 (0, 49)	0.9	29 (0, 62)	0.36
HFH	1.6	13 (0, 30)	3.4	32 (9, 55)	0.39
CVH	0	0	2.5	20 (5, 35)	0.06
Recurrence within 1 year					
MACE	4.1	31 (5, 50)	5.7	58 (16, 79)	0.46
ACD	2.6	26 (3, 49)	0.6	26 (0, 61)	0.14
HFH	2.7	20 (2, 37)	3.1	29 (6, 53)	0.93
*CVH	0	0	2.7	22 (6, 39)	0.03
Recurrence during the whole period					
MACE	6.6	58 (34, 82)	2.9	16 (3, 29)	0.15
ACD	1.7	20 (0, 55)	0.6	28 (0, 56)	0.55
HFH	4.2	34 (15, 54)	1.1	7 (0, 16)	0.06
CVH	1.8	57 (0, 100)	1.8	10 (0, 20)	0.65

Asterisk (*) indicates statistical significance ($P < 0.05$).
CI, confidence interval; ACD, all-cause death; CVH, cardiovascular hospitalization; HFH, heart failure hospitalization; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse clinical events. P-values express results of log-rank analysis for cumulative incidence.

57% [17/30 events]). Notably, most HFH events developed within 4 years after the procedure in both the groups. In the systolic impairment group, most of the patients who experienced ACD died from cardiac causes (4/6 patients [67%]); however, all of those in the HFpEF group died from non-cardiac causes. Regarding CVH events, the majority of the events in the HFpEF group were diseases associated with bradycardia, such as sick sinus syndrome and atrioventricular block, although all patients in the systolic impairment group developed stroke.

3.5. Proportion of patients with ATA recurrence who developed MACE

Fig. 4 compares the proportion of patients with ATA recurrence in the systolic impairment and HFpEF groups who developed MACE. Most of the patients who developed MACE experienced recurrence during the entire follow-up period in both groups (systolic impairment, 21/23 [91%]; HFpEF, 17/22 [77%]; $P = 0.19$, Fig. 4A). However, the proportion of patients with HFpEF who experienced recurrence within 1 year was significantly lower than that of patients with systolic impairment (systolic impairment, 16/23 [70%]; HFpEF, 6/22 [27%]; $P = 0.004$, Fig. 4B).

3.6. Analysis for predicting MACE

Table 4 shows the ROC analysis for predicting MACE in each period. In the systolic impairment group, recurrence within 1 year showed the highest predictability for MACE (AUC: 0.73). In contrast, there were few differences among periods in the HFpEF group (AUC: 0.53–0.54 of each period). Table 5A shows the univariate and multivariate analyses for predicting MACE in the systolic impairment group. Among the three follow-up periods, we imputed ATA recurrence within 1 year in the analysis because this period had the highest feasibility from the AUC analysis. ATA recurrence within 1 year was the only factor that showed significance in both univariate and multivariate analyses. Regarding other factors, age $\geq$ 75 years was also significant after multivariate adjustment. We also performed the analysis in the HFpEF group (Table 5B). The result showed that ATA reccurence within 1 year did not manifest as a predictive factor for MACE in the HFpEF group.

4. Discussion

4.1. Main findings

The important findings of this study are as follows: First, although the cumulative long-term MACE incidence in the systolic impairment group was similar between patients with and without ATA recurrence at 3 months, the incidence in patients with recurrence was significantly higher than in those without recurrence at other periods. Second, recurrence within 1 year was the most feasible predictor of long-term MACE. In addition, recurrence within 1 year was an independent predictive factor for long-term MACE based on the multivariate analysis. Third, in the HFpEF group, the incidence of long-term MACE was comparable between patients with and without recurrence in each period.

