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Original Article

Additional complex fractionated atrial electrogram ablation does not improve the outcomes of non-paroxysmal atrial fibrillation: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Non-paroxysmal atrial fibrillation (AF) has a complex pathophysiological process. The standard catheter ablation approach is pulmonary vein isolation (PVI). The additional value of complex fractionated electrogram (CFAE) ablation is still unclear. We aimed to investigate the additional value of CFAE ablation for non-paroxysmal AF.

Methods: We performed a systematic review and meta-analysis of randomized controlled studies up to May 2020. Articles comparing pulmonary vein isolation (PVI) plus CFAE ablation and PVI alone for AF were obtained from the electronic scientific databases. The pooled mean difference (MD) and pooled risk ratio (RR) were assessed.

Results: A total of 8 randomized controlled trials (RCTs) including 1034 patients were involved. Following a single catheter ablation procedure, the presence of any atrial tachyarrhythmia (ATA) with or without the use of antiarrhythmic drugs (AADs) between both groups were not significantly different (RR = 1.1; 95% confidence interval [CI] = 0.97–1.24; p = 0.13). Similar results were also obtained for the presence of any ATA without the use of AADs (RR = 1.08; 95% CI = 0.96–1.22; p = 0.2). The additional CFAE ablation took longer procedure times (MD = 46.95 min; 95% CI = 38.27–55.63; p = < 0.01) and fluoroscopy times (MD = 11.69 min; 95% CI = 8.54–14.83; p = < 0.01).

Conclusion: Additional CFAE ablation failed to improve the outcomes of non-paroxysmal AF patients. It also requires a longer duration of procedure times and fluoroscopy times.

1. Introduction

Atrial fibrillation (AF) is well known as the most common heart rhythm disorder encountered by the physician in daily clinical practice and is related to significant mortality, morbidity, and healthcare costs.[1,2] Worldwide, the prevalence of AF is estimated to increase.[3–5] AF could undergo the evolution from self-terminating short episodes (paroxysmal AF) to longer episodes (persistent AF or long-standing persistent AF), which require cardioversion for the conversion into sinus rhythm, or it can progress into the permanent AF.[6,7] The evolution of AF is caused by the atrial remodeling caused by itself, the progression of the underlying heart disease, or both.[8–10] Generally, the treatment approach for AF includes rhythm control, rate control, and prevention of thromboembolism. The conversion into sinus rhythm can be achieved through of antiarrhythmic drugs (AADs) administration, electrical cardioversion, or catheter ablation.[11–14] To date, several major cardiovascular associations give a class I recommendation for rhythm control using catheter ablation only for patients with recurrent paroxysmal AF who are refractory or intolerance to class I or III AADs, especially.[11–13]

Prior studies have demonstrated that pulmonary vein isolation (PVI) is effective in maintaining the sinus rhythm in 78 to 79.5% of paroxysmal paroxysmal AF patients at five years follow-up period.[15,16] However, a study in persistent AF and long-standing persistent AF revealed that arrhythmia free survival at a one-year follow-up period was 66.7%.[17] Non-paroxysmal AF that includes persistent AF, long-standing persistent AF, and permanent AF, has a more complex pathophysiological process than paroxysmal AF.[8–10] This condition led to the need for an additional ablation strategy to

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modify the AF substrate, such as complex fractionated atrial electrogram (CFAE) and linear ablation. The additional value of CFAE ablation for AF is still unclear. We aimed to investigate whether the additional CFAE ablation could give the additional value for the rhythm control strategy in non-paroxysmal AF.

2. Methods

2.1. Study design

We performed a systematic review and meta-analysis study in May 2020 of published studies up to May 2020, according to the direction from Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.[18] Articles published in the electronic scientific database such as PubMed, ScienceDirect, Cochrane, ProQuest, and ClinicalTrials.gov were searched and identified based on the eligibility criteria. Eligible articles were processed and analyzed to determine the pooled mean difference (MD) for continuous data or pooled risk ratio (RR) for categorical data using a fixed-effect or random-effect analysis. We also assess its corresponding 95% confidence interval (CI).

2.2. Search strategy

Up to May 2020, articles comparing PVI plus CFAE ablation and PVI for AF were obtained from the electronic scientific database such as PubMed, ScienceDirect, Cochrane, ProQuest, and ClinicalTrials.gov. We used the following keywords: “non-paroxysmal atrial fibrillation” or “non-paroxysmal AF,” AND “catheter ablation,” AND “complex fractionated atrial electrogram” or “CFAE” AND “pulmonary vein isolation” or “PVI.” We also searched for potentially relevant information through the reference lists of all accessed papers.

2.3. Eligibility criteria

The inclusion criteria included: (1) studies comparing PVI versus PVI plus CFAE ablation for non-paroxysmal AF including persistent AF, long-standing persistent AF, or permanent AF; (2) the purpose of AF ablation was for rhythm control; (3) availability of the information about the procedure times, fluoroscopy times, or ablation times; (4) at least six months' duration of follow-up; (5) availability of data about the arrhythmia detection method; (6) availability of the information about atrial tachyarrhythmia (ATA), AF, atrial flutter (AFL), or atrial tachycardia (AT) during the follow-up period; and (7) articles written in English. We excluded the articles which met the following criteria: (1) duplications; (2) review articles; (3) case reports; (4) editorials; (5) non-English language; (6) unavailable full-text; (7) incomparable approach in the treatment and control groups; (8) did not report the outcome of interest; (9) sub-study of the included studies (10) studies involved paroxysmal AF patients; or (11) non-RCT studies.

2.4. Exposure and outcome

The exposure variable was the CFAE ablation in addition to PVI. Therefore, patients were grouped into the “CFAE group” and “No CFAE group.” The primary outcome was the presence of any ATA, including AF, AFL, or AT, with or without the use of AADs following a single catheter ablation procedure. The secondary outcome of this study included: (1) the presence of any ATA including AF, AFL, or AT without the use of AADs following a single catheter ablation procedure; (2) repeat ablation procedure following a single catheter ablation procedure; (3) procedure-related complications; and also (4) procedure times and fluoroscopy times.

