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Pathophysiological and clinical insights for atrial fibrillation/flutter or heart failure

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Pathophysiological and clinical insights for atrial fibrillation/flutter or heart failure

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Editorial: Pathophysiological and clinical insights for atrial fibrillation/flutter or heart failure

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Editorial on the Research Topic
Pathophysiological and clinical insights for atrial fibrillation/flutter or heart failure

Geriatric atrial fibrillation (AF) and atrial flutter (AFL) frequently coexist and complicate each other's treatment. Anti-arrhythmic drugs may not be effective, and cardioversion to sinus rhythm may be necessary. Anticoagulation therapy's side effects are also worthy of attention. Recent techniques, such as left atrial appendage occlusion, are becoming attractive for AF/AFL management. Novel drugs targeting specific ion channels are also being investigated. Despite progress in geriatric AF/AFL or heart failure (HF), their mechanisms and treatments require further investigation. The current research topic includes 13 studies on current advancements in mechanisms and treatment options for geriatric AF/AFL or HF.

For HF

Elderly patients have a higher incidence of chronic heart failure (CHF), which can lead to acute kidney injury (AKI) and poor prognosis. In a retrospective cohort study, Hou et al. found that a decreased change in N-terminal pro-brain natriuretic peptides (NT-proBNP) may improve survival outcomes and prevent severe AKI in elderly patients with CHF. However, an excessive decrease in NT-proBNP can increase the risk of non-recovery of renal function following AKI.

In elderly patients with acute heart failure (AHF) and oliguria, high doses of loop diuretics are often ineffective and may adversely affect prognosis. Liu et al. conducted a retrospective cohort study and found that the addition of tolvaptan (TLV) effectively increased urine output and had favorable effects on alleviating AHF progression. TLV may also reduce the risk of all-cause mortality in elderly patients with AHF and oliguria.

For AF/AFL

AF and AFL, these two "cousin" arrhythmias, might present relevant distinctions (Saglietto et al.). In particular, the ventricular response is completely irregular during AF, while generally regular during AFL, and their pathophysiology is different. The AF-related

beat-to-beat variability alters deep cerebral microvascular perfusion as it induces transient and repetitive hypoperfusion or hypertension. A differential risk of dementia between AF and AFL was found in a national cohort study (1).

Research has shown that AF and AFL induce tachycardiomyopathy (TCM) which leads to reversible HF for many years. However, the knowledge of TCM is still limited. Ermert et al. demonstrated that approximately 5% of all patients hospitalized for HF suffer from AF/AFL-induced TCM. Age, NT-pro-BNP level, and resting heart rate >112 beats/minute can improve the discrimination between AF/AF- induced TCM and HFrEF with AF/AFL. These parameters may allow for an earlier diagnosis and improved therapy.

Atrial fibrosis represents a major hallmark in the disease progression of AF. Circulating microRNA-21 (miR-21) has been validated as a biomarker that reflects the extent of left atrial fibrosis in AF patients. Furthermore, Pradhan et al. revealed that under tachyarrhythmic conditions, miR-21-5p is released in-vitro from cardiomyocytes and stimulates collagen production by fibroblasts in a paracrine mode.

AF is prone to HF and stroke. Early management can effectively reduce the stroke rate and mortality. In a population of 18,738 elderly people (aged over 60 years old) in Chinese communities, He et al. found that a combination of age, atrial premature beats, atrial flutter, left ventricular hypertrophy, hypertension, and heart disease may be used to screen high-risk individuals for AF episodes.

According to Guo et al., elderly Chinese patients with AF are generally multimorbid and polypharmacy. They also report a high rate of inappropriate prescribing. The ABC (Age, Biomarkers, and Clinical history)-bleeding risk score may be useful in assessing the risk of major bleeding in Chinese patients with AF on oral anticoagulation therapy in real-world practice, and they suggest that this score performed better in stratifying patients with a high risk than the modified HAS-BLED score (Wang et al.).

The angiotensin receptor-neprilysin inhibitor (ARNI) is a potential upstream treatment option for AF. ARNI could reduce atrial electrical instability in AF in comparison with ARB in both retrospective studies and animal experiments (Zhu et al.).

The left atrial appendage (LAA) and structure may be predictors of AF recurrence after CA, but the results of studies evaluating them are contradictory. A meta-analysis (Han et al.) showed that AF recurrence after CA is more likely in patients with large LAA structures (LAA volume, orifice area, orifice long/short axis, and volume index) and decreased LAA function prior to ablation (LAA emptying flow velocity, filling flow velocity, ejection fraction, and LASEC).

Atrial fibrosis is associated with left atrial low-voltage areas (LVAs); however, it is unclear how these areas affect recurrence after CA. According to Mao et al., LVAs can reduce the risk of arrhythmia recurrence after conventional ablation in AF patients. Moreover, additional substrate modification in LVAs patients could reduce the possibility of arrhythmia recurrence.

AF-CA is associated with a number of serious complications, including acute pericardial tamponade (APT). In pericardial autotransfusion (DAT), pericardial blood is injected directly into patients' veins without a cell-salvage system. There is limited information available regarding DAT for APT. Zhao et al. displayed that DAT could be a feasible and safe method to deal with APT during the AF-CA procedure.

Inflammatory conditions such as periodontitis (PD), a chronic inflammatory disease, may contribute to the development of AF. According to Tashiro et al., PD is independently associated with an increased risk of arrhythmia recurrence after the first CA for paroxysmal atrial fibrillation.

As a whole, the current Research Topic provides up-to-the-minute information on many aspects of pathophysiology and clinical considerations associated with AF/AFL or HF. New perspectives may emerge as a result of more comprehensive knowledge based on these discoveries.

Author contributions

CL is responsible for literature reading and article writing. JFL is responsible for literature selection, guidance and revision of the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

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GENERAL COMMENTARY
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Commentary: Differential Risk of Dementia Between Patients With Atrial Flutter and Atrial Fibrillation: A National Cohort Study

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Keywords: atrial fibrillation, atrial flutter, dementia, cognitive decline, RR interval irregularity

A Commentary on

Differential Risk of Dementia Between Patients With Atrial Flutter and Atrial Fibrillation: A National Cohort Study

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Atrial fibrillation and atrial flutter: cousin arrhythmias, but non that close. The recent article by Wang et al. (1) provides unprecedented insights on an issue that the scientific community overly takes for granted. Since decades, atrial fibrillation (AF) and atrial flutter (AFL) have been considered as different manifestation of the same disease, and practical guidelines recommend a similar management, in terms of oral anticoagulation prescription, for both AF and AFL (2). However, the pathophysiological background and the clinical presentation of the two conditions are different, particularly related to the ventricular response, completely irregular ("irregularly irregular") during AF, while generally regular (or, at least, a "regular/modular irregularity") during AFL. Based on this profound hemodynamic difference, there is a strong scientific rationale that the two "cousin" arrhythmias might present relevant distinctions. Indeed, it was recently suggested that a differential risk in hard clinical endpoints truly exists, with AF presenting a 63, 70, and 8% increased risk of ischemic stroke, heart failure hospitalization and mortality, respectively, if compared to patients with AFL only (3). In his recent article (1), Wang extends the spectrum of clinical differences between AF and AFL. On two propensity-matched cohorts from Taiwan's National Health Insurance Research Database and another dataset (study period 2001–2013), AF relates to an increased risk of dementia compared to AFL, independently from oral anticoagulation (hazard ratio, HR 1.14, 95% CI 1.04–1.25 in patients without oral anticoagulation, and 1.57, 95% CI 1.00–2.45 in patients on warfarin therapy). If on one hand this increased risk of dementia can be partly explained by an increased propension of AF patients to suffer an ischemic stroke, both in non-anticoagulated (HR 1.76, 95% CI 1.56–1.98) and anticoagulated subjects (HR 2.54, 95% CI 1.56–4.12), other mechanisms might certainly be involved.

AF patients are known to be more susceptible to subclinical cardiogenic microembolic phenomena leading to silent cerebral ischemias (4), likely not completely preventable by oral anticoagulation therapy. In addition, a critical role might be played by the rhythm itself, considering the irregularly irregularity of AF, compared to the more regular ventricular response in AFL. In fact, recent evidences point toward a critical role of AF rhythm *per se* on cerebral hemodynamics:

-Reduced mean cerebral blood flow: Gardsdottir et al. (5) demonstrated, at phase contrast MRI, that cerebral blood flow in patients with persistent AF is reduced by about 10%, compared to both paroxysmal AF patients (in sinus rhythm at the time of the test) and controls. In a subsequent analysis, persistent AF patients undergoing elective electrical cardioversion, showed,

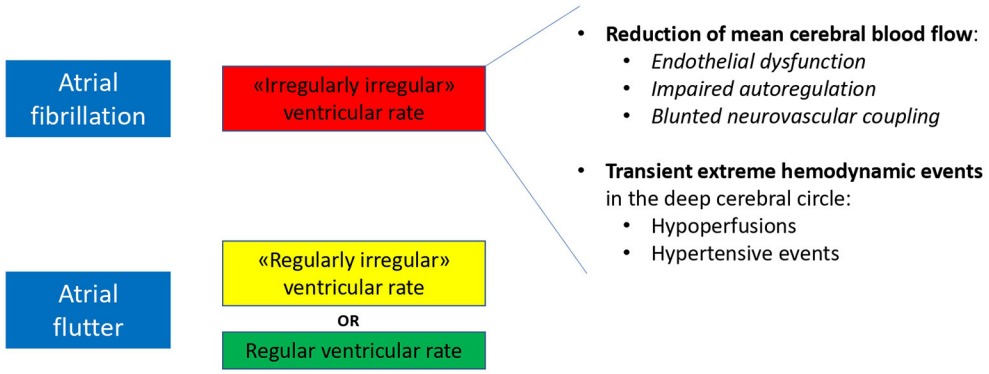

FIGURE 1 | Proposed hemodynamic determinants of a differential risk of dementia in patients with AF and AFL.

in case of successful and sustained restoration of sinus rhythm 10 weeks later, an improved cerebral blood flow; no difference could be found, instead, in patients with unsuccessful cardioversion (6). AF, in addition, likely triggers a cerebrovascular hemodynamic dysfunction. The RR variability-induced turbulent blood flow and shear stress pattern alterations induce reduced nitric oxide bioavailability and endothelial dysfunction. Impaired autoregulation and a blunted neurovascular coupling, ultimately result in a chronic reduction of mean cerebral blood flow during ongoing arrhythmia (7).

-Extreme hemodynamic events: AF-related beat-to-beat variability, assessed by spatially resolved near-infrared spectroscopy, alters cerebral microvascular perfusion by inducing transient and repetitive hypoperfusions or hypertensive events in the deep cerebral circle. Interestingly, while these events disappear after sinus rhythm restoration by electrical cardioversion, the same does not occur in a comparable subgroup of AFL patients, supporting the hypothesis that a more regular ventricular response results less impacting on the deep cerebral circle (8).

Altogether these rhythm-induced hemodynamic mechanisms (decreased mean cerebral blood flow with superimposed transient extreme hemodynamic events in the deep cerebral circle) might concur in the process of progressive cerebral damage differently leading to dementia in AF and AFL patients (**Figure 1**).

AUTHOR CONTRIBUTIONS

AS conceived the commentary. All authors contributed in manuscript writing.

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Multimorbidity, polypharmacy and inappropriate prescribing in elderly patients with atrial fibrillation: A report from the China Atrial Fibrillation Registry Study

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Background: Multimorbidity, polypharmacy and inappropriate prescribing is common in elderly patients worldwide. We aimed to explore the current status of multimorbidity, polypharmacy and the appropriateness of pharmacological therapy among elderly patients with atrial fibrillation (AF) in China.

Materials and methods: We randomly selected 500 patients aged 65 years or older from the China AF Registry study. Multimorbidity was defined as ≥2 comorbidities and polypharmacy was defined as ≥5 long-term prescribed drugs. Appropriateness of prescribing was evaluated using the Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria version 2. Patients' attitudes toward polypharmacy were evaluated by the Patients' Attitudes Towards Deprescribing (PATD) questionnaire.

Results: Among the 500 patients included (mean age 75.2 ± 6.7 years, 49.0% male), 98.0% had multimorbidity and 49.4% had polypharmacy. The prevalence of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) was 43.6% (n = 218) and 71.6% (n = 358), respectively. Traditional Chinese medicine attributed largely to PIMs. Anticoagulants were the most common PPOs. Many clinical factors increased the risk of PIMs and PPOs. However, polypharmacy increased the risk of PIMs (OR 2.70, 95%CI 1.78–4.11; $p < 0.0001$), but not PPOs. In addition, 73.7% patients with polypharmacy were willing to have one or more of their medications prescribed if advised by their doctor.

Conclusion: Multimorbidity and polypharmacy were highly prevalent in elderly patients with AF in China. A high prevalence of inappropriate prescribing was also observed. Therefore, much more attention should be paid to the serious health problem in the elderly population.

KEYWORDS

atrial fibrillation, elderly patients, multimorbidity, polypharmacy, inappropriate prescribing

Introduction

As a popular cardiovascular disease, atrial fibrillation (AF) poses significant burden to our society, and about five million new cases are diagnosed annually (1, 2). As is well known, the prevalence and incidence of AF increases significantly with age (3). Older adults often have multiple clinically significant comorbidities, for example, hypertension, hyperlipidemia, diabetes mellitus and coronary artery disease, with the need for multiple medications for symptoms and diseases control (4, 5). Therefore, polypharmacy, generally defined as administration of five or more concomitant drugs, is common in elderly patients with AF (6, 7). However, polypharmacy is associated with increased risk of inappropriate medication use, adverse drug reactions, drug-drug interactions, and poor clinical outcomes (8–10). In fact, patients' attitudes toward their medications exert a great impact on optimizing therapy (8).

Currently, data is limited as to the current status of polypharmacy and the appropriateness of pharmacological therapy among Asian patients with AF. In this study, we aimed to (1) describe the patterns of comorbidities and medications among elderly patients with AF; (2) identify potentially inappropriate medications (PIMs), potential prescribing omissions (PPOs) and the associated factors in this population; and (3) measure patients' attitudes toward prescribing.