4.2. Association between the period of recurrence and long-term MACE

To the best of our knowledge, this is the first study to analyze the association between periods of ATA recurrence and long-term MACE in patients who underwent CA for AF. In particular, we highlight that recurrence within 1 year had the highest impact on long-term MACE in patients with systolic impairment, although it had few impacts in patients with HFpEF. We infer that the discrepancy may stem from the variation in the proportion of HFH and ACD among MACE between patients with systolic impairment and HFpEF, rather than from

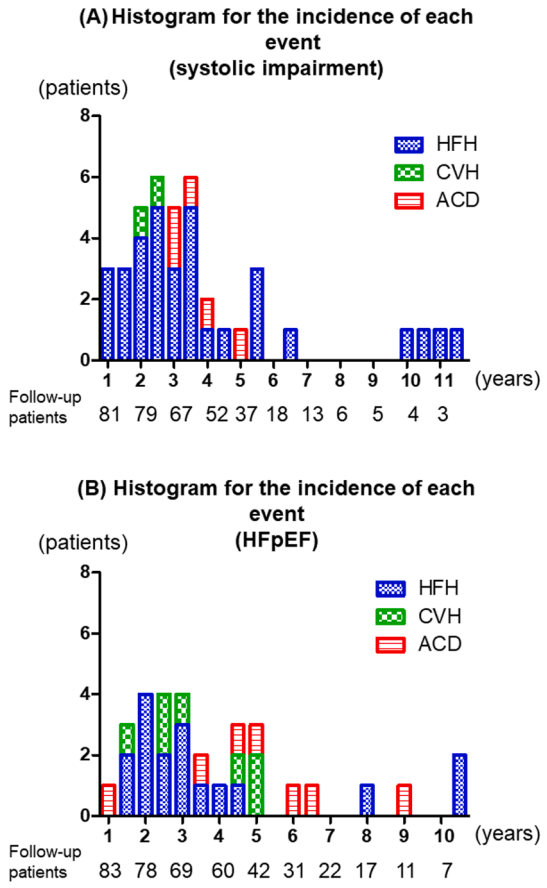

Fig. 3. Histogram showing the incidence of events that comprised MACE
A. Histogram illustrating the number and types of events that comprised MACE at a semi-annual scale in a group with systolic impairment (blue: HFH, green: CVH, red: ACD). B. Histogram illustrating the number and types of events that comprised MACE at a semi-annual scale in a group with HFpEF (blue: HFH, green: CVH, red: ACD). ACD, all-cause death; CVH, cardiovascular hospitalization; HFH, heart failure hospitalization; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse clinical events. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

differences in ablation efficacy. Recent *meta*-analyses suggested that the efficacy, including success and complication rates, was comparable between patients with HFpEF and HFrEF [11,12]. Our results also showed similar success rates between groups in each period. With regard to clinical events, previous studies have reported that patients with HFpEF tended to develop various types of events that reflected multiple comorbidities and underlying inflammatory substrates, apart from

Table 4
Area under the curve for predicting long-term MACE.

	AUC	95% CI	P-value
Systolic impairment			
Recurrence at 3 months	0.39	0.29–0.5	Reference
*Recurrence within 6 months	0.69	0.58–0.81	0.002
*Recurrence within 1 year	0.73	0.61–0.84	0.0005
HFpEF			
Recurrence at 3 months	0.54	0.47–0.62	Reference
Recurrence within 6 months	0.54	0.44–0.64	0.9
Recurrence within 1 year	0.53	0.41–0.64	0.72

Asterisk (*) indicates statistical significance ($P < 0.05$).
AUC, area under the curve; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse clinical events.

Table 5A
Uni- and multivariate analysis to detect predictors for long-term MACE in patients with systolic impairment.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
*ATA recurrence until 1 year	3.1	1.2–7.4	0.01	3.2	1.02–10.5	0.045
HFH within 1 year following the procedure	6.4	2.5–16	<0.0001	1.8	0.63–5.3	0.26
*Age ≥ 75 years	2.1	0.88–5.3	0.09	3.1	1.005–9.6	0.049
LVEF < 35 %	2.7	1.2–6.2	0.02	1.8	0.56–6.1	0.31
LAD ≥ 45 mm	4.5	1.8–11.5	0.001	2.9	0.96–8.7	0.06
eGFR < 45 mL/min/1.73 m^2	5.9	2.5–13.7	<0.0001	1.7	0.51–5.7	0.38

Asterisks (*) indicate statistical significance after adjustment in multivariate analysis ($P < 0.05$).
ATA, atrial tachyarrhythmia; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; HR, hazard ratio; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; MACE, major adverse clinical events.