2.5. Quality of studies assessment and data extraction

The quality assessment of the collected randomized controlled trials (RCTs) was conducted using the modified Jadad scale.[19] It is consists of 8 criteria with a range of values of 0–8. RCTs with a modified Jadad scale of 4–8 were considered as a high-quality study.[20] This systematic review and meta-analysis study only included high-quality RCTs. Data about (1) the first author name; (2) acronym of the study; (3) year of publication; (4) design; (5) center involved; (6) type of AF; (7) ablation strategy; (8) CFAE ablation site; (9) CFAE detection method; (10) blanking period; (11) duration of follow-up period; (12) arrhythmia detection method; (13) primary endpoint; (14) definition of recurrent arrhythmia; (15) number of patients; (16) age; (17) gender; (18) valvular AF; (19) duration of AF; (20) left ventricular ejection fraction (LVEF); (21) anteroposterior diameter of left atrium (LA); (22) occurence of ATA including AF, AFL, and AT with or without AADs; (23) repeat ablation procedure; (24) the use of AADs during follow up period; (25) procedure-related complications; (26) procedure times; and (27) fluoroscopy times were extracted from the included articles.

2.6. Statistical analysis

The statistical analysis process was carried out according to the standard guideline.[21] Data were assessed for heterogeneity and potential publication bias before determining the conclusion. Q test was used to evaluate the presence of heterogeneity. We used the cut off value of p for heterogeneity (pHet) 0.1. In the presence of heterogeneity ($pHet < 0.1$), we used the random-effect analysis model. In contrast, in the absence of heterogeneity ($pHet \geq 0.1$), we used the fixed-effect analysis model.[22] The existence of publication bias was evaluated using two methods, including funnel plot analysis and the Egger test. The presence of significant publication bias was identified if p Egger (pE) < 0.05.[23] For categorical data, the pooled RR and 95% CI were measured using the Mantel-Haenszel statistical method. The inverse variance statistical method was used to measure the pooled MD and 95% CI for continuous data. Statistically significant was considered if a p-value < 0.05. Comprehensive Meta-Analysis version 3.0 (CMA, New Jersey, US) and Review Manager Version 5.3 (Cochrane, Copenhagen, Denmark) were used for the data analysis process.

3. Results

3.1. Eligible studies

A total of 442 articles were identified through PubMed, ScienceDirect, Cochrane, ProQuest, and ClinicalTrials.gov, while three articles were identified through reference lists of accessed full-text articles. Three hundred forty-one records were excluded because of duplications. We excluded 25 review articles, 17 case reports, 6 editorials, 9 articles written in a non-English language, and 10 articles without full-text availability during the initial screening. In further screening, 29 articles were excluded due to the following reasons: (1) incomparable approach in the treatment and control group ($n = 11$); (2) did not report the outcome of interest ($n = 3$); (3) sub-study of included studies ($n = 4$); (4) Involved paroxysmal AF patients ($n = 8$); and cohort studies ($n = 3$). In the end, 8 RCTs were included in this study.[24–31] The flow diagram of the study selection process is shown in Fig. 1.

3.2. Baseline characteristics

All included studies have a modified Jadad scale ≥ 4, therefore considered as the high-quality study (Supplementary Table 1).

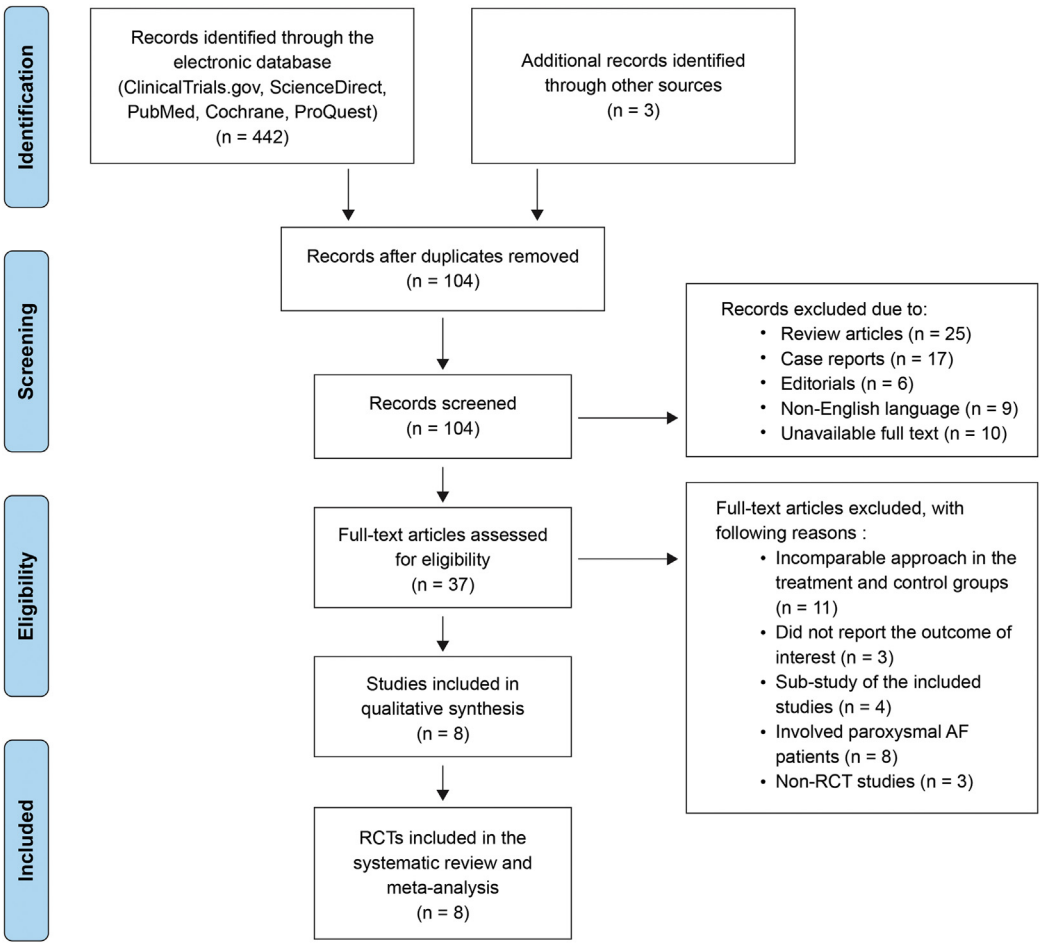


Fig. 1. Flow diagram of the study selection process. AF = atrial fibrillation; RCTs = randomized controlled trials.