Materials and methods

Study design and participants

This was a cross-sectional survey of 500 randomly selected participants of the China AF Registry (China-AF) study enrolled between 2011 and 2017. The rationale and design of the study have been previously published (11). In brief, it is an on-going, prospective, hospital-based registry study of AF patients in Beijing, China. Out-patients and in-patients from 19 tertiary and 12 non-tertiary hospitals were enrolled. All the enrolled patients had AF documented via either ECG or Holter within the past 6 months. Patients with transient and reversible AF, life expectancy less than 1 year, and those diagnosed with rheumatic heart disease were excluded from the study. All participants were managed by their local physicians or general practitioners during follow up.

Participants were eligible for inclusion in this survey if they were aged 65 years or older, and did not have moderate or severe cognitive impairment. We randomly selected eligible individuals from the pool of patients registered in the China-AF study using a computer-generated random number method.

The China-AF study was reviewed and approved by the Ethics committee of Beijing Anzhen Hospital. All patients provided their written informed consent to be followed up and contacted for future sub-studies. We obtained a separate ethic approval from the same hospital for this study. Randomly selected participants were contacted and provided additional verbal consent to be involved in this sub-study for further information collection.

Data collection and measurement

Key data elements like demographic and socioeconomic characteristics, medical conditions and medications related to AF were collected by trained cardiologists and research coordinators from medical records and interviews with patients at the time of enrollment, and updated every 6 months. Further information of general comorbidities and medication use for this analysis were collected via participant self-report during sampling investigation. Recorded medications included all over-the-counter, prescription and herbal/complementary medicines with long-term use (≥1 month). Similar to previous studies (6, 12), we defined polypharmacy as ≥5 long-term prescribed drugs and multimorbidity as 2 or more long-term health conditions (≥3 months).

Inappropriate prescribing encompasses PIMs and PPOs. We used the Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria version 2 to evaluate the appropriateness of prescribing (13, 14). The criteria, including 80 STOPP items and 34 START items, are widely used to screen PIMs and PPOs respectively (13). And the screening tool has

been translated and adapted from English into several languages to facilitate the application worldwide (15, 16).

For our study population and setting, we made two modifications to the STOPP/START tool. Firstly, we added a condition for START criteria A1: Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic AF with high-risk of stroke. High risk patients were defined by a CHA2DS2-VASc score (one point each for hypertension, heart failure, diabetes mellitus, vascular disease, age between 65 and 74 years, female sex; two points each for prior stroke/transient ischemic attack/thromboembolism and age ≥75 years) ≥2 in male and ≥3 in female (17). Secondly, because of insufficient evidence of traditional Chinese medicine (TCM) in the management of AF, we defined the use of TCM for AF as PIMs, referred to the STOPP criteria "drugs without an evidence-based clinical indication" (18).

We used the Patients' Attitudes Towards Deprescribing (PATD) questionnaire to measure patients' attitudes and beliefs toward their medicines and potential deprescribing (19). And "deprescribing" is referred as appropriate cessation or reduction of medications to optimize medication regimens (20). In consideration of different acceptance of medication and surrounding beliefs between polypharmacy and non-polypharmacy individuals, the PATD questionnaire was administrated only in participants who were currently taking more than five medications. The questionnaire was originally developed and validated in Australia. In our study, it was translated into the Chinese (with permission from PATD authors) by three bilingual investigators. The translated version was then piloted in 50 older adults to ensure that the wording and content was appropriate for the population and setting.

Statistical analysis

Categorical variables were reported as frequencies and percentages. And continuous variables were expressed as mean ± standard deviation or medians with interquartile range (IQR), as appropriate. To observe the patterns of polypharmacy and PIMs/PPOs, patients were stratified by age (65–69 years, 70–74 years, 75–79 years, and ≥80 years) and number of comorbidities. The trend was tested using trend Chi-square tests.

Multivariable logistic regression was performed to identify independent risk factors associated with PIMs/PPOs. Apart from variables that were significant in the univariate analysis, we also adjusted for variables with potential influence, regardless of their statistical significance at univariate analysis. Potential confounders included age, sex, hospital level, AF type, education, health insurance coverage, cardiovascular disease, endocrine disease, previous bleeding and systemic embolism. For the first 10 questions of PATD questionnaire, participants who "agreed" or "strongly agreed" were grouped together and analyzed against those responding "unsure," "disagree" or "strongly disagree." All data was processed using SPSS (version 21.0; SPSS Inc., Chicago, IL, United States. P-value < 0.05 was considered statistically significant.

Results

Participant characteristics

Characteristics of randomly selected participants were shown in **Table 1**. The mean age was (75.2 ± 6.7) years, and 49.0% of the participants were men. Among the participants, 249 (49.8%) had persistent AF and 353 (70.6%) were high school or college educated. The vast majority of participants (96.8%) were totally or partially covered by medical insurance.

Burden of comorbidities

Cardiovascular conditions accounted for the largest burden of comorbidities (86.0%), followed by endocrine conditions (60.8%) and musculoskeletal conditions (23.8%) (**Figure 1**). The most common cardiometabolic comorbidities were hypertension (74.8%), hyperlipidemia (43.0%), diabetes mellitus (28.8%), coronary artery disease (27.8%), congestive heart failure (17.6%), and stroke/transient ischemic attack/peripheral embolism (18.0%). Almost all participants (98.0%) had at least one comorbidity in addition to AF, 32.6% had five or more medical conditions and 1.4% had 10 or more. The median number of comorbidities was 4 (IQR 2–5).

TABLE 1 Demographic and clinical characteristics of enrolled patients (N = 500).

Characteristics	n (%)
Age (years)*	75.2 ± 6.7
Male	245 (49.0)
Education	
Did not complete high school	147 (29.4)
Completed high school	228 (45.6)
College educated	125 (25.0)
Health insurance coverage	
Total	47 (9.4)
Partially	437 (87.4)
None	16 (3.2)
Hospital level	
Tertiary	363 (72.6)
Non-tertiary	137 (27.4)
Type of atrial fibrillation	
Paroxysmal atrial fibrillation	251 (50.2)
Persistent atrial fibrillation	249 (49.8)

*Mean ± standard deviation.

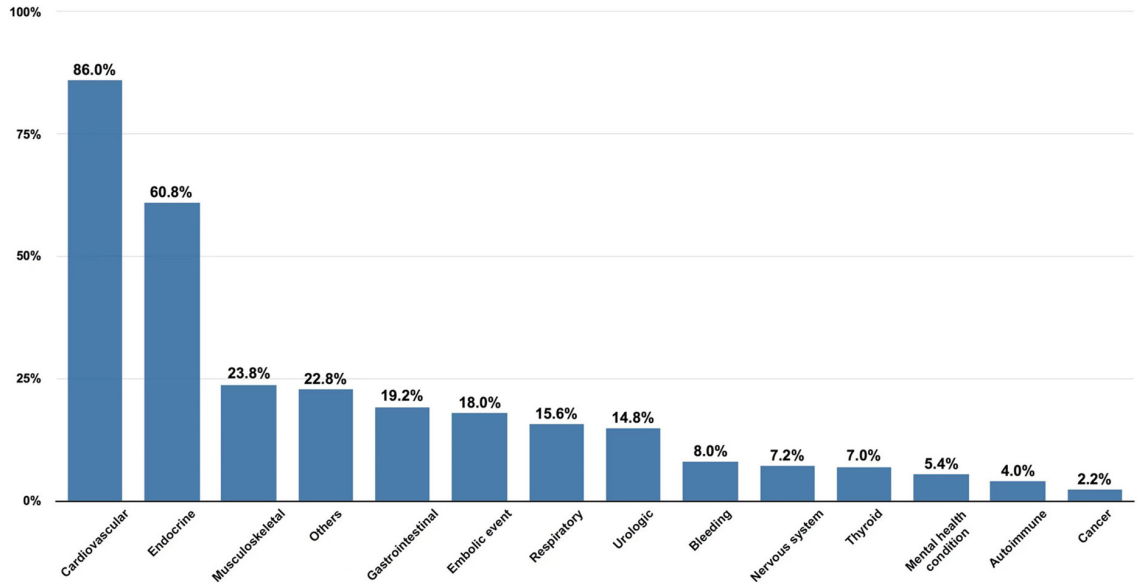

FIGURE 1
Prevalence of comorbidities in participants. Autoimmune: systemic lupus erythematosus, Sjögren's syndrome, psoriatic arthritis, rheumatoid arthritis and Takayasu's arteritis; Bleeding: a history of bleeding with clinical symptoms significantly; Cancer: all kinds of malignant tumors; Cardiovascular: atherosclerosis, arrhythmia other than atrial fibrillation, coronary artery disease, congestive heart failure, hypertension, cardiomyopathy, peripheral arterial disease, deep vein thrombosis; Endocrine: diabetes mellitus, hyperlipidemia, hyperuricemia, hyperhomocysteinemia, gout and adrenal disease; Gastrointestinal: chronic gastritis, ulcer disease, gastroesophageal reflux disease, Crohn's disease, ulcerative colitis, hepatobiliary calculus, liver dysfunction and cirrhosis; Musculoskeletal: spondyloarthritis, fibromyalgia, osteoarthritis, osteoporosis and osteopenia; Nervous system: dementia, Parkinson's disease, Alzheimer's disease, epilepsy, vertigo, migraine and peripheral neuropathy; Others: anemia, implantation of cardiac implantable electronic devices, chronic pain, chronic infectious disease and gynecological disease; Mental health condition: depression, anxiety, phobias, bipolar disorder and sleep disorder; Respiratory: asthma, chronic bronchitis, emphysema, chronic obstructive pulmonary disease chronic rhinitis, allergic rhinitis, obstructive sleep apnea and pulmonary embolism; Embolic event: a history of stroke, transient ischemic attack or systemic embolism; Thyroid: hyperthyroidism and hypothyroidism; Urologic: chronic kidney disease, urolithiasis and benign prostatic hyperplasia.

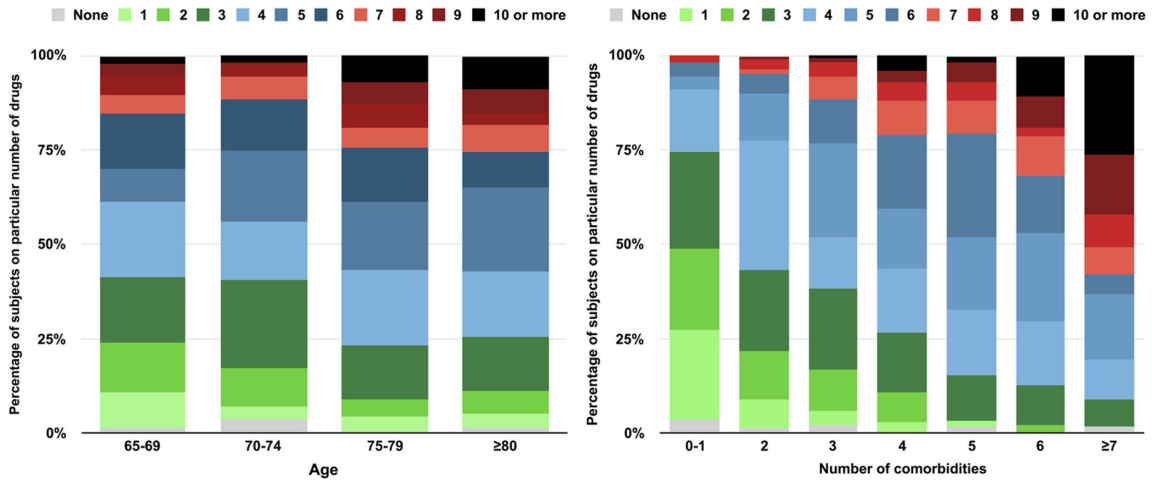

FIGURE 2
Number of medications taken by participants stratified by age and number of comorbidities.

Polypharmacy

The median number of concomitant medication types and tablets/capsules taken daily was 4 (IQR, 3–6) and 8 (IQR, 4–13). About half of the patients (49.4%) received five or more different types of medications (polypharmacy). The number of medications increased significantly with age ($p < 0.05$) and comorbidities ($p < 0.001$). Polypharmacy was present in 38.8, 44.1, 56.7, and 57% of participants aged 65–69, 70–74, 75–79 years, and aged ≥80 years respectively, and from 9.1 to 48.0%, 66.1 and 80.7% in patients with 0–1, 3, 5, and ≥7 comorbidities (Figure 2).

The most common used drugs were β-blockers (55.4%), followed by statins (47.8%) and angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists (ACEIs/ARBs, 37.8%). Oral anticoagulant agents were used in 41.6% of participants (32.2% on warfarin and 9.4% on non-vitamin K antagonist oral anticoagulants). More than a third of participants were taking TCM which was prescribed for symptom relief or an alternative for anticoagulants (Table 2).

TABLE 2 Distribution of most commonly used drugs of enrolled patients ($N = 500$).

Drug class	n (%)
β-blockers	277 (55.4)
Statins	239 (47.8)
Traditional Chinese medicine	193 (38.6)
ACEIs/ARBs	189 (37.8)
Aspirin	186 (37.2)
Warfarin	161 (32.2)
Calcium channel blockers	129 (25.8)
Hypoglycemic drugs	98 (19.6)
Nitrates	98 (19.6)
Diuretics	63 (12.6)
Class IIb/IIIa antiarrhythmic drugs	61 (12.2)
Digoxin	52 (10.4)
NOACs	47 (9.4)
Antiplatelet agents other than aspirin	45 (9.0)

ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists; NOACs, non-vitamin K antagonist oral anticoagulants.

Inappropriate prescribing (potentially inappropriate medications and potential prescribing omissions)

According to the STOPP criteria, a total of 256 PIMs events were identified, and PIMs use occurred in 43.6% of participants. Moreover, 38.4, 2.8, and 2.4% were prescribed one, two, and three PIMs, respectively. No patient was prescribed four or more PIMs (Table 3). The most frequent PIM used was TCM, and the rate was as high as 38.6% in all enrolled patients, which also account for 75.3% of all PIMs events (Supplementary Table 1).