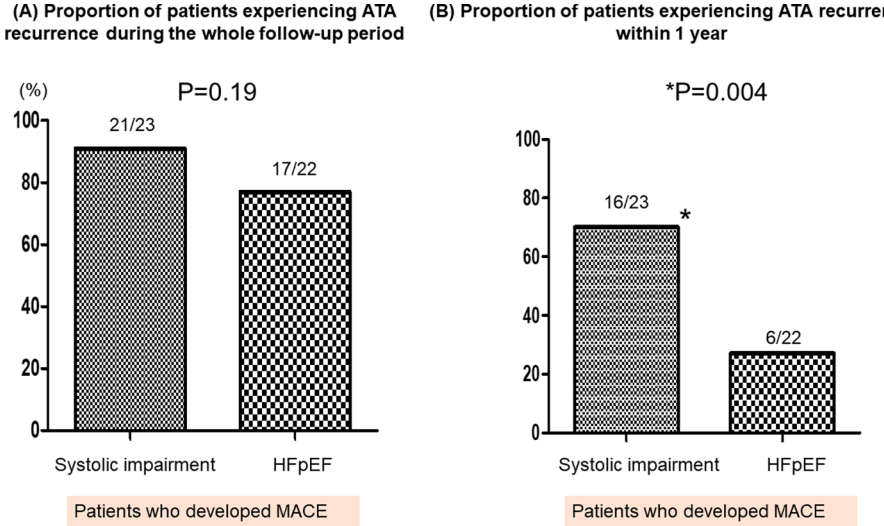

Fig. 4. Bar charts comparing the proportion of patients experiencing ATA recurrence who developed MACE
A. The bar chart compares the proportion of patients experiencing ATA recurrence who developed MACE in systolic impairment (left) and HFpEF (right) groups during the whole follow-up period. B. The bar chart compares the proportion of patients experiencing ATA recurrence who developed MACE in systolic impairment (left) and HFpEF (right) groups within 1 year. ATA, atrial tachy-arrhythmia; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse clinical events * $P < 0.005$.

Table 5B
Uni- and multivariate analysis to detect predictors for long-term MACE in patients with HFpEF.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
ATA recurrence until 1 year	0.7	0.27–1.8	0.45	0.6	0.18–1.4	0.2
HFH within 1 year following the procedure	1.5	0.2–11.1	0.7	0.52	0.06–4.7	0.56
*Age $\geq$ 75 years	3.3	1.4–8.2	0.008	2.8	1.1–7.1	0.03
LAD $\geq$ 45 mm	1.8	0.76–4.1	0.18	1.9	0.8–4.9	0.13
eGFR $<$ 45 mL/min/1.73 m^2	2.9	1.2–7.1	0.02	2.5	0.99–6.3	0.051

Asterisks (*) indicate statistical significance after adjustment in multivariate analysis ($P < 0.05$). Abbreviations are as table 5A.

patients with HFrEF who developed mainly HF-related events [9,13,14]. Similarly, in our study population, patients with systolic impairment predominantly developed HFH. Hence, our results of the association between MACE and ATA recurrence within 1 year would reflect the association between HFH and ATA recurrence. It is well known that ATA directly worsens hemodynamic status because the loss of atrial contractility, fast heart rate, and irregularity (in the case of AF) impair both left ventricular filling and left ventricular systolic function [15]. We speculate that such a deteriorating effect owing to ATA recurrence could be directly involved in the development of HFH. In contrast, in patients with HFpEF, the proportion of non-HFH events, such as non-cardiac death and cardiovascular events, which did not directly connect with ATA development, accounted for nearly half of the total events. In addition, a small proportion of the patients experienced recurrence within 1 year after CA, although most of the patients who developed long-term MACE experienced ATA recurrence during the entire follow-up period. This discrepancy suggests that such patients may require a long time to develop ATA recurrence. In particular, patients with HFpEF tend to develop a higher incidence of non-cardiac death. ATA recurrence in such patients could play a role as a result of worsening of the systemic condition, which is likely to predispose to atrial arrhythmia [16], rather than as a trigger for clinical events. Hence, we speculate that it would be difficult to predict long-term MACE by ATA recurrence during the early period after the procedure when non-HF-related events are moderately included.