Baseline characteristics of the involved RCTs are summarized in Table 1. CFAE ablation on the LA was conducted in four studies,[24,25,28,31] while CFAE ablation on both atria was also conducted in four studies.[26,27,29,30] Most of the included studies used automatic CFAEs detection algorithm.[24,25,27,28,30,31] The blanking period ranged from 2 to 3 months, and the mean follow-up period was at least 10 months. Ambulatory heart rhythm monitor devices were used to detect the episode of arrhythmia during follow up period.[24–31]

A total of 1034 patients with non-paroxysmal AF were included in our study. Additional CFAE ablation procedure was conducted in 607 patients in addition to the PVI with or without linear ablation. PVI with or without linear ablation was performed in 427 patients. All included studies were dominated by male patients, with the proportion of male patients ranged from 64.8 to 90%. The patients have the mean age ranged from 58 to 64.6 years old, and the mean duration of they had non-paroxysmal AF for was 3.6 to 9 years. The mean LA diameter was 42 to 48 mm, while the mean LVEF was 50.1 to 61.69%. The summary of baseline characteristics of the included patients is shown in Table 2.[24–31]

3.3. Heterogeneity and publication bias

The presence of heterogeneity was assessed using the Q-test. We did not find any heterogeneity in our meta-analysis, so we used the fixed-effect model to determine the correlation and effect estimation (Figs. 2,3, and 4). From our analysis, the publication bias was present only in the analysis of procedure-related complications, which was supported by the asymmetrical funnel plot (Fig. 5) and pE = 0.02 (Table 3). The presence of heterogeneity and publication bias are summarized in Table 3 and Table 4.

3.4. Outcome

Following a single catheter ablation procedure, the presence of any ATA (RR = 1.1; 95%CI = 0.97–1.24; p = 0.13), AF (RR = 0.94; 95% CI = 0.79–1.22; p = 0.5), and AFL or AT (RR = 1.3; 95% CI = 0.92–1.82; p = 0.14) with or without the use of AADs between both groups were not significantly different (Fig. 2). The similar results were also obtained for the presence of any ATA (RR = 1.08; 95%CI = 0.96–1.22; p = 0.2), AF (RR = 0.97; 95%CI = 0.82–1.14; p = 0.68), AFL or AT (RR = 1.1; 95%CI = 0.76–1.6; p = 0.61), and repeat ablation procedure (RR = 1.17; 95%CI = 0.95–1.44; p = 0.14) without the use of AADs in between both groups (Fig. 3).

We also conducted analysis of the procedural aspects (Fig. 4). As we expected, the additional CFAE ablation took longer procedure times (MD = 46.95 min; 95% CI = 38.27–55.63; p = < 0.01) and fluoroscopy times (MD = 11.69 min; 95% CI = 8.54–14.83; p = < 0.01) (Fig. 4). The procedure-related complications between CFAE group and no CFAE group were not significantly different (RR = 1.49; 95%CI = 0.75–2.96; p = 0.26) (Fig. 3). It included

Table 1
Baseline characteristics of the involved randomized controlled trials.

First author, year (Ref)	Design	Type of AF	Size, n	Ablation strategy			CFAE ablation site	CFAE detection method	CFAE definition	Blanking period	Follow up	Arrhythmia detection method	Definition of recurrent arrhythmia
				Group 1	Group 2	Group 3							
Bassiouny, 2016 [24]	RCT-SC	Persistent AF	90	PVAI + posterior wall and septum ablation	PVAI + posterior wall and septum ablation + CFAE	No	LA	Automated	Cycle length between 50 and 120 ms, using automated electrographic analysis	3 months	12 months	• Weekly follow-up telephone calls and transtelephonic ECG transmissions (first 4–6 months) • Follow-up appointments and 24 to 48-h Holter monitor recording (4–6 months and then every six months after that) • Earlier visits if symptoms develop.	AF, AFL, or focal AT episode lasting >30 s after 3 months blanking period.
Dixit, 2012 [25]	RCT-SC	Persistent AF	156	PVI	PVI + non-PV trigger	PVI + CFAE	LA	Automated	Mean fractionation interval < 120 ms	6 weeks	12 months	• At least 3 outpatient visits • Before or immediately after each visit, patients underwent 30-day periods of transtelephonic monitoring • Additional transtelephonic monitoring was performed if patients reported arrhythmia symptoms in-between visits. • At each outpatient visit, patients were queried for symptoms, and a 12-lead ECG was obtained	Any symptomatic or asymptomatic AF or OAT episode that lasted for ≥30 s
Elayi, 2008 [26]	RCT-MC	Longstanding permanent AF	144	PVI-CPVA	PVI-PVAI	PVI-PVAI + CFAE	Both atria	Visual	• Atrial electrograms with fractionation and composed of 2 defections or more and/or with continuous activity of the baseline or • Atrial electrograms with a cycle length < 120 ms	2 months	16 months	• 12-lead ECG during outpatient visits • Patients were asked to record (using event recorder) 4 times per week even if they were asymptomatic and any time if they experienced symptoms (at least the first 6 months) • A 48-h Holter monitor recording (3, 6, 9, 12, and 15 months post-ablation) • Device interrogation in patients with implanted devices	Episodes of AF/AT that lasted ≥ 1 min during the follow-up period
Elayi, 2011 [27]	RCT-SC	Longstanding persistent AF	98	PVI-PVAI	PVI-PVAI + CFAE	No	Both atria	Automated	• Atrial electrograms with fractionation and composed of 2 defections or more and/or with continuous activity of the baseline or • Atrial electrograms with a cycle length < 120 ms	2 months	17.2 ± 5.2 months	• Outpatients clinic visits with 48-h Holter monitor recording (3-month intervals for 1 year) • Event recorder (3-month follow-up visit for 3 months duration) • Patients were asked to record at least 3 times a week at baseline, and anytime they had symptoms	Any episode of AF