According to the START criteria, a total of 637 PPOs events were identified, and the prevalence of PPOs was 71.6%. One, two, three, and four or more PPOs were identified in 35.2, 22.2, 9.6, and 4.6% of participants, respectively (Table 4). Over half (58.1%) of high-risk participants did not receive adequate anticoagulant therapy. Of the 197 participants with systolic heart failure, 124 (62.9%) were not taking ACEIs/ARBs. Similarly, statins were not prescribed in 69 out of 189 (36.5%) participants with an indication for lipid-lowering therapy. And β-blockers were also underused (Supplementary Table 2).

Factors associated with potentially inappropriate medications and potential prescribing omissions

After adjustment for potential confounders, the following factors were found to be independently associated with PIMs: education level [college education: odds ratio (OR) 2.11, 95% confidence interval (CI) 1.16–3.85; $p = 0.04$], paroxysmal AF (OR 1.58, 95%CI 1.02–2.46; $p = 0.04$), gastrointestinal disease (OR 1.78, 95%CI 1.09–2.92; $p = 0.02$), mental health condition (OR 4.38, 95%CI 1.54–12.50; $p < 0.001$), and polypharmacy (OR 2.70, 95%CI 1.78–4.11; $p < 0.001$) (Table 5).

Independent predictors of PPOs were age over 75 years (OR 1.68, 95%CI 1.04–2.70; $p = 0.03$), non-tertiary hospital management (OR 5.55, 95%CI 2.74–11.24, $p < 0.001$), paroxysmal AF (OR 2.26, 95%CI 1.35–3.76, $p = 0.001$), history of cardiovascular diseases (OR 4.90, 95%CI 2.55–9.42; $p < 0.0001$), and history of bleeding (OR 3.23, 95%CI 1.14–9.20; $p = 0.03$). No significant association was observed between polypharmacy and PPOs (OR 1.03, 95%CI 0.63–1.68; $p = 0.90$) (Table 5).

Attitudes toward deprescribing

The PATD questionnaire was administrated to 247 participants with polypharmacy, and the response was presented in Figure 3. 61.0% of participants agreed that they were taking a large number of medications (Question 1) and 50.6% reported to be uncomfortable with current number of medications (Question 2). Approximately three quarters (73.7%) of participants agreed or strongly agreed that they would be willing to have one or more of their medications prescribed if advised by their doctor (Question 4). Experiencing a side-effect and financial burden as a consideration for deprescribing were reported by 25.5 and 32.0% of participants (Question 9 and 10). At the meantime, most participants (76.1%) believed the medications they were taking were necessary (Question 3) and 42.5% were willing to accept taking more medications for their health conditions

TABLE 3 Distribution of PIMs between different age groups according to the STOPP criteria.

Age group	Patients number	Median number of medications (IQR)	Total PIMs events, n	≥1 PIMs *n* (%)	1 PIM n (%)	2 PIMs n (%)	3 PIMs n (%)	≥ 4 PIMs n (%)
65–69	129	4 (3–6)	54	48 (37.2)	43 (33.3)	4 (3.1)	1 (0.8)	0 (0.0)
70–74	111	4 (3–6)	52	50 (45.0)	48 (43.2)	2 (1.8)	0 (0.0)	0 (0.0)
75–79	111	5 (4–6)	66	54 (48.6)	46 (41.4)	4 (3.6)	4 (3.6)	0 (0.0)
≥80	149	5 (3–7)	84	66 (44.3)	55 (36.9)	4 (2.7)	7 (4.7)	0 (0.0)
Total	500	4 (3–6)	256	218 (43.6)	192 (38.4)	14 (2.8)	12 (2.4)	0 (0.0)

IQR, interquartile range; PIMs, potentially inappropriate medications; STOOP, screening tool of older people's prescriptions.

TABLE 4 Distribution of PPOs between different age groups according to the START criteria.

Age group	Patients number	Median number of medications (IQR)	Total PPOs events, n	≥1 PPOs n (%)	1 PPO n (%)	2 PPOs n (%)	3 PPOs n (%)	≥4 PPOs n (%)
65–69	129	4 (3–6)	110	75 (58.1)	48 (37.2)	21 (16.3)	4 (3.1)	2 (1.5)
70–74	111	4 (3–6)	135	75 (67.5)	39 (35.1)	17 (15.3)	14 (12.6)	5 (4.5)
75–79	111	5 (4–6)	151	91 (82.0)	46 (41.4)	32 (28.8)	11 (10.0)	2 (1.8)
≥80	149	5 (3–7)	241	117 (78.5)	43 (28.9)	41 (27.5)	19 (12.7)	14 (9.4)
Total	500	4 (3–6)	637	358 (71.6)	176 (35.2)	111 (22.2)	48 (9.6)	23 (4.6)

IQR, interquartile range; START, screening tool to alert to right treatment; PPOs, potential prescribing omissions.

(Question 7). The maximum ideal number of medications was reported in 30.8% for 8 tablets/capsules taken daily, 25.6% for 12 and 21.1% for 16 (Question 13) (**Supplementary Table 3**).

Discussion

In this study, we found that multimorbidity was present in almost all older adults with AF. Nearly half of the participants had polypharmacy and both over- and under-treatment were identified in this population. More than half patients did not receive proper anticoagulant therapy. ACEIs/ARBs, β-blockers, and statins were also underused according to the STOPP/START criteria. However, agents without sufficient clinical indications were commonly used. About three quarters of participants with polypharmacy expressed the willingness to stop one or more medications under the guidance of the clinician.

We confirmed multimorbidity was common in elderly AF patients, and the rate was as high as 98.0%. Indeed, multimorbidity prevalence in AF was ranged from 69.5 to 98%, for different study setting and population (21–23). A Swedish study of 272186 AF patients reported 69.5% prevalence of at least one other comorbidity (21). A study in Belgium reported that 92% of patients with AF had 3 or more comorbidities (22). A study in the United States using the data from National Health and Wellness survey (NHWS) found that 98% of participants with AF had at least one additional comorbidity (23). Generally, the number of comorbidities increases with age in the older population (24). And in our study the mean age of the AF patients was 75.2 years old.

Moreover, we identified the general comorbidity pattern and drew a relatively comprehensive picture of the total disease burden in the elderly AF patients in China, which would help to improve treatment and health outcomes. The incidence of cardiovascular diseases other than AF was 86.0%, which exerted the biggest comorbidity burden in our population, and hypertension was the most prevalent comorbidity. In fact, hypertension is closely associated with the development of AF (25). Unlike with studies from western countries (23, 26), we found that the incidence of non-cardiometabolic conditions was low in our study.

Polypharmacy is becoming increasingly common in clinical practice due to the aging society and the high burden of comorbidities (27, 28). Indeed, multimorbidity acts as a driver of polypharmacy. In patients with high morbidity, the proportion of polypharmacy is also high (29). The prevalence of polypharmacy was 49.4% in our study. Previous studies have reported rates of polypharmacy in 40–77% of patients with AF, with varying prescription patterns and inclusion and exclusion criteria (6, 12, 30). The potential harms of polypharmacy have been widely reported, including inappropriate prescribing, increased risk of adverse drug events and poor clinical outcomes (8–10, 31). Unfortunately, polypharmacy may bring unique risk in older adults with AF. Several studies found that polypharmacy was an independent risk factor for bleeding and thromboembolic events in patients with AF (6, 12).

Inappropriate prescribing, including PIMs and PPOs, was also prevalent in our study population. Almost half of our enrolled participants were taking at least one PIMs, such as

TABLE 5 Multivariable analysis of clinical factors associated with PIMs and PPOs.

Factors	PIMs			PPOs		
	All patients n/N (%)	Adjusted OR (95%CI)	*P-Value*	All patients n/N (%)	Adjusted OR (95%CI)	*P-Value*
Age						
≥75	120/260 (46.2)	1.17 (0.77–1.78)	0.47	208/260 (80.0)	1.68 (1.04–2.70)	0.03
65–74	98/240 (40.8)	1.00		150/240 (62.5)	1.00	
Gender						
Female	114/255 (44.7)	1.05 (0.70–1.59)	0.81	180/255 (70.6)	0.80 (0.50–1.30)	0.37
Male	104/245 (42.4)	1.00		178/245 (72.7)	1.00	
Hospital level						
Non-tertiary	53/137 (38.7)	0.84 (0.50–1.42)	0.52	123/137 (89.8)	5.55 (2.74–11.24)	<0.001
Tertiary	165/363 (45.5)	1.00		235/363 (64.7)	1.00	
Health insurance coverage						
Total	24/47 (51.1)	1.19 (0.58–2.43)	0.89	34/47 (72.3)	1.04 (0.23–4.70)	0.97
Partially	189/437 (43.2)	1.11 (0.29–4.30)		313/437 (71.6)	0.94 (0.26–3.39)	
None	5/16 (31.3)	1.00		11/16 (68.8)	1.00	
Education						
College educated	67/125 (53.6)	2.11 (1.16–3.85)	0.04	86/125 (68.8)	0.84 (0.45–1.56)	0.70
High school educated	100/228 (43.9)	1.58 (0.95–2.63)		154/228 (67.5)	0.74 (0.36–1.50)	
Under high school	51/147 (34.7)	1.00		118/147 (80.3)	1.00	
AF type						
Paroxysmal	122/251 (48.6)	1.58 (1.02–2.46)	0.04	179/251 (71.9)	2.26 (1.35–3.76)	0.001
Persistent	96/249 (38.6)	1.00		179/249 (71.3)	1.00	
Catheter ablation*						
Yes	52/99 (52.5)	1.45 (0.86–2.44)	0.16	67/99 (67.7)	–	–
No	166/401 (41.4)	1.00		291/401 (72.6)	–	
Cardiovascular disease						
Yes	190/430 (44.2)	1.17 (0.63–2.20)	0.62	331/430 (77.0)	4.90 (2.55–9.42)	<0.001
No	28/70 (40.0)	1.00		27/70 (38.6)	1.00	
Endocrine disease						
Yes	138/304 (45.4)	1.10 (0.72–1.70)	0.66	217/304 (71.4)	0.77 (0.46–1.29)	0.32
No	80/196 (40.8)	1.00		141/196 (71.9)	1.00	
Previous bleeding						
Yes	18/40 (45.0)	1.09 (0.54–2.23)	0.81	34/40 (85.0)	3.23 (1.14–9.20)	0.03
No	200/460 (43.5)	1.00		324/460 (70.4)	1.00	
Previous systematic embolism						
Yes	35/90 (38.9)	0.64 (0.37–1.08)	0.09	75/90 (83.3)	1.60 (0.82–3.10)	0.17
No	183/410 (44.6)	1.00		283/410 (69.0)	1.00	
Respiratory disease †						
Yes	36/78 (46.2)	–	–	64/78 (82.1)	1.96 (0.97–3.96)	0.06
No	182/422 (43.1)	–		294/422 (69.7)	1.00	
Gastrointestinal disease*						
Yes	56/96 (58.3)	1.78 (1.09–2.92)	0.02	71/96 (74.0)	–	-
No	162/404 (40.1)	1.00		287/404 (71.0)	–	
Urologic disease						
Yes	41/74 (55.4)	1.58 (0.90–2.76)	0.11	64/74 (86.5)	1.83 (0.84–3.99)	0.13
No	177/426 (41.5)	1.00		294/426 (69.0)	1.00	

(Continued)

TABLE 5 (Continued)

Factors	PIMs			PPOs		
	All patients n/N (%)	Adjusted OR (95%CI)	*P-Value*	All patients n/N (%)	Adjusted OR (95%CI)	*P-Value*
Thyroid disease†						
Yes	17/35 (48.6)	–	–	19/35 (54.3)	0.47 (0.21–1.04)	0.06
No	201/465 (43.2)	–		339/465 (72.9)	1.00	
Psychological disease*						
Yes	22/27 (81.5)	4.38 (1.54–12.50)	<0.001	22/27 (81.5)	–	–
No	196/473 (41.4)	1.00		336/473 (71.0)	-	
Polypharmacy						
Yes	138/247 (55.9)	2.70 (1.78–4.11)	<0.001	186/247 (75.3)	1.03 (0.63–1.68)	0.90
No	80/253 (31.6)	1.00		172/253 (68.0)	1.00	
Multimorbidity						
≥2	201/445 (45.2)	1.19 (0.56–2.54)	0.66	332/445 (74.6)	1.88 (0.85–4.18)	0.12
0–1	17/55 (30.9)	1.00		26/55 (47.3)	1.00	

AF, atrial fibrillation; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions. *The factor was not taken into the multivariable analysis of PPOs. †The factor was not taken into the multivariable analysis of PIMs.

TCM. In fact, some TCMs were reported to have antithrombotic effect and interact with anticoagulant agents, for example, danshen (Salvia miltiorrhiza), danshen (Salvia miltiorrhiza), Asian ginseng (Panax ginseng) and so on (18, 32). Concomitant use of TCM would increase the risk of bleeding. Thus, clinicians may need to specifically ask about TCM use before prescribing anticoagulants.

Currently, anticoagulant therapy is recommended among AF patients with high or moderate risk of stroke (17). In this study, 90.8% of participants had an indication for anticoagulant therapy, but only 41.9% were prescribed these medications (35.5% on warfarin and 6.4% on NOACs). This proportion was similar to the number we observed in our previous China-AF sub-study (33). Although great improvement in anticoagulant usage has been achieved in recent years, the gap is still large between clinical practice and guideline recommended therapy in China (33, 34). As stated in our previous study (33), There are some reasons for the underuse of anticoagulants. First, the high risk of bleeding restricts use of anticoagulants in the elderly. Second, patient education and monitoring are inadequate, which impairs the clinicians from prescribing anticoagulants and patients to adhere to therapy. Compared with warfarin, the rate of NOACs was much lower, and the high cost of NOACs may be the reason, because NOACs are unaffordable for the vast majority of patients in China. Meanwhile, ACEIs/ARBs, β-blockers and statins were the most common PPOs in this study, which was consistent with prior data (34). It indicated that the importance of cardiovascular risk factor modification is often neglected. Thus, integrated care is in urgent need in the management of AF patients.