4.3. Clinical implication

Our study highlights the association between ATA recurrence within 1 year and long-term MACE in patients with systolic impairment. In particular, multivariate analysis indicated that ATA recurrence within 1 year was an independent predictor of MACE. Our results suggest that patients with LVEF $<$ 50% could have a high risk of developing long-term MACE when they experienced ATA recurrence within 1 year after CA. Identification of ATA recurrence within 1 year may be useful to stratify the risk of MACE, especially HFH, during long-term follow-up when clinicians follow patients who underwent CA for AF. In contrast, our data also imply that the association between ATA recurrence within 1 year and long-term MACE could not be extrapolated for patients with HFpEF, probably owing to the difference in the components of MACE. Future studies to identify other risk markers are required.

4.4. Limitations

Our study has several limitations. First, we could have missed unmeasured variables associated with HF prognosis because we retrospectively collected the data. The scope of our study is constrained due to its single-center nature, which may render our results susceptible to selection bias. Moreover, our population with a limited sample size precluded a comprehensive analysis of the impact of ATA recurrence within one year, accounting for additional cardiovascular risk factors. Future investigations with more expansive cohorts are warranted to substantiate our findings. Second, our HFpEF population was mainly composed of older patients who tend to have multiple comorbidities and develop noncardiac events [17]. It remains unclear whether our results could be extrapolated to other populations composed of other HFpEF phenotypes, such as patients with obesity phenotype. Third, most parts of the follow-up period in the present study were in an era when evidence of a new pharmacological strategy for HF had not been established. It is uncertain whether our results can be applied to the current clinical settings when new therapeutic agents, such as sacubitril/valsartan and sodium-glucose cotransporter-2 inhibitors, which showed beneficial evidence for patients with HF across the spectrum of LVEF, are widely available [18,19]. Fourth, our patients with HFpEF had relatively high LVEF (mean, 62 $\pm$ 9%). A previous analysis showed that HFpEF with low LVEF (50–60%) could have demographic characteristics similar to systolic HF [20,21]. ATA recurrence within 1 year might have an impact on predicting long-term MACE for such patients because they would develop more HF-related events than patients with HFpEF in the present population.

5. Conclusions

Our study showed that ATA recurrence within 1 year could predict long-term MACE, especially HFH, for patients with systolic impairment, although it was not extrapolated for patients with HFpEF. These data would be useful to stratify the risk when clinicians follow patients who have undergone CA for AF for a long period.

6. The statement of authorship

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

7. Fu**nding

This research did not receive specific grants from public, commercial, or not-for-profit funding agencies.

8. IRB information

This study followed the Declaration of Helsinki and ethical standards of the responsible committee on human experimentation. The Institutional Review Boards of Yamaguchi University Hospital (H2019-044-2) approved this study.

CRediT authorship contribution statement

Hironori Ishiguchi: Conceptualization, Methodology, Software, Investigation, Writing – original draft, Visualization. **Yasuhiro Yoshiga:** Conceptualization, Resources, Data curation. **Akihiko Shimizu:** Writing – review & editing, Supervision. **Masakazu Fukuda:** Formal analysis, Resources. **Masahiro Hisaoka:** Validation, Resources. **Shintaro Hashimoto:** Validation. **Takuya Omuro:** Validation. **Takayuki Okamura:** Writing – review & editing. **Shigeki Kobayashi:** Writing – review & editing. **Masafumi Yano:** Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank all medical professionals who are associated with our practice.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101228.

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