Kim, 2017 [28]	RCT-SC	Longstanding persistent AF	137	PVI-CPVI + linear	PVI-CPVI + linear + CFAE	No	LA	Automated	CFAE cycle length of <120 ms	3 months	22.3 ± 13.2 months	• ECG during outpatient clinic visits (1, 3, 6, and 12 months after RFCA and then every 6 months after that or whenever they experienced symptoms) • 24-h Holter recording (3 and 6 months and then every 6 months after that) • Patients reporting symptoms of palpitations underwent Holter monitor or event monitor recording and were evaluated for the possibility of arrhythmia recurrence	Any episode of AF or AT ≥ 30 s in duration
Oral, 2009 [29]	RCT-SC	Longstanding persistent AF	119	AF terminated during PVAI	PVI-PVAI	PVI-PVAI + CFAE	Both atria	Visual	• Electrograms with a cycle length < 120 ms or shorter than the AF cycle length in the coronary sinus or • Electrograms that were fractionated or displayed continuous electrical activity	8–12 weeks	10 ± 3 months	• Outpatients clinic visits (3 months following ablation procedure and then every 3–6 months after that) • A 30-day auto-triggered event monitor 6 months after ablation	Any episode of ATA ≥ 30 s in duration beyond 12 weeks after ablation
Verma, 2015 [30]	RCT-MC	Persistent AF	589	PVI	PVI + CFAE	PVI + linear	Both atria	Automated	Mean cycle length of <120 ms	3 months	18 months	• Clinical assessments, 12-ECG, and 24-h Holter-monitor recording (baseline and at 3, 6, 9, 12, and 18 months after the initial ablation) • Transtelephonic monitor (Tele-ECG-Card, Vitaphone) for the 18-month follow-up period • Patients were asked to transmit rhythm recordings weekly, and any time they had symptoms.	AF lasting >30 s after one ablation procedure, with or without the use of antiarrhythmic medications
Wong, 2015 [31]	RCT-CM	Persistent AF	130	PVI-CPVA + linear	PVI-CPVA + linear + CFAE	No	LA	Automated	CFAE mean of <120 ms	3 months	35 ± 5 months	• 12-lead ECG (every 3 months during the first year following ablation procedure and then every 3–6 months after that) • Holter monitor recording was arranged if patients had symptoms	Any episode of symptomatic or asymptomatic atrial arrhythmia documented on ECG or Holter monitor after the 3 months blanking period

AADs = antiarrhythmic drugs; AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; ATA = atrial tachyarrhythmia; CFAE = complex fractionated atrial electrogram; CPVA = circumferential pulmonary vein ablation; CPVI = circumferential pulmonary vein isolation; CS = cohort study; ECG = electrocardiography; LA = left atrium; MC = multicenter; OAT = organized atrial tachycardia; PVAI = pulmonary vein antrum isolation; PVI = pulmonary vein isolation; RCT = randomized controlled trial; SC = single center.

Table 2
Baseline characteristics of the included patients.

First author, year (Ref)	Patients, n		Age, mean ± SD, years		Male, %		Valvular AF, %		Duration of AF, mean ± SD, years		LA diameter, mean ± SD, mm		LVEF, mean ± SD, %	
	CFAE	No CFAE	CFAE	No CFAE	CFAE	No CFAE	CFAE	No CAFE	CFAE	No CFAE	CFAE	No CFAE	CFAE	No CFAE
Bassiouny, 2016 [24]	44	46	64.6 ± 9.4	62.2 ± 9.4	75	74	16	13	NA	NA	42 ± 9.8	45 ± 8.8	50.1 ± 12.4	50.5 ± 9.8
Dixit, 2012 [25]	51	55	60 ± 9	59 ± 8	90	87	NA	NA	3.6 ± 3.3	4.7 ± 5.4	NA	NA	56 ± 14	56 ± 9
Elayi, 2008 [26]	49	48	59.2 ± 11.5	58.1 ± 10.3	65	69	6	8	6.3 ± 2.5	5.5 ± 3.5	46.2 ± 6.4	45.1 ± 6.6	55 ± NA	52 ± NA
Elayi, 2011 [27]	50	48	62.2 ± 10.2	60.9 ± 8.9	82	79	NA	NA	9 ± 6.3	8.2 ± 5.6	47 ± 6.5	48 ± 7.3	54 ± 5	57 ± 7
Kim, 2017 [28]	54	54	59.31 ± 11.44	62.59 ± 9.68	81.5	64.8	NA	NA	4.79 ± 4.23	5.15 ± 5.31	45.24 ± 5.40	45.43 ± 6.14	61.69 ± 8.21	58.94 ± 9.82
Oral, 2009 [29]	50	50	62 ± 8	58 ± 10	82	82	4	6	5 ± 4	6 ± 5	46 ± 6	47 ± 6	54 ± 9	53 + 12
Verma, 2015 [30]	244	61	60 ± 9	58 ± 10	81	78	NA	NA	4.2 ± 5.0	4.3 ± 6.3	44 ± 6	44 ± 6	57 ± 10	55 ± 11
Wong, 2015 [31]	65	65	61 ± 11	61 ± 9	77	74	NA	NA	NA	NA	45 ± 6	46 ± 7	NA	NA

AF = atrial fibrillation; CFAE = complex fractionated atrial electrogram; LA = left atrium; LVEF = left ventricular ejection fraction.

femoral access complications, stroke, pericardial tamponade, pulmonary vein stenosis, sinus node syndrome not requiring pacemaker, temporary respiratory arrest associated to anesthesia, and atrio-esophageal fistula.[25,26,27,28,30] The analysis results of the procedural aspects are summarized in Tables 3 and 4.