We identified that polypharmacy as well as several medical conditions, such as gastrointestinal disease and mental health condition, increased the risk of PIMs. This may explain the common overprescribing of drugs in specific conditions, such as long-term benzodiazepine use. On the other hand, it also indicated that increased complexity of the disease can lead to inappropriate prescribing (35). Furthermore, PIMs were more common in patients with high education level. The possible reason may be that patients with high education level always have good economic conditions, and they prefer to take TCM as complementary and alternative medicine. In addition, we observed that polypharmacy could not decrease the risk of PPOs. By reviewing the most commonly prescribed PIMs/PPOs, we assumed that the occurrence of PPOs (including anticoagulants, ACEIs/ARBs, etc.) might result in worse clinical outcomes than PIMs (like TCM) in older AF patients. Therefore, an evidence-based drug therapy but within limited number of concomitant medications is vital for this population. Single-pill combination may be a good solution for all the questions.

Inappropriate medication use in older patients is common, which indicates deprescribing is not happening as often as it should. Approximately three quarters of our participants with polypharmacy were willing to have one or more of their medications prescribed if their doctor said it was possible. In fact, deprescribing involves an implicit partnership between the doctor and the patient (36). Not only in China, older individuals in the other countries are also eager to undertake deprescribing, especially when they have a large number of medications, experience side effects or feel some medications are unnecessary (36–38). A meta-analysis of 40 studies and 10,816 participants

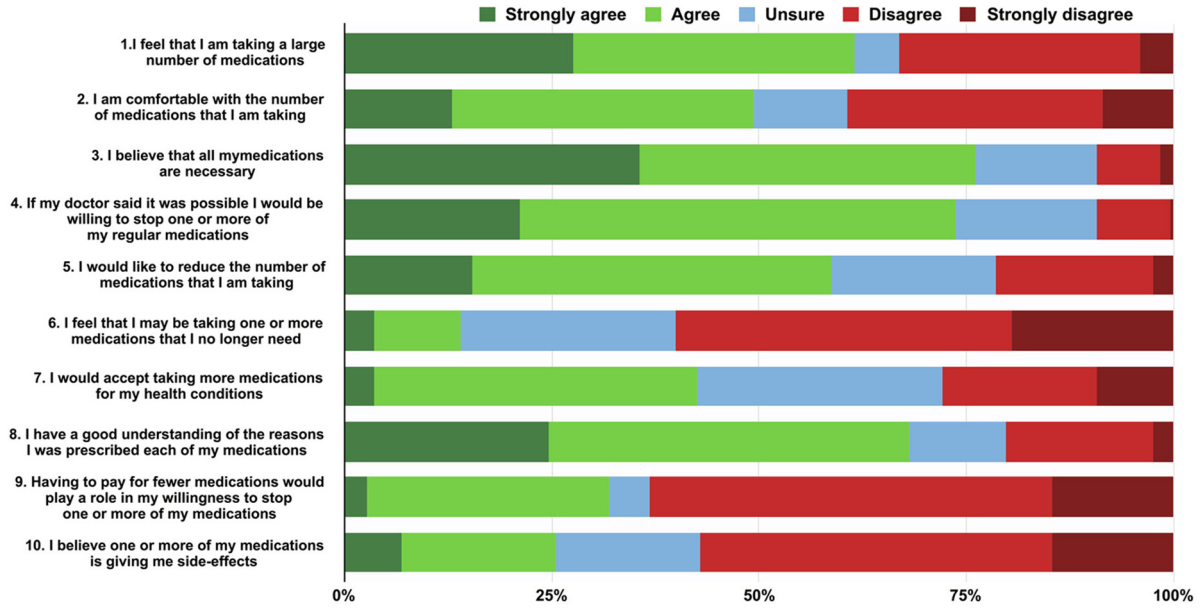

FIGURE 3
Participants responses to the PATD (patients' attitudes toward deprescribing) questionnaire (questions 1–10).

found that the proportion of patients who agreed or strongly agreed with deprescribing was as high as 84% (39).

There are many factors influencing the patients' attitudes toward medications, such as insurance coverage status and physician trust (40). Our data suggested that patients' attitudes and beliefs were important factors in prescribing and deprescribing. Given the complicated nature and associated risks of polypharmacy, it is important to optimize the medication regimen in older adults with AF. In particular, this is a population with high prevalence of cognitive decline (41), which can impact self-medication management. Good communication about the reasons for prescribing and/or deprescribing may help facilitate shared-decision making with older adults and their caregivers. Compared with taking multiple pills, polypill-based regimens have emerged as a promising strategy to increase patient adherence and reduce burden (42). New technologies such as mobile applications may also facilitate optimizing medications (43).

Limitations

There are some limitations of our study. First, the sample population was recruited from hospitals in Beijing, and the majority of them were from high-volume tertiary medical centers. This may produce biased participant selection, for patients who attend tertiary hospitals usually have a high social economic status and degree of education. Second, our data was patient self-reported, and the estimate of polypharmacy was not validated. Third, the STOPP/START criteria version 2 was published in 2014, and due to the expanding therapeutics evidence base, it could not include every detail on potentially inappropriate prescribing. Finally, the PATD questionnaire was originally designed and validated in Australia, while we conducted piloting in our population, we did not conduct a formal validation process.

Conclusion

Multimorbidity and polypharmacy were highly prevalent in elderly patients with AF in China. Inappropriate prescribing, including over- and under-treatment, was common in this population. Moreover, many patients expressed their willingness to deprescribing. Thus, drug regimens should be adjusted timely, to satisfy the need of the patients. In the future, much more attention should be paid to the elderly AF population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics committee of Beijing Anzhen Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a shared parent affiliation with several of the authors, XG, XD, CJ, SL, RT, CS, RY, DL, JD, and CM at the time of review.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.988799/full#supplementary-material

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A systematic review and meta-analysis of the safety and efficacy of left atrial substrate modification in atrial fibrillation patients with low voltage areas

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Background: The left atrial low-voltage areas (LVAs) are associated with atrial fibrosis; however, it is not clear how the left atrial LVAs affect the recurrence of arrhythmias after catheter ablation, and the efficacy and safety of the left atrial substrate modification based on LVAs as a strategy for catheter ablation of atrial fibrillation (AF) are not evident for AF patients with LVAs.

Methods: We performed a systematic search to compare the arrhythmia recurrence in AF patients with and without LVAs after conventional ablation and arrhythmia recurrence in LVAs patients after conventional ablation with and without substrate modification based on LVAs.

Result: A total of 6 studies were included, involving 1,175 patients. The arrhythmia recurrence was higher in LVA patients after conventional ablation (OR: 5.14, 95% CI: [3.11, 8.49]; $P < 0.00001$). Additional LVAs substrate modification could improve the freedom of arrhythmia in LVAs patients after the first procedure (OR: 0.30, 95% CI: [0.15, 0.62]; $P = 0.0009$). However, there was no significant difference after multiple procedures ($P = 0.19$). The procedure time (MD: 26.61, 95% CI [15.79, 37.42]; $P < 0.00001$) and fluoroscopy time (MD: 6.90, 95% CI [4.34, 9.47]; $P < 0.00001$) in LVAs patients with additional LVAs substrate modification were significantly increased compared to LVAs patients' without substrate modification. Nevertheless, there were no higher LVAs substrate modification-related complications ($P = 0.93$) between LVAs patients with and without additional LVAs substrate modification. In the subgroup analysis, the additional LVAs substrate modification reduced the risk of arrhythmia recurrence in LVAs patients during the follow-up time, which was 12 months (OR: 0.32, 95% CI (0.17, 0.58); $P = 0.002$), and box isolation (OR: 0.37, 95% CI (0.20, 0.69); $P = 0.002$) subgroups, but the type of AF, follow up >12 months and homogenization

subgroups were not statistically significant. Trial sequential analysis shows conclusive evidence for the LVAs ablation.

Conclusion: This study has shown that LVAs could improve the risk of arrhythmia recurrence in AF patients after conventional ablation. And additional LVAs substrate modification after conventional ablation could increase the freedom of arrhythmia recurrence in LVAs patients. Interestingly, the box isolation approach appeared more promising.

Systematic review registration: [http://www.crd.york.ac.uk/prospero], identifier [CRD42021239277].

KEYWORDS

atrial fibrillation, catheter ablation, low-voltage areas, recurrence, meta-analysis

Introduction

Catheter ablation is an effective strategy for rhythm control of atrial fibrillation (AF) (1, 2). The procedure of pulmonary vein isolation (PVI) is the cornerstone of catheter ablation for all types of AF. However, the PVI alone has reported recurrence rates as high as 40% within one year (3). This may be because triggers are not limited in pulmonary veins but also appear in other left atrial substrates, especially in persistent AF (4). Previous studies have found that the left atrial low-voltage areas (LVAs), as left atrial substrates, are independent predictors of recurrence after PVI (5–7). In addition, LVAs have been reported to be associated with atrial fibrosis which can lead to conduction slowing and arrhythmia, as verified by late gadolinium enhancement (LGE) magnetic resonance imaging (8–10). Therefore, in order to improve freedom for AF arrhythmia, the voltage mapping-guided LVAs substrate modification could be an established ablation strategy to eliminate the LVAs arrhythmic substrate. It has been shown that left atrial substrate modification based on LVAs has superb application prospects in many previous studies (11–14). However, some studies have found inconsistent results (15–17).

The systematic review and meta-analysis synthesize the limited data regarding the left atrial substrate modification by targeting LVAs ablation, and attempt to determine whether this ablation strategy is more superior in LVAs patients.

Methods

The systematic review and meta-analysis was conducted using the guidelines described in the Preferred Reporting Items for Systematic.

Reviews and Meta-Analysis (PRISMA) (18), and registered with International Prospective Register of Systematic Reviews (PROSPERO).

Search strategy

The PubMed, Embase, Web of Science, the Cochrane Library, the China National Knowledge Infrastructure (CNKI), Wanfang, and VIP Databases were searched from inception to 1 April, 2021. Search terms included: ("AF" OR "atrial fibrillation") AND ("ablation" OR "catheter ablation" OR "radiofrequency ablation") AND ("low-voltage areas" OR "low-voltage zones" OR "low-voltage substrate" OR "LVAs" OR "LVZs" OR "LVS"). We performed a systematic search using population, intervention, comparison, outcomes, study (PICOS) criteria to retrieve all relevant studies. The population of interest included patients with AF who underwent voltage mapping, and the intervention was additional left atrial substrate modification by targeting LVAs. Comparison was performed between study (conventional ablation + LVAs substrate modification) versus control (conventional ablation). The primary outcome was recurrence of arrhythmia, including atrial tachycardia (AT) or AF, and the secondary outcomes contain procedural complications, procedure time, and fluoroscopy time. Studies included randomized controlled trial (RCT) and other trials. Articles following predefined explicit criteria were used: (1) human study and published, (2) all patients performed the left atrial voltage mapping in study, (3) voltage mapping defined LVAs as mapping at sites with voltage <0.5 mV during sinus rhythm, (4) included with and without LVAs ablation in LVAs patients, (5) reported at least one clinical outcome. Exclusion criteria were: (1) conference abstract, (2) degree paper, (3) the study population was not grouped as described, (4) full text was unavailable.

Data extraction

Two investigators independently screened abstracts and full-text versions of all the studies, and all disagreements

were resolved via discussion. We created groups based on characteristics of patients. Patients without LVAs were defined as no-LVAs, LVAs patients with substrate modification were defined as LVAs-ablation, LVAs patients without substrate modification were defined as LVAs-non-ablation. The risk of bias of the randomized control trials was assessed using the Cochrane risk of bias tool, and the seven measures that were graded were as follows: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, (7) other bias. The risk of bias of a non-randomized study quality was assessed using the Newcastle-Ottawa Scale (NOS) quality assessment scale, and the eight measures that were graded were as follows: (1) representativeness of the cohort, (2) selection of the non-exposed cohort, (3) ascertainment of exposure, (4) outcome absence at start of study, (5) comparability of cohorts, (6) assessment of outcome, (7) adequacy follow-up time, (8) adequacy of follow up of cohorts.

Statistical analysis

Data analysis was performed using Review Manager (RevMan. Version 5.4. The Cochrane Collaboration, 2020) and Stata/IC 15.0. The Q test was used to test the heterogeneity: $P \geq 0.1$ and $I^2 < 50\%$ suggested homogeneity between studies, and if $P < 0.1$, $I^2 > 50\%$ suggested high heterogeneity between studies. To provide more reliable data the random effects model was used in all meta-analyses, and the sensitivity analysis of the index was performed to find the source of heterogeneity. The odds ratio (OR) was calculated and the CI was 95% for dichotomous variables and mean difference (MD), and 95% for continuous variables. P values were two tailed, and P values <0.05 were considered statistically significant. Continuous variables are not expressed as a mean and standard deviation in literature could be transformed by the formula.[1]

1 https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html

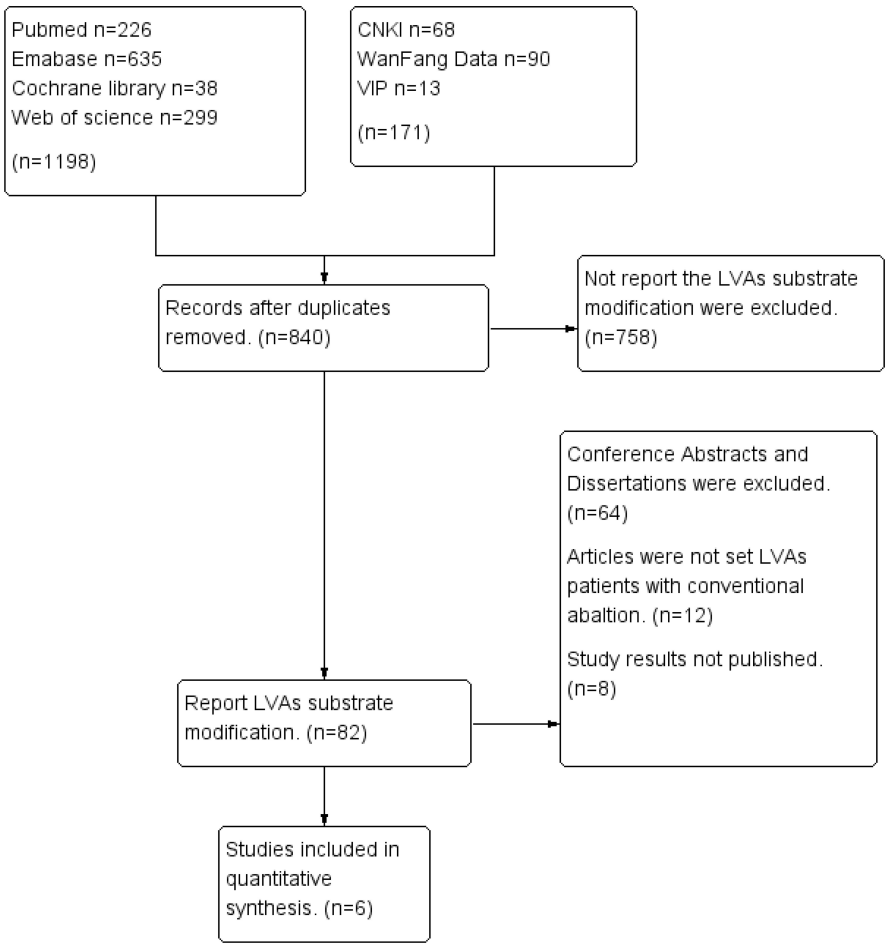

FIGURE 1
Study selection diagram.

TABLE 1 Characteristics of the included studies.

Study	Study design	Sample size, *n*		Age, y	Male, *n* (%)	Paroxysmal AF, *n* (%)	Persistent AF, *n* (%)	Long-standing persisitent AF, *n* (%)	Hypertension	Diabetes melltus	LAD (mm)	CHA2DS2-VASc	LVEF (%)	AF duration, mo
Rolf et al. (19)	Retrospective	no-LVAs	131	59 ± 9	96 (73%)	56 (43%)	75 (57%)	0	91 (75%)	17 (13%)	43 ± 6	NA	60 (55, 62)	66 (24, 110)
		LVAs-ablation	47	67 ± 8	25 (53%)	6 (22%)	41 (78%)	0	40 (85%)	12 (26%)	45 ± 8	NA	60 (50, 63)	35 (16, 90)
		LVAs-non-abaltion	26	67 ± 9	15 (58%)	9 (35%)	17 (65%)	0	23 (89%)	4 (15%)	43 ± 6	NA	57 (45, 65)	60 (33, 84)
Yamaguchi et al. (20)	Retrospective	no-LVAs	62	58 ± 10	48 (77%)	0	47 (76%)	15 (24%)	29 (27%)	4 (6%)	41 ± 5	1 (0∼2)	64 ± 8	NA
		LVAs-ablation	39	66 ± 7	24 (62%)	0	21 (54%)	18 (46%)	27 (69%)	6 (15%)	44 ± 6	2 (1∼3)	62 ± 13	NA
		LVAs-non-abaltion	16	60 ± 9	11 (69%)	0	14 (88%)	2 (13%)	13 (81%)	4 (25%)	43 ± 3	3 (1∼3)	64 ± 8	NA
Zhou et al. (22)	Prospective	no-LVAs	35	58.7 ± 10.6	20 (57%)	0	35 (100%)	0	23 (66%)	6 (17%)	37.3 ± 3.7	NA	63 ± 7	27.0 ± 7.3
		LVAs-ablation	34	60.4 ± 10.6	19 (56%)	0	34 (100%)	0	21 (62%)	6 (18%)	37.6 ± 4.6	NA	62 ± 6	28.2 ± 6.9
		LVAs-non-abaltion	29	60.5 ± 9.0	15 (52%)	0	29 (100%)	0	15 (52%)	7 (24%)	38.1 ± 4.4	NA	62 ± 7	28.9 ± 8.8
Zhou et al. (21)	Prospective	no-LVAs	96	61.0 (52.3∼66.8)	54 (56.3%)	96 (100%)	0	0	63 (65.63%)	17 (17.71%)	36 (34∼37)	NA	65 (57∼68)	27.0 ± 7.3
		LVAs-ablation	74	61.5 (56.8∼69.3)	53 (71.6%)	74 (100%)	0	0	49 (66.22%)	13 (17.57)	36 (34∼37.25)	NA	64 (58∼65)	28.2 ± 6.9
		LVAs-non-abaltion	73	60.0 (52.5∼68.0)	40 (54.8%)	73 (100%)	0	0	40 (54.79%)	18 (24.66)	35 (34∼37.5)	NA	65 (58∼66)	28.9 ± 8.8
Kumagai et al. (17)	Prospective	no-LVAs	61	60 ± 10	57 (93%)	0	20 (33%)	41 (67%)	NA	NA	44 ± 5	NA	59 ± 8	NA
		LVAs-ablation	33	65 ± 8	25 (76%)	0	11 (33%)	22 (67%)	NA	NA	46 ± 5	NA	61 ± 7	NA
		LVAs-non-abaltion	21	65 ± 10	14 (67%)	0	9 (43%)	12 (57%)	NA	NA	46 ± 5	NA	61 ± 8	NA
Masuda et al. (16)	Randomized	no-LVAs	336	67.8 ± 11.6	205 (61%)	336 (100%)	0	0	195 (58%)	51 (15%)	37 ± 6	2.4 ± 1.4	66 ± 9	6 (2, 35)
		LVAs-ablation	30	75.3 ± 7.2	9 (30%)	30 (100%)	0	0	20 (67%)	10 (33%)	40 ± 6	3.6 ± 1.2	64 ± 14	4 (2, 14)
		LVAs-non-abaltion	32	74.7 ± 8.0	9 (28%)	32 (100%)	0	0	16 (50%)	6 (19%)	38 ± 5	3.3 ± 1.3	65 ± 10	5 (2, 23)

LVAs, low voltage areas; AF, atrial fibrillation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

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TABLE 2 Detailed procedures of included trials.

Study	Rolf et al. (19)	Yamaguchi et al. (20)	Zhou et al. (22)	Zhou et al. (21)	Kumagai et al. (17)	Masuda et al. (16)
During the mapping of voltage	SR	SR	SR	SR	SR	SR
Definition of LVAs	>0.5 mV = healthy; 0.2 to 0.5 mV = diseased; <0.2 mV = likely scar tissue; ≥3 adiacent low-volatge point <0.5 mV	<0. 5 mV and covering >5% LA surface areas = LVA; <0.1 mV = scar areas.	<0.05 mV = scar areas; <0.5 mV = LVAs	<0.1 mV = scar areas; 0.1∼0.4 mV = LVAs; 0.4∼1.3 mV = transition areas; >1.3 mV = healthy myocardial areas	<0.5 mV and covering >5% LA surface areas = LVAs	<0.5 mV and covering >5 cm^2 = LVAs
Ablation strategy and LVAs ablation	PVI. Homogenization of LVAs or when not accomplished, linear lesions connect non-conducting tissues and other non-conducting anatomical structures travers target LVAs, or surround large LVAs.	PVI. Non-PV trigger ablation. SVC and CTI physcian's discretion. All LVAs ablated aiming at homogenization. Futher linear lesion to connect LVAs to anatomical obstacles.	PVI. Anterior LVAs ablated and connected to mitral valve annulus and pulmonary veins. Box iaolation the posterior LVAs.	PVI. Box isolation the LVAs.	PVI. Box isolation the posterior during AF. SVC isolation, CTI isolation, mitral isthums ablation and focal ablation where atrial arrhythmia induced. Box isolation LVAs to connect anatomical obstacles.	PVI. Homogoneously ablated LVAs and posterior LVAs could isolation by PVI, roof and bottom line.
Endpoint of the ablation	PVI: bidirectional conduction block and pace-and-ablate; LVAs: local electrograms, fragmentation, and capture loss; Linear lesion: confirmation of double potentials and analysis of activation sequence.	PVI: bidirectional conduction block; LVAs: homogenization of LVAs and electrogram voltage reduction >50%; LL: creation of double potentials or electrogram voltage reduction of >50%.	PVI: bidirectional conduction block. LVAs: no electrical conduction in all ablated LVAs.	PVI: bidirectional conduction block; box isolation LVAs: ablated to voltage<0.1 mV	PVI: bidirectional conduction block; box isolation the posterior: bidirectional conduction block; LVAs: lack of potential and loss of pacing capture.	PVI: bidirectional conduction block; LVAs: electrogram voltage reduction >50%; LL: bidirectional conduction block.
Monitor of arrhythmia recurrence	Serial 7-day-Holter ECGs at predischagre, 3, 6, and 12 months. Additional Holter or ECGs in case of symptoms.	Visit and ECGs at 2 week, 1 month, and every 3 month. 24-h Holter at 1, 3, and every 6 month.	Visit and ECG or 24 h-Holter at 1, 3, 6, and 12 month.	Visit at 1, 3, 6, 12 month and ECGs once a month within 3 months and Hoter once a month from 3 to 12 months postopeartively.	Monitor of arrhythmia recurrence every month and a questionnaire survey every 3 months. Visit at 3, 6, 12 months and then every 6 months thereafter. 7-day Holter at 6 and 12 months.	Visit and ECGs at 1, 3, 6, 9, and 12 months. 24 h-Holter at 6 and 12 months.
Definition of arrhythmia recurrence	Documented AT/AF > 30 s.	Documented atrial arrhythmia ≥30 s	Documented AT/AF > 30 s.	Documented AT/AF > 30 s.	Documented atrial arrhythmia >30 s.	Doucumented AF/atrial arrhythmia >30 s.
Definition of blanking period	3-month after the procedure.	3-month after the procedure.	3-month after the procedure.	3-month after the procedure.	3-month after the procedure.	3-month after the procedure.
Follow up time	Minimum of 12 months	Minimum of 9 months and end-up 36 months.	12 months	12 months	above 12 months	12 months

SR, sinus rhythm; LVAs, low voltage areas; PVI, pulmonary vein isolation; SVC, superior vena cava; CTI, cavotricuspid isthmus; LL, linear ablation; AF, atrial fibrillation; AT, atrial tachycardia; ECGs, electrocardiograms.

TABLE 3 Quality assessment of cohort study.

Study	Representativeness of the cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome absence at start of study	Comparability of cohorts	Assessment of outcome	Adequacy follow-up time	Adequacy of follow up of cohorts	Score
Rolf et al. (19)	*		*	*	*	*	*	*	7
Yamaguchi et al. (20)	*		*	*	*	*	*	*	7
Zhou et al. (22)	*	*	*	*	*	*	*	*	8
Zhou et al. (21)	*	*	*	*	*	*	*	*	8
Kumagai et al. (17)	*	*	*	*	*	*	*	*	8

Quality assessment of cohort study was evaluated by Newcastle-Ottawa Scale (NOS) quality assessment scale. All 5 cohort studies were high-quality. *Mean 1 point.

Trial sequential analysis

Trial sequential analysis (TSA) was performed to analyze the outcomes in order to calculate the required information size (RIS) and correct the risks of type I error. For dichotomous outcomes, the result is conclusive if the cumulative Z-value reaches the TSA threshold or the expected information value. The risk of type I error was maintained at 5% with a power of 80%, and the analysis was performed using the TSA program V.0.9.5.10 Beta.

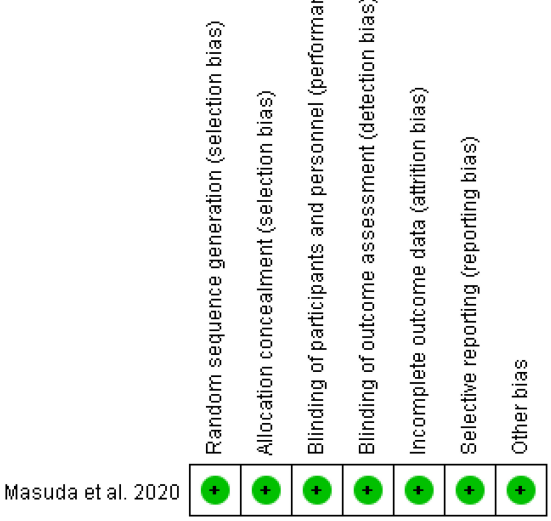

FIGURE 2
Quality assessment of RCT was evaluated by Cochrane risk of bias tool. The RCT was high-quality.

Results

Search result

We searched a total of 1,299 reports from all databases, and six studies (16, 17, 19–22) were finally included by excluding duplicates and browsing the abstracts and full text (**Figure 1**). Of these, two studies were retrospective studies, whose LVAs-non-ablation group was a historical control, three studies were prospective studies and one study was a randomized controlled study.

Study characteristics and study quality

The characteristics of baseline information for all literature are summarized in **Table 1**, and the analysis methods and control of potential confounding in the included studies are shown in **Supplementary Table 1**. A total of 1,175 patients, 712 paroxysmal AF patients and 224 paroxysmal AF patients with LVAs (31.46%), 463 non-paroxysmal AF patients and 230 non-paroxysmal AF patients with LVAs (49.68%), with 257 LVAs patients (with LVAs substrate modification) and 197 LVAs patients (without LVAs substrate modification) were included in the six studies. Other baseline information included gender, age, type of AF, comorbidity, left atrial diameter (LAD), CHA2DS2-VASc score, duration of AF, etc. The characteristics of the procedural information for all literature are summarized in **Table 2**. Procedural information included the definition of LVAs, procedure strategy, procedural endpoint, blanking period, follow-up survey, follow-up time, etc. The quality of assessment of included studies is shown in **Table 3** and **Figure 2**. One point was deducted because two retrospective studies (19, 20) of the non-exposed population and exposed population were not in the same cohort, and one point was deducted because five cohort

studies (17, 19–22) were not adjusted for the most important confounding factors in comparability of cohorts. The bias risk of assessment of RCT was judged to be low.

Arrhythmia recurrence

Arrhythmia recurrence is significantly higher in the LVAs group compared with the no-LVAs group in the conventional ablation group (OR: 5.14, 95% CI: [3.11, 8.49]; $P < 0.00001$). Heterogeneity among studies is not significant ($I^2 = 37\%$, $P = 0.16$; **Figure 3A**). Left atrial substrate modification based on LVAs reduce the arrhythmia recurrence in patients with LVAs (OR: 0.30, 95% CI: [0.15, 0.62]; $P = 0.0009$). There is a moderate degree of heterogeneity ($I^2 = 61\%$, $P = 0.03$, **Figure 3B**). There is no significant difference in arrhythmia recurrence after multiple procedures (LVAs-ablation group versus LVAs-non-ablation group) ($P = 0.19$, **Figure 3C**).