4. Discussion

4.1. Main findings and comparison with the previous studies

We performed a meta-analysis of 8 RCTs. During the 10 to 35 months mean follow-up period, the presence of any ATA, AF, and AFL or AT with or without the use of AADs after a single ablation procedure between the CFAE group and no CFAE group were not significantly different. Our results supported the results of the previous studies. However, those previous studies included both paroxysmal AF and non-paroxysmal AF patients.[32,33] According to the included studies, our study differed from Providência et al.,[33] which included cohort studies. Compared with a study from Kong et al.,[32] which only included RCTs, we were able to add 6 RCTs to be included in our meta-analysis.[24,25,27,28,30,31] We used a different method to extract data from the study conducted by Elayi et al.,[26] where the patients were divided into three groups: CFAE ablation continued by pulmonary vein antrum isolation (PVAI) group, PVAI group, and circumferential pulmonary vein ablation (CPVA) group. The study of Kong et al. merged the PVAI group and the CPVA group as the control group.[32] In this study, we needed to know the additional benefit of CFAE ablation for non-paroxysmal AF. Therefore, we only used the PVAI group as the control group.

The goal of our study was to determine whether CFAE ablation provided additional benefit for non-paroxysmal AF. The use of AADs after ablation could be the potential confounder. Therefore, we conducted the meta-analysis in patients who were not treated with AADs after a single ablation procedure. No significant difference was found in the presence of any ATA without the use of AADs after a single ablation procedure between the CFAE group and no CFAE group. Prior meta-analysis studies showed conflicting results. One study revealed that CFAE ablation did not provide additional value for non-paroxysmal AF patients,[34] while another study revealed different result.[35] Therefore, we identified the specific types of ATA that occurred after a single ablation procedure without AADs. No significant difference was also found in the presence of AF and AFL or AT without the use of AADs after a single ablation procedure between the CFAE group and the no CFAE group. The earlier studies did not provide the data about the specific types of ATA that occurred after a single ablation procedure without AADs.[34,35] The need for repeat ablation procedure was also not different between both groups. Our result was not different from the earlier study on paroxysmal AF and non-paroxysmal AF.[32]

Additional CFAE ablation was significantly correlated with increased duration of procedure times and fluoroscopy times. It was not different from the results of the previous meta-analysis.[32,34,35] In our meta-analysis, CFAE was not correlated with an increase of procedure-related complications. Our findings in procedure-related complications should not be extrapolated. We found the potential of publication bias supported by the consistent result funnel plot analysis and the Egger test (Figs. 4 and 5, and Table 3).

4.2. Non-paroxysmal AF and substrate modifying ablation

Electrical trigger, arrhythmogenic substrate, and modulating factors are essential factors in the pathogenesis of AF.[36] Electrical triggers play a vital role in AF initiation, while modulating factors and arrhythmogenic substrate are responsible for its perpetuation or maintenance.[37,38] In AF, most of the ectopic activities or electrical triggers are pulmonary veins origin. Ablation in those locations can prevent the recurrence of AF.[39] Localized re-entry, rotors, and triggered activity were the underlying mechanisms in the focal ectopic activity induction.[40,41] Modulating factors include atrial stretch, increased vagal tone, dispersion and shortening of the atrial refractory period, calcium load, inflammation, cardiovascular risk factors, or genetic predisposition.[8,10,37] Anatomical remodeling (atrial dilatation, fibrosis, adipose tissue) and electrical remodeling (shortening of the action potential) are the arrhythmogenic substrates in AF.[8,10,37,38] Paroxysmal AF shows a predominance of local electrical triggers, mainly pulmonary veins origin.[10] Earlier studies revealed that the success rate of PVI ranged from 78 to 79.5%.[15,16] In this situation, PVI could be an effective strategy. As AF becomes more persistent and finally permanent (non-paroxysmal), arrhythmogenic substrates (at the beginning functional and eventually become structural) predominate.[10] In this meta-analysis, the structural changes in LA had already occurred because most all studies involved patients with large LA size.[24,26–31] Anteroposterior LA diameter measured by echocardiography > 40 mm and >38 mm are considered large for male and female respectively.[42] Earlier study in persistent AF showed the lower success rate of PVI, which was around 66.7%.[17] Substrate modifying ablation approach, such as CFAE ablation, might be a solution to solve it.

4.3. The possible explanation for CFAE ablation did not give an additional benefit for non-paroxysmal AF

In our meta-analysis, there were several reasons for CFAE ablation did not give an additional benefit for non-paroxysmal AF. First, in some studies, the CFAE detection method was conducted using an automatic CFAEs detection algorithm,[24,25,27,28,30,31] while other studies used direct visual inspection.[26,29] Although the automatic mapping systems were used, there were differences in their set up and algorithms for defining and classifying fractionated electrograms.[24,25,27,28,30,31] The heterogenous CFAE definition, different CFAEs detection algorithm among studies, or direct visual inspection could be the potential confounder. Second, the location of the CFAE ablation site also could be the possible confounder. CFAE ablation was conducted in LA[24,25,28,31] and both atria.[26,27,29,30] Third, the kind of ablation catheters used, the contact force used, and radiofrequency applications in this meta-analysis were heterogeneous.[24–31] Fourth, an additional CFAE ablation is associated with the wider area of scar tissues. It could be seen using cardiac magnetic resonance (CMR) with the late-gadolinium enhancement (LGE).[43] Previous studies revealed that poor scar formation was associated with recurrent ATA after catheter ablation procedure for AF.[43,44]

4.4. Strengths and limitations

There were several strengths of our study. First, our meta-analysis represents the largest pooled analysis of RCTs of the additional value of CFAE ablation for non-paroxysmal AF to the best of our knowledge. Second, we provided the data about the

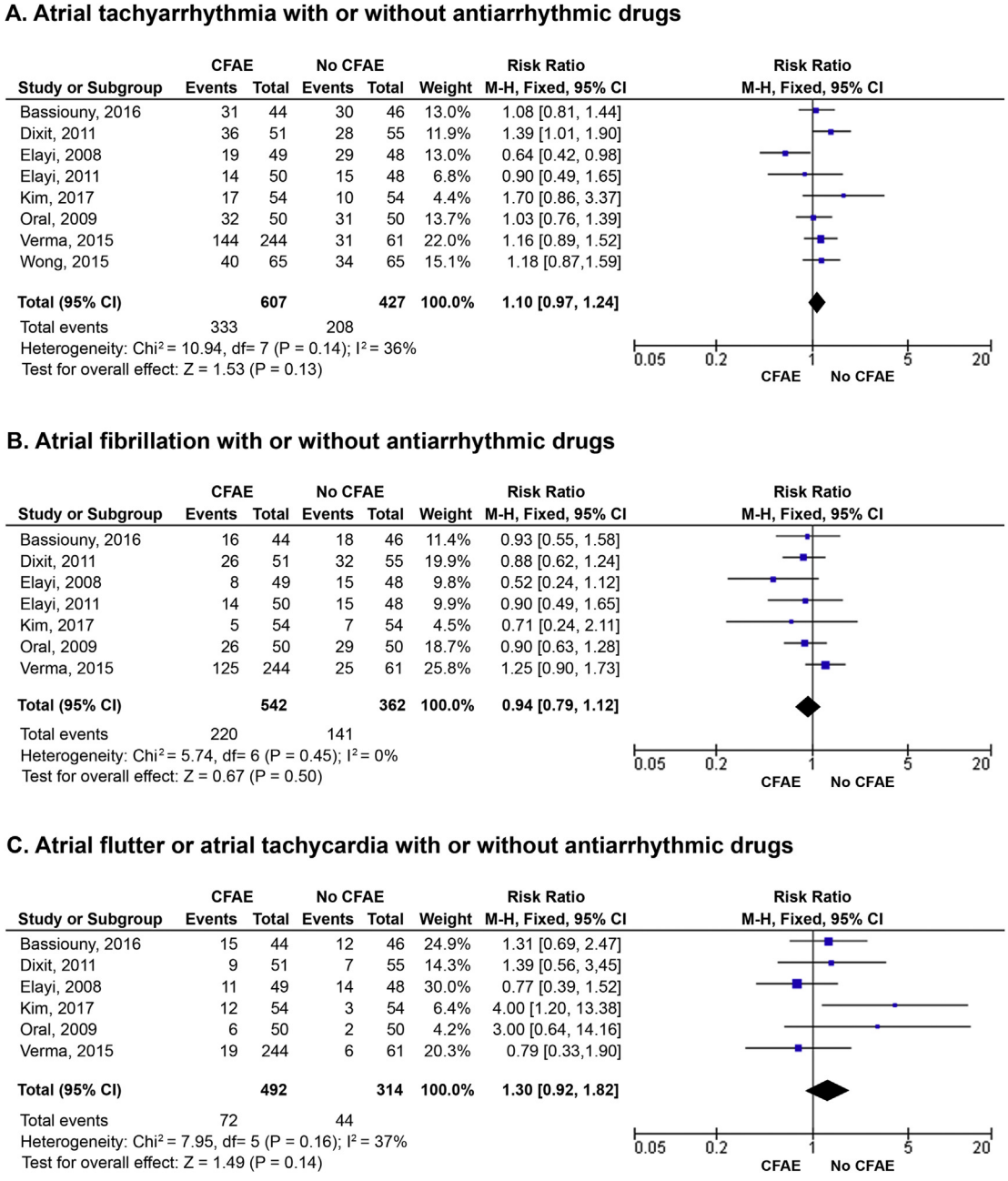
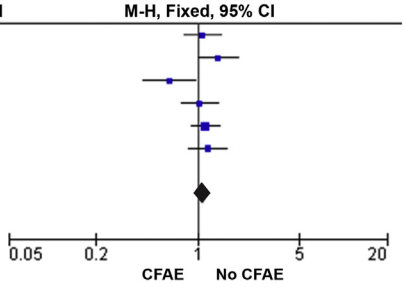


Fig. 2. Atrial tachyarrhythmia (A), atrial fibrillation (B), and atrial flutter or atrial tachycardia (C) after single catheter ablation procedure with or without antiarrhythmic drugs. CI = confidence interval; CFAE = complex fractionated atrial electrogram; M–H = Mantel-Haenszel.

A. Atrial tachyarrhythmia without antiarrhythmic drugs

Study or Subgroup	CFAE Events	CFAE Total	No CFAE Events	No CFAE Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bassiouny, 2016	31	44	30	46	14.1%	1.08 [0.81, 1.44]
Dixit, 2011	36	51	28	55	12.9%	1.39 [1.01, 1.90]
Elayi, 2008	19	49	29	48	14.1%	0.64 [0.42, 0.98]
Oral, 2009	32	50	31	50	14.9%	1.03 [0.76, 1.39]
Verma, 2015	163	244	36	61	27.7%	1.13 [0.90, 1.42]
Wong, 2015	40	65	34	65	16.3%	1.18 [0.87, 1.59]
Total (95% CI)		**503**		**325**	**100.0%**	**1.08 [0.96, 1.22]**
Total events	321		188			

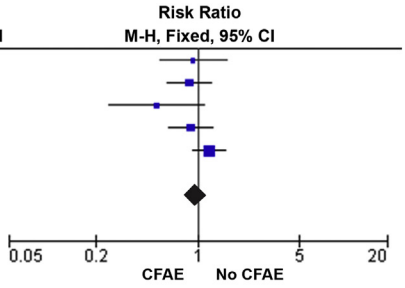
Heterogeneity: Chi² = 8.89, df= 5 (P = 0.11); I² = 44%
Test for overall effect: Z = 1.27 (P = 0.20)



B. Atrial Fibrillation without antiarrhythmic drugs

Study or Subgroup	CFAE Events	CFAE Total	No CFAE Events	No CFAE Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bassiouny, 2016	16	44	18	46	12.2%	0.93 [0.55, 1.58]
Dixit, 2011	26	51	32	55	21.4%	0.88 [0.62, 1.24]
Elayi, 2008	8	49	15	48	10.5%	0.52 [0.24, 1.12]
Oral, 2009	26	50	29	50	20.2%	0.90 [0.63, 1.28]
Verma, 2015	154	244	32	61	35.6%	1.20 [0.93, 1.56]
Total (95% CI)		**438**		**260**	**100.0%**	**0.97 [0.82, 1.14]**
Total events	230		126			

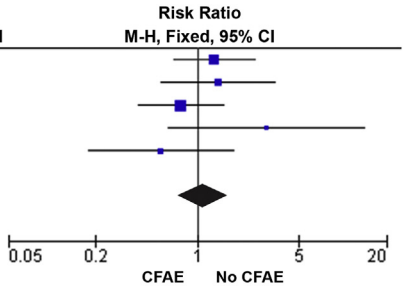
Heterogeneity: Chi² = 5.79, df= 4 (P = 0.22); I² = 31%
Test for overall effect: Z = 0.41 (P = 0.68)