Procedural data

The occurrence of ablation complications between the LVAs-non-ablation group and LVAs-ablation group shows no statistical difference ($P = 0.93$, **Figure 4A**). Substrate modification is associated with higher procedure time (MD: 26.61, 95% CI [15.79, 37.42]; $P < 0.00001$) and higher fluoroscopy time (MD: 6.90, 95% CI [4.34, 9.47]; $P < 0.00001$). Heterogeneity among studies was not significant ($I^2 < 50\%$, $P \geq 0.1$) (**Figures 4B,C**).

Subgroup analysis

We planned several subgroup analyses in advance. The additional LVAs substrate modification reduced the risk of arrhythmia recurrence in LVAs patients whose a follow up time was 12 months (OR: 0.32, 95% CI (0.17, 0.58); $P = 0.002$) and box

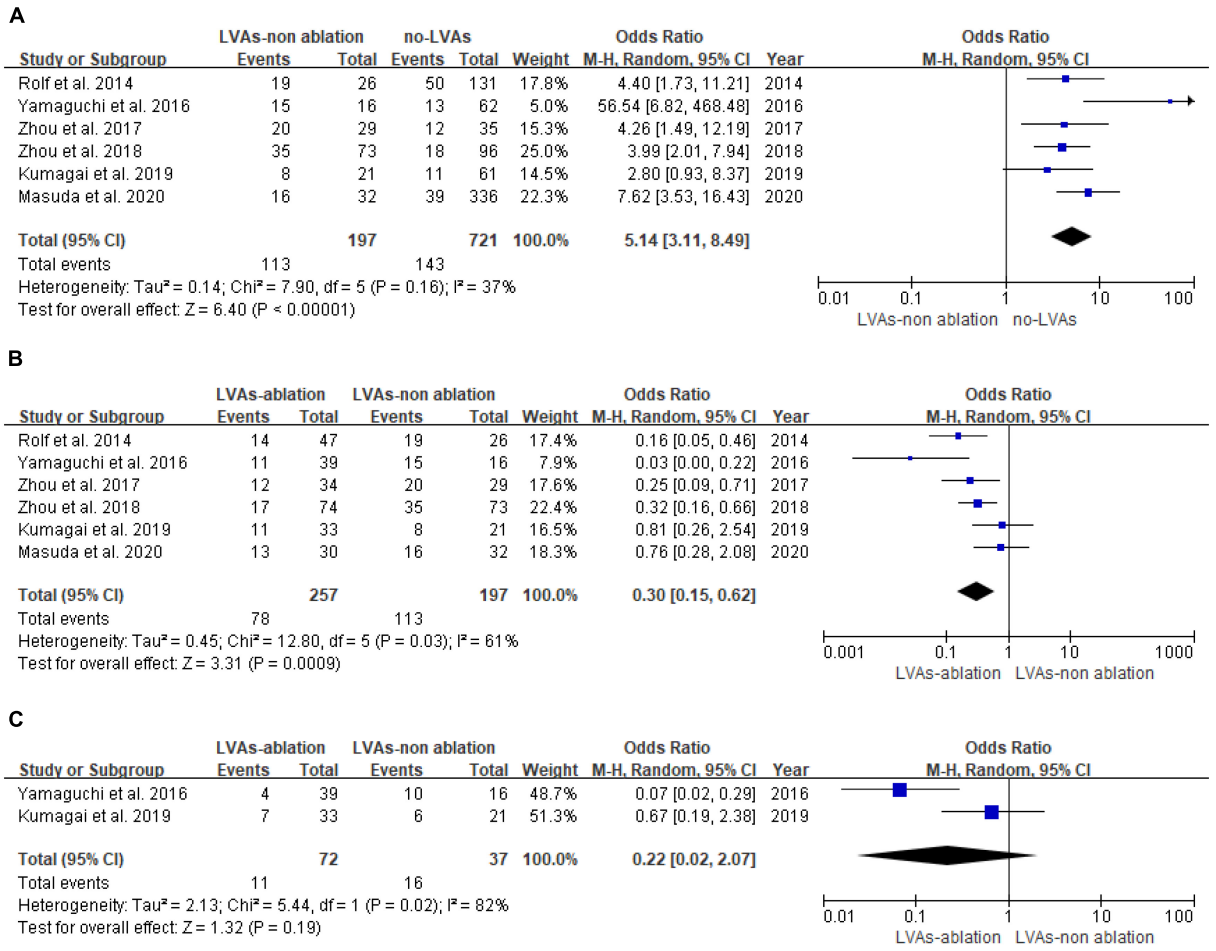

FIGURE 3
Forest plot of arrhythmia recurrence. **(A)** Recurrence of atrial fibrillation patients with or without LVAs after conventional ablation. **(B)** Recurrence of LVAs patients with or without LVAs substrate modification after first procedure. **(C)** Recurrence of LVAs patients with or without LVAs substrate modification after multiple procedures.

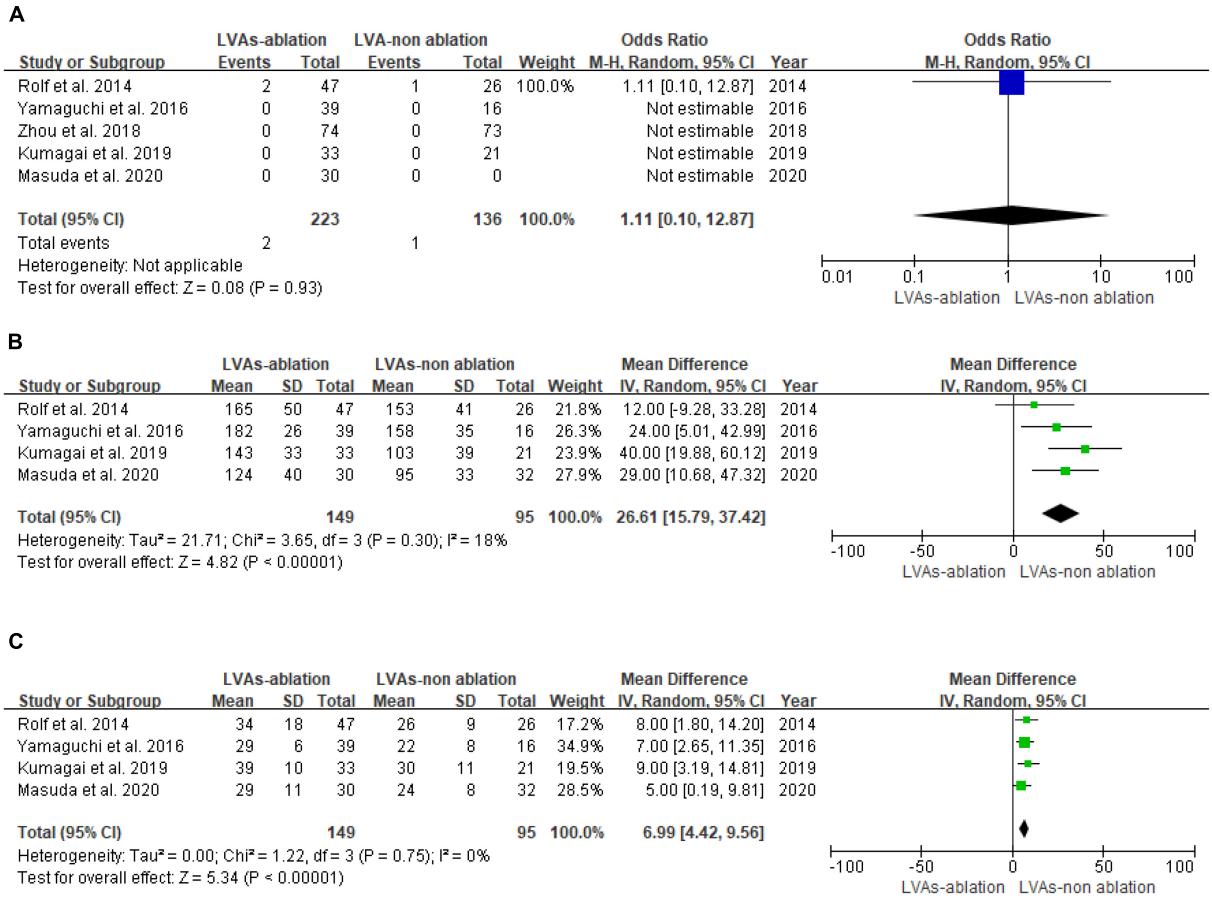

FIGURE 4
Forest plot of procedural data. **(A)** Complication of LVAs patients with or without LVAs substrate modification. **(B)** Procedure time of LVAs patients with or without LVAs substrate modification. **(C)** Fluoroscopy time of LVAs patients with or without LVAs substrate modification.

isolation (OR: 0.37, 95% CI (0.20, 0.69); $P = 0.002$) subgroups, but the type of AF, follow up >12 months, and homogenization subgroups were not statistically significant (Table 4).

Sensitivity analysis

Sensitivity analyses were conducted by excluding the included studies one by one. The pooled patients with LVAs underwent substrate modification of results that remained unchanged (Figure 5).

Trial sequential analysis

TSA software was used for trial sequential analysis. The relative risk reduction was 70%, and the incidence in the control arm was 57%. The results showed that the fourth item of the cumulative Z value crossed the required information size (RIS) value, suggesting that the total clinical efficacy of LVAs ablation in the treatment of AF patients with LVAs has definite evidence and that further research cannot reverse this finding (Figure 6).

Discussion

This meta-analysis evaluated 1,175 patients from 6 published original articles. To the best of our knowledge, this is the first meta-analysis to evaluate the safety and efficacy of left atrial substrate modification in atrial fibrillation patients with LVAs. In this meta-analysis, the results demonstrated that the recurrence of arrhythmia after ablation was significantly increased in patients with LVAs and additional LVAs ablation after PVI could prove to be effective and safe. However, the effectiveness was limited after multiple procedures. With left atrial substrate modification based on LVAs, the procedure time and fluoroscopy time were increased, but the complication rate was not increased. Compared with the homogenization of the LVAs, box isolation of the LVAs was a better ablation strategy to reduce the arrhythmia recurrence.

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TABLE 4 Subgroup analysis according to type of AF, follow-up time, type of procedure.

	No. of studies	I^2 (%	OR (95% CI)	*P* value
Total	6	61	0.30 (0.15, 0.62)	0.0009
Type of AF				
Paroxysmal AF	2	47	0.46 (0.20, 1.06)	0.07
Non-paroxysmal AF	3	76	0.22 (0.04, 1.08)	0.06
Paroxysmal AF + non-paroxysmal AF	1	NA	0.16 (0.05, 0.46)	0.0007
Follow-up time				
12 months	4	39	0.32 (0.17, 0.58)	0.002
>12 months	2	88	0.16 (0.01, 5.28)	0.31
Type of procedure				
Homogenization	3	80	0.18 (0.03, 0.96)	0.05
Box isolation	3	21	0.37 (0.20, 0.69)	0.002

Low-voltage areas as a mark of fibrosis

The mechanisms of AF are complex, including atrial remodeling (structural and electrical remodeling), autonomic nervous system dysfunction, genetic factors, and deregulated calcium homeostasis, etc. (23). Atrial fibrosis is the most predominant characteristic of atrial structural remodeling, linking with all the AF-related mechanisms. Furthermore, many studies have proved that atrial fibrosis is associated with AF recurrence after ablation (24–26). Likewise, many prior studies have demonstrated that patients with LVAs have higher risks of arrhythmia recurrence after ablation than those without LVAs (6, 7), which is similar to our present conclusion. In addition, atrial fibrosis and atrial LVAs have similar upstream factors, such as aging, sex, and atrial size, and the conduction velocity slowing areas are predominantly confined to LVAs, promoting the formation of reentrant (27).

The LGE derived from cardiac magnetic resonance (CMR) remains the gold standard for measuring atrial fibrosis. Oakes et al. examined 81 patients who underwent CMR imaging before the ablation and demonstrated a strong association between LGE and LVAs (28). Spragg et al. found that the LGE of scar imaging agreed with LVAs, and the sensitivity and specificity of LGE for identification of LVAs were 84 and 68% (29), respectively. Nevertheless, another study found some LGE areas were less co-localization with LVAs (30). It may be associated with other tissues that may contribute to reduce the voltage, such as fatty infiltration and amyloidosis.

Despite lack of clear consensus on voltage mapping to identify AF substrates, LVAs, using voltage mapping to describe the areas of scar, are proved to be surrogates for the atrial fibrosis (31–34). In other words, the wider the range of LVAs, the more severe atrial fibrosis and the higher the recurrence rate of arrhythmias. Consistent with the above reports, additional LVAs substrate modification could improve the freedom arrhythmia after conventional ablation.

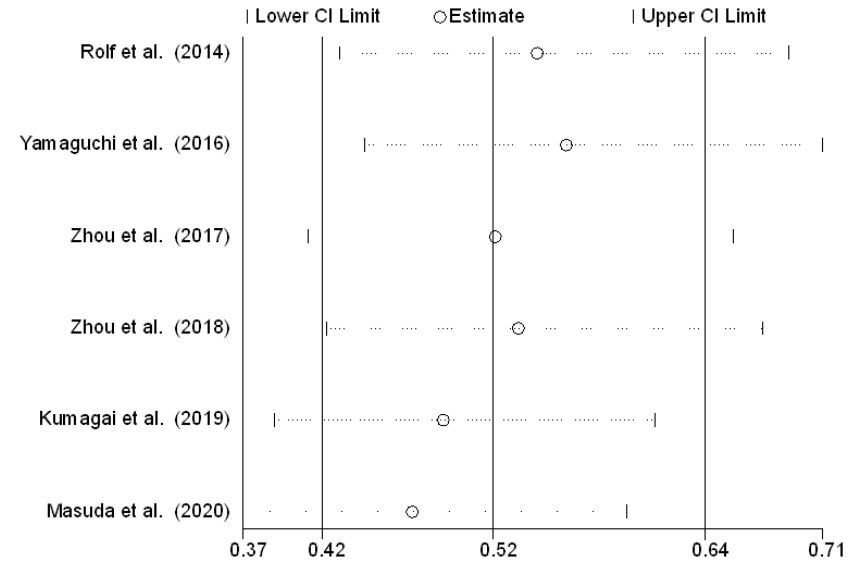

FIGURE 5
Sensitivity analysis of LVAs ablation in AF patients with LVAs.

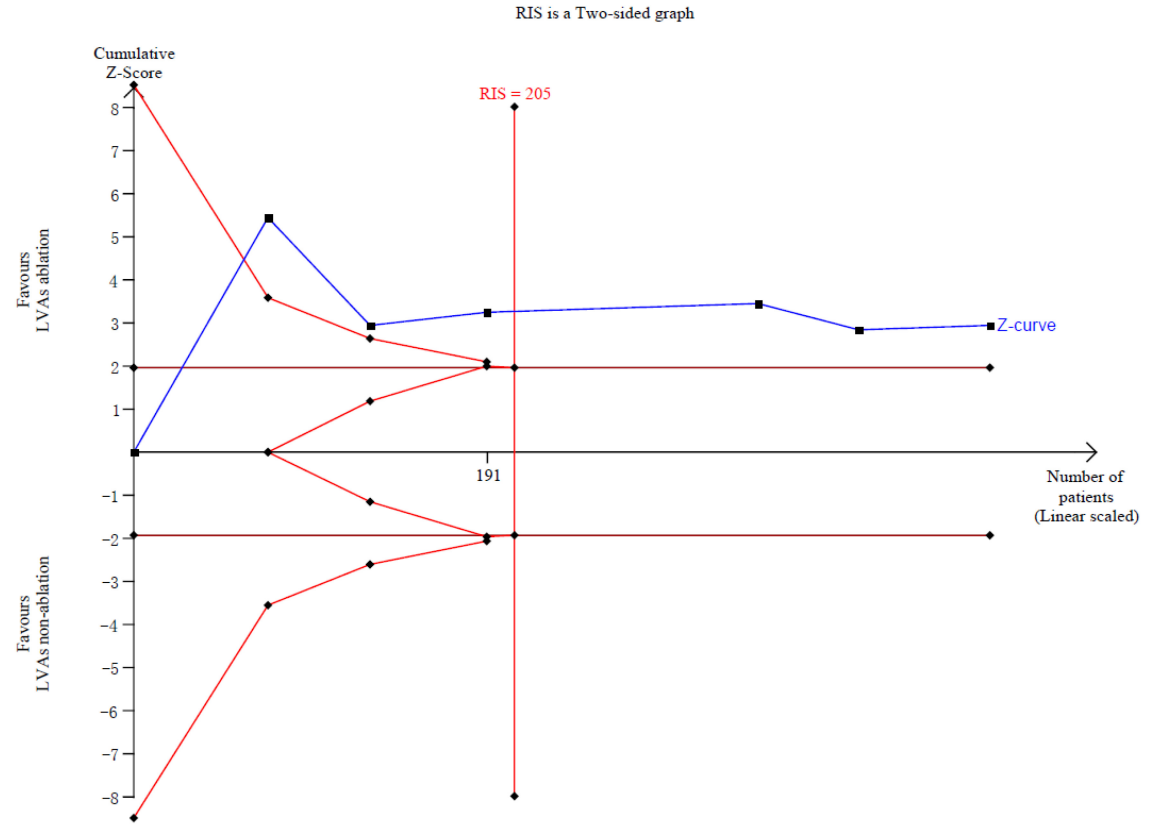

FIGURE 6
Trial sequential analysis of the LVAs ablation.

Outcomes of low-voltage areas ablation

A recent meta-analysis (35) showed that LVAs modification strategy was superior to traditional ablation strategy, but it was not further explored whether LVAs modification had the same benefit in AF patients with LVAs. Our study further verified that LVAs modification in AF patients with LVAs can further reduce arrhythmia recurrence. As mentioned above, the atrial LVAs, identified on the endocardial voltage map, was correlated with atrial fibrosis and could predict the recurrence after ablation. In this context, many studies have begun to explore the effectiveness of LVAs-guided substrate modification after PVI. Rolf et al. first reported that the AF-free survival was 70 and 67% in the patients with and without LVAs and the success rate in the group of LVAs patients without substrate modification was 27% (19). Subsequently, many researchers investigated the feasibility of LVAs-guided ablation. Most of the research demonstrated a favorable effect on additional LVAs ablation following PVI. However, many operators just performed additional LVAs ablation for all LVAs patients, they did not set PVI alone in LVAs patients as control (12, 36). Finally, our study included six studies which set LVAs patients without substrate modification as the control group, and the outcome of additional LVAs ablation was in agreement with most of the previous studies (OR: 0.30, 95% CI: [0.15, 0.62]; $P = 0.0009$) and related complications were not increased ($P = 0.93$). In contrast, the outcome of multiple procedures did not show a significant difference (study vs. control, $P = 0.19$). This difference of result might be at least partially explained by the small sample size (study vs. control 72 vs. 37), because only two studies are included in this meta-analysis. Platonov et al. had provided histological evidence of a strong correlation between the extent of structural changes with AF duration time and clinical type (25). Unfortunately, no significant difference was found in the AF type subgroup analysis, which may be due to the reduced population after subgroup analysis.

Our results suggested that the outcome of undergoing additional LVAs ablation after PVI is reliable, and we performed a subgroup analysis to further explore the optimal strategy for LVAs ablation. The box isolation of LVAs merits further study. Many strategies have been used for the atrial substrate modification, such as circumferential PVI, linear lesion, complex fractionated atrial electrograms (CFAEs) ablation and LVAs ablation (37). Substrate and Trigger Ablation for Reduction of Atrial Fibrillation II (STAR AF II) trial assigned

589 patients with persistent AF and discovered CFAEs ablation or linear lesion showed less benefit after PVI (38). Kottkamp et al. provided box isolation of fibrotic areas (BIFA), a tailored substrate modification strategy for patients with LVAs, which performs circumferential isolation of the fibrotic areas (37, 39). This strategy was tested and a high success rate was reported by their group in patients with recurrent paroxysmal AF and non-paroxysmal AF (39). STABLE-SR (Electrophysiological Substrate Ablation in the Left Atrium During Sinus Rhythm), a multicenter and randomized clinical trial, enrolled 229 patients with non-paroxysmal and were randomized to study group (conventional ablation + additional substrate modification) or control group (conventional ablation + additional linear lesion). In the study group, patients underwent homogenization and eliminated all tissue of LVAs and CFAEs, respectively. Compared with the control group, there was no significant difference in the success rate after 18 months of follow-up (40). Although two strategies for LVAs substrate modification showed outstanding results, our subgroup analysis demonstrated that the box isolation of the LVAs brings more benefit for LVAs patients. We analyzed the possible reasons for these differences. The homogenization of ablation, endpoint of the reduction in local electrogram region, electrogram amplitude, and loss of capture, did not mean a generation of transmural damage. Furthermore, a half-baked homogenization of the lesion may promote the creation of iatrogenic atrial tachyarrhythmia.

According to the result of the subgroup analysis about follow-up time, the arrhythmia recurrence rate increased when the follow-up interval became longer. In the follow-up time = 12 month subgroup, the additional LVAs substrate modification could reduce the arrhythmia recurrence, however, in the follow-up time >12 month subgroup, additional ablation did not lead to a better result. In our opinions, this phenomenon could be associated with the limited ablation strategy (complete conduction block with transmural lesion creation is difficult to achieve) and age-related atrial fibrosis (41). Furthermore, this outcome could also be related to the characteristics of the population and sample size.

In addition, in terms of safety, although LVAs substrate modification did not increase the resulting complications, the increase in procedure time and fluoroscopy time caused by it should be considered. Recently, the high-power short-duration (HPSD) ablation strategy has gained popularity to improve procedure efficiency (42, 43). This HPSD ablation strategy can be used as a standard approach in LVAs substrate modification in the future.

Limitation

The strength of this meta-analysis is that we included the control group (conventional ablation) and study group (conventional ablation + additional LVAs ablation) to explore the efficacy and safety of LVAs substrate modification. To figure out the difference of LVAs substrate modification strategy, we performed the subgroup analyses; besides, we conducted sensitivity analyses to strengthen the robustness of the results. However, the results of this study should be interpreted with several potential limitations in mind. First, five of the included studies were retrospective and prospective studies in nature, while there was only one randomized controlled trial and the result of this study has low power for the small sample size. Second, the method for the identification of arrhythmia recurrence varies between studies and this is a major limitation. Third, because of the differences in the type of AF, the degree of ablation, operator expertise, etc., moderate heterogeneity existed among these trial results. Finally, due to the limited number of studies, our findings raise concern about publication bias, which might lead to an overestimation of the pooled effect estimate.

Conclusions

This meta-analysis has shown that additional LVAs substrate modification after conventional ablation could improve the freedom of arrhythmia recurrence. The box isolation approach appeared more promising. Further large randomized controlled trials are required to confirm these findings.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

BL designed the study, and reviewed and approved the final manuscript. SM, HF, LW, YW, XW, JZ, BY, YZ, and WZ extracted and analyzed data, and revised the manuscript. SM wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.969475/full#supplementary-material

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Direct autotransfusion in the management of acute pericardial tamponade during catheter ablation for atrial fibrillation: An imperfect but practical method

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Background: Acute pericardial tamponade (APT) is one of the most serious complications of catheter ablation for atrial fibrillation (AF-CA). Direct autotransfusion (DAT) is a method of reinjecting pericardial blood directly into patients through vein access without a cell-salvage system. Data regarding DAT for APT are rare and provide limited information. Our present study aims to further investigate the safety and feasibility of DAT in the management of APT during the AF-CA procedure.

Methods and results: We retrospectively reviewed 73 cases of APT in the perioperative period of AF-CA from January 2014 to October 2021 at our institution, among whom 46 were treated with DAT. All included patients successfully received emergency pericardiocentesis through subxiphoid access guided by X-ray. Larger volumes of aspirated pericardial blood (658.4 ± 545.2 vs. 521.2 ± 464.9 ml), higher rates of bridging anticoagulation (67.4 vs. 37.0%), and surgical repair (6 vs. 0) were observed in patients with DAT than without. Moreover, patients with DAT were less likely to complete AF-CA procedures (32/46 vs. 25/27) and had a lower incidence of APT first presented in the ward (delayed presentation) (8/46 vs. 9/27). There was no difference in major adverse events (death/disseminated intravascular coagulation/multiple organ dysfunction syndrome and clinical thrombosis) (0/0/1/0 vs. 1/0/0/0), other potential DAT-related complications (fever/infection and deep venous thrombosis) (8/5/2 vs. 5/3/1), and length of hospital stay (11.4 ± 11.6 vs. 8.3 ± 4.7 d) between two groups.

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Conclusion: DAT could be a feasible and safe method to deal with APT during AF-CA procedure.

KEYWORDS

atrial fibrillation, direct autotransfusion, acute pericardial tamponade, catheter ablation, pericardiocentesis

Introduction

Acute pericardial tamponade (APT), one of the most serious complications in catheter ablation for atrial fibrillation (AF-CA), usually represents a life-threatening condition requiring emergency pericardiocentesis (1–3). The incidence of APT in AF-CA is approximately 1.0–2.0% (4–6). In a previous global survey, APT-related deaths accounted for a quarter of perioperative deaths of AF-CA (1). In recent years, along with the increasing number of AF-CA worldwide, APT cases have risen rapidly (7). Several reasons might be responsible for APT in the AF-CA procedure: the need for transseptal punctures, the intense and long catheter manipulation in the atrium, using high-power ablation with risk of steam pops, and the need for intense systemic anticoagulation. Although many measures have been taken to prevent APT (for example, the use of transesophageal echocardiography (TEE) or intracardiac ultrasound catheter (ICE) for safer access to the left atrial, Contact Force (CF)–sensing catheter for ablation), APT still has a certain probability. How to deal with APT safely and efficiently is an eternal topic.

In the event of APT, emergency pericardiocentesis is necessary to stabilize hemodynamics and inhibit progressive shock (8). Once pericardial hemorrhage cannot stop, emergency surgical repair may be inevitable. Direct autotransfusion (DAT), a method of reinjecting aspirated pericardial blood directly back into the body via venous access without a cell-salvage system, may be easy to operate and can quickly stabilize hemodynamic status and buy time for anticoagulation reversal or cardiac surgical repair. Previous studies had reported cases of applying DAT to deal with APT during the perioperative period of AF-CA (9–13). However, despite the many potential advantages, DAT has not been conventionally adopted yet, due to the lack of consensus on security. Herein, our present study aims to further investigate the clinical feasibility and safety of DAT in the treatment of APT during AF-CA.

Methods

Patients

Our study retrospectively reviewed APT cases of AF-CA in Beijing Anzhen Hospital Electrophysiological Center from January 2014 to October 2021. During this period, 73 patients suffered from APT, including 46 patients who received DAT without a cell-salvage system (Figure 1).

We collected the demographics, laboratory data, procedure details, and medical histories of all enrolled participants. All subjects signed written consent forms, and the study was approved by the hospital's institutional review board.

Perioperative anticoagulation

Patients with left atrial and left atrial appendage thrombosis were excluded by TEE 24–48 h before the ablation procedure. Perioperative anticoagulation with warfarin or non-vitamin K antagonist oral anticoagulants (NOACs) was administered as follows: from 2014 to 2018, uninterrupted warfarin strategy or OAC bridging with low-molecular-weight heparin (LMWH) strategy was alternatively performed (about 80% of patients received bridging OAC with LWMH); from 2019 to 2021, an uninterrupted dabigatran strategy was routinely adopted.