C. Atrial Flutter or atrial tachycardia without antiarrhythmic drugs

Study or Subgroup	CFAE Events	CFAE Total	No CFAE Events	No CFAE Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bassiouny, 2016	15	44	12	46	28.6%	1.31 [0.69, 2.47]
Dixit, 2011	9	51	7	55	16.4%	1.39 [0.56, 3.45]
Elayi, 2008	11	49	14	48	34.5%	0.77 [0.39, 1.52]
Oral, 2009	6	50	2	50	4.9%	3.00 [0.64, 14.16]
Verma, 2015	9	244	4	61	15.6%	0.56 [0.18, 1.77]
Total (95% CI)		**438**		**260**	**100.0%**	**1.10 [0.76, 1.60]**
Total events	50		39			

Heterogeneity: Chi² = 4.51, df= 4 (P = 0.34); I² = 11%
Test for overall effect: Z = 0.51 (P = 0.61)



D. Repeat ablation procedure

Study or Subgroup	CFAE Events	CFAE Total	No CFAE Events	No CFAE Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bassiouny, 2016	14	44	12	46	11.0%	1.22 [0.64, 2.34]
Dixit, 2011	24	51	14	55	12.6%	1.85 [1.08, 3.17]
Elayi, 2008	10	49	12	48	11.3%	0.82 [0.39, 1.71]
Oral, 2009	17	50	18	50	16.8%	0.94 [0.55, 1.61]
Verma, 2015	63	244	13	61	19.4%	1.21 [0.72, 2.05]
Wong, 2015	34	65	31	65	28.9%	1.10 [0.78, 1.55]
Total (95% CI)		**503**		**325**	**100.0%**	**1.17 [0.95, 1.44]**
Total events	162		100			

Heterogeneity: Chi² = 4.48, df= 5 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)

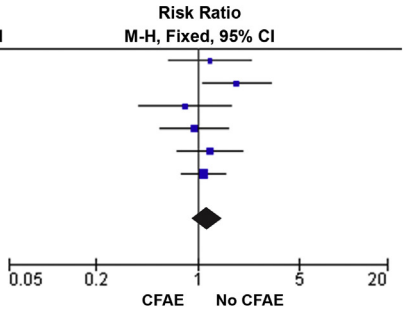


Fig. 3. Atrial tachyarrhythmia (A), atrial fibrillation (B), atrial flutter or atrial tachycardia (C), and repeat ablation procedure (D) after single catheter ablation procedure without antiarrythmic drugs. CI = confidence interval; CFAE = complex fractionated atrial electrogram; M–H = Mantel-Haenszel.

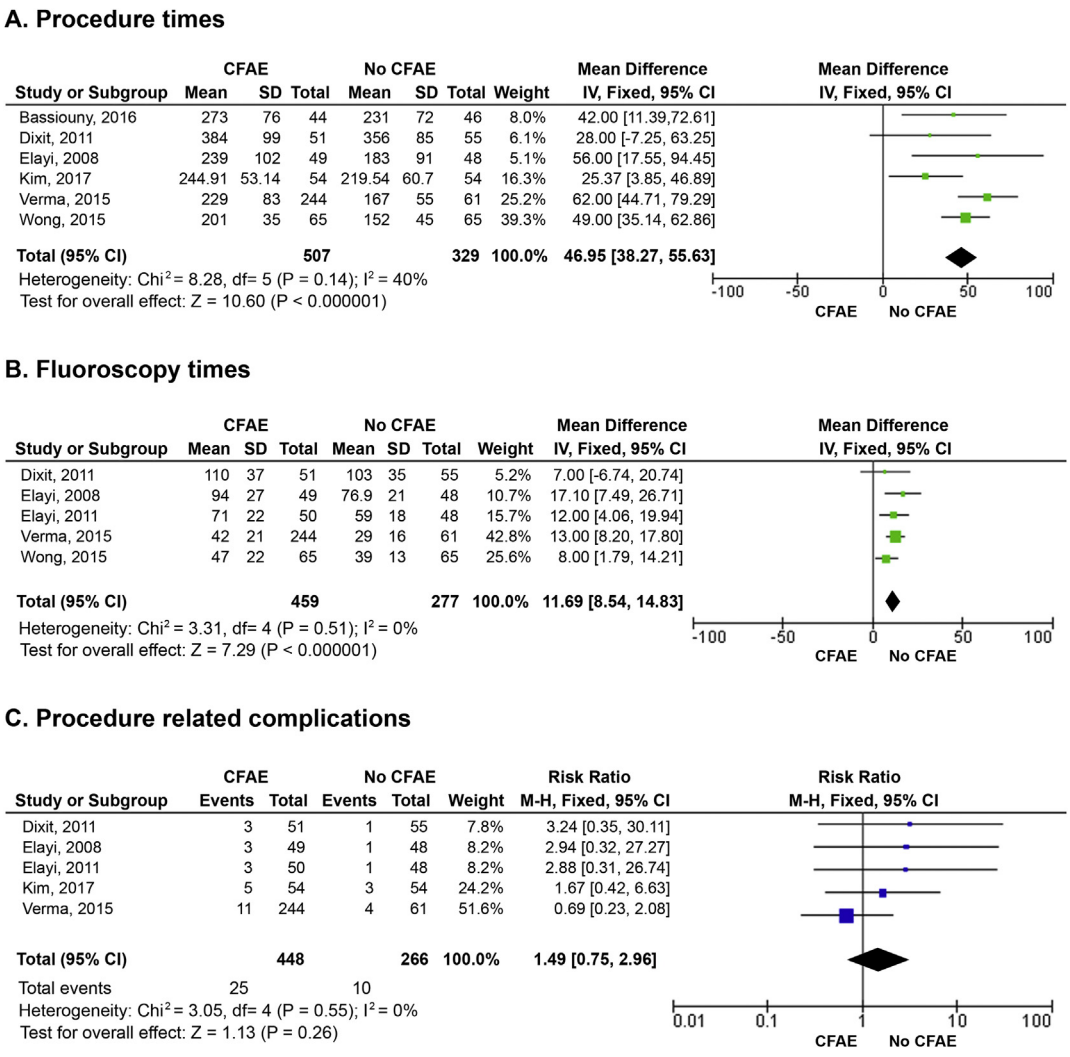


Fig. 4. Procedure times (A), fluoroscopy times (B), and procedure-related complications (C). CI = confidence interval; CFAE = complex fractionated atrial electrogram; IV = inverse variance; M–H = Mantel-Haenszel.

recurrent ATA, including AF, AFL, or AT, after a single catheter ablation procedure. Third, arrhythmia detection following a single catheter ablation was conducted using ambulatory heart rhythm monitors in all studies. In addition to those strengths, our study also had several limitations. First, as well as other meta-analysis studies, the possibility of publication bias cannot be avoided. To overcome

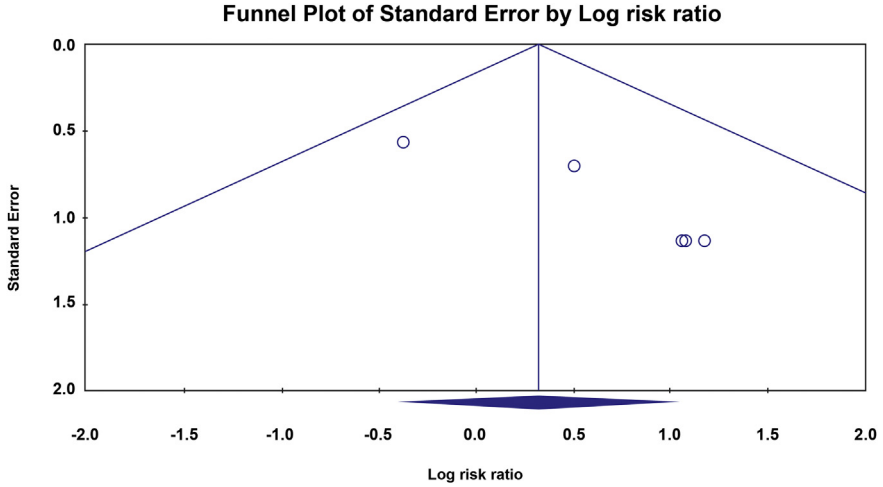


Fig. 5. Funnel-plot analysis. Funnel-plot analysis showing asymmetrical funnel plot for procedure-related complications.

Table 3
Summary of the association between CFAE ablation and the study endpoints.

Parameters	Number of studies	CFAE		No CFAE		Model	RR	95% CI	pHet	pE	p
		Event, n (%)	Total, n	Event, n (%)	Total, n						
ATA with or without AADs	8	333 (54.86)	607	208 (48.71)	427	Fixed	1.1	0.97–1.24	0.14	0.76	0.13
AF with or without AADs	7	220 (40.59)	542	141 (38.95)	362	Fixed	0.94	0.79–1.12	0.45	0.13	0.5
AFL or AT with or without AADs	6	72 (14.63)	492	44 (14.01)	314	Fixed	1.3	0.92–1.82	0.16	0.12	0.14
ATA without AADs	6	321 (63.81)	503	188 (57.84)	325	Fixed	1.08	0.96–1.22	0.11	0.23	0.2
AF without AADs	5	230 (52.51)	438	126 (48.46)	260	Fixed	0.97	0.82–1.14	0.22	0.06	0.68
AFL or AT without AADs	5	50 (11.41)	438	39 (15)	260	Fixed	1.1	0.76–1.6	0.34	0.66	0.61
Repeat ablation procedure	6	162 (32.21)	503	100 (30.77)	325	Fixed	1.17	0.95–1.44	0.48	0.95	0.14
Procedure-related complications	5	25 (5.58)	448	10 (3.76)	266	Fixed	1.49	0.75–2.96	0.55	0.02	0.26

AADs = antiarrhythmic drugs; AF = atrial fibrillation; AFL = atrial flutter AT = atrial tachycardia; ATA = atrial tachyarrhythmia; CFAE = complex fractionated atrial electrogram; CI = confidence interval; RR = risk ratio; pE = p Egger; pHet = p heterogeneity.

Table 4
Summary of procedure times and fluoroscopy times.

Parameters	Number of studies	CFAE, n	No CFAE, n	Model	Mean difference, minutes	95% CI	pHet	pE	p
Procedure times	6	507	329	Fixed	46.95	38.27–55.63	0.14	0.7	<0.01
Fluoroscopy times	5	459	277	Fixed	11.69	8.54–14.83	0.51	0.97	<0.01

CFAE = complex fractionated atrial electrogram; CI = confidence interval; pE = p Egger; pHet = p heterogeneity.

that problem, we used two methods mentioned above to identify any publication bias. The publication bias was found only in procedure-related complications. Second, the published experience of CFAE ablation for non-paroxysmal AF is currently modest. Consequently, our sample size might have lost the additional benefit of CFAE ablation even though the data are pooled. Third, the drawback of access to individual patient-level data restricted our capability to measure the real effects of patient-level characteristics on our outcomes. That is the standard issue in performing a meta-analysis. Fourth, the CFAE detection method widely varied among the included studies. The diversity in methodology could affect the analysis results. However, our results likely reflect current real-world clinical practice highlighting the absence of a clear CFAE definition. The last, the differences in the extent or location of CFAE ablation might influence the outcomes.

5. Conclusion

Our meta-analysis of RCTs revealed that additional CFAE ablation failed to improve the outcomes of non-paroxysmal AF patients. It also requires a longer duration of procedure times and fluoroscopy times. The universal definition of CFAE has to be established. Further multicenter RCTs with large homogenous participants and a more extended follow-up period are required to provide high-quality evidence about the benefit of additional CFAE ablation for patients with non-paroxysmal AF.

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Authors contributions

Idea/concept: YW. Design: YW. Control/supervision: AR. Data collection/processing: YW/DS/IJA. Extraction/Analysis/interpretation: YW/DS/IJA. Literature review: YW/AR/DS/IJA. Writing the article: YW/AR. Critical review: YW/AR. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Declaration of competing interest

All authors declared that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2020.11.004.

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