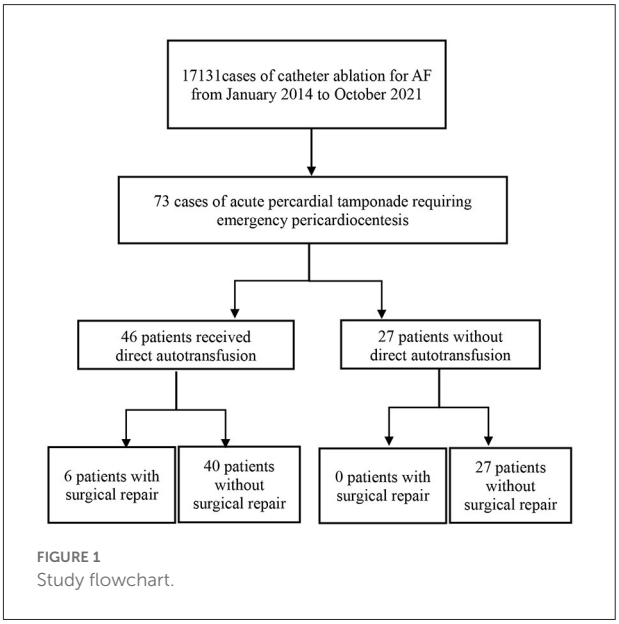

FIGURE 1
Study flowchart.

TABLE 1 Baseline characteristics of the study population.

Demographic variables	$n = 73$ (total)	$n = 46$ (DAT)	$n = 27$ (non-DAT)	p-value
Age, years	65.7 ± 9.8	65.1 ± 9.6	66.7 ± 10.1	0.348
Male, *n* (%)	40 (54.8)	28 (60.9)	12 (44.4)	0.173
BMI, kg/m^2	24.2 ± 2.7	24.7 ± 2.8	23.4 ± 2.2	0.079
Type of AF				0.562
Persistent AF, *n* (%)	24 (32.9)	14 (30.4)	10 (37.0)	
Paroxysmal AF, *n* (%)	49 (67.1)	32 (69.6)	17 (63.0)	
Hypertension, *n* (%)	44 (60.3)	32 (69.6)	12 (44.4)	0.034*
Diabetes mellitus, *n* (%)	8 (11.0)	5 (10.9)	3 (11.1)	0.975
Coronary artery disease, *n* (%)	15 (20.5)	10 (21.7)	5 (18.5)	0.742
Congestive heart failure, *n* (%)	9 (12.3)	7 (15.2)	2 (7.4)	0.327
Stroke/TIA, *n* (%)	8 (11.0)	6 (13.0)	2 (7.4)	0.457
Baseline laboratory characteristics				
Hemoglobin, g/dl	148.8 ± 13.3	149.1 ± 13.3	148.2 ± 13.7	0.805
Platelet, 10^9/L	219.3 ± 57.6	221.0 ± 58.5	216.3 ± 57.0	0.710
White blood cell, 10^9/L	5.6 ± 1.2	5.5 ± 1.1	5.6 ± 1.2	0.770
eGFR, ml/min/1.73 m^2	89.8 ± 13.9	89.7 ± 13.7	90.0 ± 14.4	0.846
Echocardiographic parameters				
LAD, mm	39.5 ± 5.8	39.8 ± 5.6	39.0 ± 6.3	0.432
LVEDD, mm	46.7 ± 4.4	47.2 ± 4.7	45.8 ± 3.8	0.213
LVEF, %	62.7 ± 6.2	63.2 ± 7.0	61.7 ± 4.5	0.121
CHA_2DS_2-VASC score	2.5 ± 1.7	2.5 ± 1.6	2.4 ± 1.9	0.589
HAS-BLED score	1.3 ± 0.9	1.3 ± 0.9	1.2 ± 0.8	0.734
Preoperative anticoagulation therapy				
Warfarin, *n* (%)	9 (12.3)	7 (15.2)	2 (7.4)	0.327
NOACs bridging with LMWH, *n* (%)	41 (56.2)	31 67.4)	10 (37.0)	0.012*
Uninterrupted dabigatran, *n* (%)	23 (31.5)	8 (17.4)	15 (55.6)	0.001*
Antiplatelet medications				
Aspirin, *n* (%)	2 (2.7)	2 (4.3)	0 (0.0)	0.272
Clopidogrel, *n* (%)	1 (1.4)	1 (2.2)	0 (0.0)	0.440

Values are given as number (percent) or mean ± SD.
AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; LAD, left atrium diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischemic attack. *$p < 0.05$.

During the AF-CA procedure, all subjects were administered unfractionated heparin (100 IU/kg) after transseptal puncture, and intravenous heparin was administered to maintain an activated clotting time (ACT) in excess of 300 s.

Catheter ablation procedure

All patients underwent AF-CA procedures following a sequential strategy at our institution, which has been well established previously. In brief, one transseptal puncture guided by ICE and/or X-ray was performed routinely in all patients. In patients with paroxysmal AF, pulmonary vein isolation (PVI) was performed with the endpoint of electrical isolation. In patients with persistent AF, along with PVI, additional ablation (such as mitral isthmus line, left atrial roof line, cavotricuspid isthmus line, and superior vena cava) was performed. Carto navigation system was used in nearly 98% of AF ablation procedures, while other navigation systems (Navex and Rhythmia) were only used in very few cases. Moreover, a novel ablation quality marker (Ablation index) was routinely introduced from 2017.

Management of acute pericardial tamponade and direct autotransfusion

APT was suspected when patients presented with dizziness, vomiting, dyspnea, and/or the systolic blood

TABLE 2 Clinical characteristics of 46 cases of direct autotransfusion.

Case	Age/ Gender	AF type	Anticoagulant	Antiplatelet	Ablation strategy	Blood drained (ml)	Autologous blood reinfused (ml)	Reversal agent	Mechanism of perforation	Surgical repair
1	68/M	PeAF	Warfarin	–	PVI + MAI + CTI + LA roof	300	250	VK1	Unknown	No
2	64/F	PeAF	Warfarin	–	PVI + MAI + CTI + LA roof	310	280	Protamine	Unknown	No
3	75/F	PeAF	LMWH	–	PVI + MAI + CTI + LA roof	240	200	Protamine	Unknown	No
4	52/M	PAF	Warfarin	–	PVI + MAI	350	300	Protamine, VK1	Unknown	No
5	65/M	PAF	Warfarin	–	PVI	230	160	Protamine	Mechanical	No
6	86/M	PAF	LMWH	–	PVI + CTI	200	160	Protamine	Mechanical	No
7	64/F	PAF	LMWH	–	PVI	550	480	Protamine	Unknown	No
8	60/M	PAF	Warfarin	–	PVI	200	180	Protamine	Unknown	No
9	76/F	PAF	LMWH	Aspirin	PVI	450	150	–	Unknown	No
10	71/M	PeAF	LMWH	–	PVI + MAI + CTI + LA roof	190	160	Protamine	Unknown	No
11	60/M	PAF	LMWH	–	PVI + MAI + CTI + LA roof	250	200	Protamine	Unknown	No
12	60/M	PeAF	LMWH	–	PVI + MAI + CTI + LA roof	600	500	Protamine	Unknown	No
13	84/M	PAF	LMWH	–	PVI	1175	1000	Protamine	Unknown	Yes
14	64/F	PAF	LMWH	–	PVI + SVC	210	180	Protamine	Steam pop	No
15	55/M	PeAF	LMWH	Aspirin	PVI + MAI + CTI + LA roof + SVC	180	150	Protamine	Unknown	No
16	74/F	PAF	LMWH	–	PVI	160	130	–	Unknown	No
17	71/M	PAF	LMWH	–	PVI + MAI + LA roof	440	300	Protamine	Steam pop	No
18	77/M	PAF	LMWH	–	PVI	300	250	Protamine	Unknown	No
19	63/F	PeAF	Warfarin	–	PVI + MAI + CTI + LA roof	240	200	Protamine	Unknown	No
20	69/M	PAF	LMWH	–	PVI + MAI + LA roof	1230	1100	Protamine	Mechanical	Yes
21	69/M	PAF	LMWH	–	PVI + CTI + MAI	690	600	Protamine	Unknown	No
22	80/M	PAF	LMWH	–	PVI + MAI	890	830	Protamine	Unknown	No
23	78/F	PAF	LMWH	–	PVI + MAI + LA roof	380	350	Protamine	Unknown	No
24	76/F	PAF	LMWH	–	PVI + MAI + CTI	1860	1550	Protamine	Steam pop	Yes

(Continued)

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TABLE 2 (Continued)

Case	Age/ Gender	AF type	Anticoagulant	Antiplatelet	Ablation strategy	Blood drained (ml)	Autologous blood reinfused (ml)	Reversal agent	Mechanism of perforation	Surgical repair
25	68/M	PAF	LMWH	–	PVI + LA roof	800	720	Protamine	Mechanical	No
26	63/F	PAF	LMWH	–	PVI + LA roof	250	200	Protamine	Unknown	No
27	60/F	PAF	LMWH	–	PVI	926	650	Protamine	Unknown	No
28	61/M	PAF	LMWH	–	PVI + MAI + CTI + LA roof	1300	240	Protamine, PCC	Unknown	No
29	58/M	PeAF	LMWH	–	PVI+MAI + CTI + LA roof	670	600	Protamine	Unknown	No
30	40/M	PAF	LMWH	–	PVI	1030	850	Protamine	Unknown	No
31	75/F	PAF	LMWH	–	PVI + CTI	580	450	Protamine	Steam pop	No
32	60/F	PAF	LMWH	–	PVI + MAI + CTI	330	260	Protamine	Mechanical	No
33	45/M	PAF	LMWH	–	PVI + CTI + SVC	350	300	–	Unknown	No
34	67/F	PAF	Warfarin	–	PVI	500	400	Protamine, VK1	Unknown	No
35	60/F	PAF	LMWH	–	PVI	330	250	Protamine	Steam pop	No
36	62/M	PeAF	LMWH	–	PVI + MAI + CTI + LA roof	1850	1600	Protamine	Steam pop	Yes
37	55/M	PAF	LMWH	–	PVI + MAI + CTI + LA roof	1740	1450	Protamine	Steam pop	Yes
38	71/M	PeAF	Dabigatran	Clopidogrel	PVI + MAI + CTI + LA roof	2350	2100	Protamine, Idarucizumab	Unknown	Yes
39	67/M	PAF	Dabigatran	–	PVI + MAI + CTI + LA roof + SVC	285	240	Protamine	Unknown	No
40	60/M	PAF	Dabigatran	–	PVI	1250	700	Protamine, Idarucizumab	Mechanical	No
41	54/F	PeAF	Dabigatran	–	–	830	700	Protamine, Idarucizumab	Mechanical	No
42	56/M	PAF	Dabigatran	–	PVI	80	60	Protamine	Unknown	No
43	52/M	PeAF	Dabigatran	–	PVI + MAI + CTI + LA roof	300	100	Protamine, Idarucizumab	Unknown	No
44	70/F	PeAF	Dabigatran	–	PVI + CTI	370	300	Protamine	Steam pop	No
45	71/M	PeAF	Dabigatran	–	PVI + MAI + CTI + LA roof	290	250	Protamine	Unknown	No
46	59/F	PAF	LMWH	–	PVI + CTI	110	80	–	Unknown	No

CTI, cavo-tricuspid isthmus; LA, left atrial; LMWH, low-molecular-weight heparin; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; PCC, prothrombin complex concentrate; PVI, pulmonary vein isolation; SVC, superior vena cava; VK1, vitamin K1.

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TABLE 3 Comparison of complications between patients with DAT and without-DAT.

Demographic variables	DAT $n = 46$	Without-DAT $n = 27$	p-value
Onset situations, *n* (%)			<0.001*
Ward	8 (17.4)	18 (66.7)	
EP-lab	38 (82.6)	9 (33.3)	
Reversal medications, *n* (%)			
Vitamin K	3 (6.5)	1 (3.7)	0.610
Protamine	41 (89.1)	10 (37.0)	<0.001*
Idarucizumab	4 (8.7)	3 (11.1)	0.735
Prothrombin complex	1 (2.2)	0 (0)	–
Blood drain volume, ml	611.9 ± 532.7	262.0 ± 98.4	0.001*
Autologous blood reinfused, ml	482.4 ± 453.7	–	–
Allogeneic blood transfusion, *n* (%)	9 (19.6)	2 (7.4)	0.161
Complete procedure, *n* (%)	32 (69.6)	25 (92.6)	0.022*
Surgical repair, *n* (%)	6 (13.0)	0 (0.0)	0.050
Major adverse events, *n* (%)			
Periprocedural death	0 (0.0)	1 (3.7)	0.370
DIC/MODS/ clinic thrombosis	1 (2.2)	0 (0.0)	0.440
Other complication, *n* (%)			
Fever	8 (17.4)	5 (18.5)	0.903
Infection	5 (10.9)	3 (11.1)	0.975
Deep venous thrombosis	2 (4.3)	1 (3.7)	0.894
Hospital stay, days	11.4 ± 11.6	8.3 ± 4.7	0.598

Direct autotransfusion DAT.
Values are given as number (percent) or mean ± SD.
EP-lab, electrophysiological laboratory; LMWH, low-molecular-weight heparin; PAF, paroxysmal atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; DIC, disseminated intravascular coagulation; MODS, mutiple organ dysfunction syndrome. *$p < 0.05$.

pressure dropped to <90 mmHg. APT was examined immediately and finally verified by echocardiography, intracardiac echocardiography, and/or fluoroscopy. Once APT was diagnosed, emergency pericardiocentesis through subxiphoid access guided by fluoroscopy was performed by experienced electrophysiologists. Then, a drainage catheter was positioned over the wire into the pericardial cavity to aspirate pericardial blood. Meanwhile, anticoagulation reversal was achieved if necessary, in brief, heparin was reversed by protamine, vitamin K1 was used to reverse warfarin, and dabigatran was reversed by idarucizumab, respectively.

Pericardial blood was aspirated with a separate 60 cc syringe, then transfused immediately via a femoral venous sheath without a cell-salvage system at the operators' discretion. Subsequently, thrombus formation in the syringe was observed, and the pericardial effusion condition was continuously monitored by echocardiography or fluoroscopy. Aspiration and DAT were stopped when pericardial hemorrhage subsided for at least 30 min. If pericardial hemorrhage could not be relieved yet, pericardiotomy and cardiac repair were performed by a cardiac surgery team.

Perioperative adverse events

Major adverse events included intraprocedural death, clinical thrombosis/adverse thrombotic events (pulmonary embolism, and ischemic stroke), coagulation disorders/disseminated intravascular coagulation (DIC), or multiple organ dysfunction syndrome (MODS). Other complications potentially relevant to DAT were defined as infection/pneumonia, fever, and deep venous thrombosis (DVT).

Statistical analysis

The data are presented as the means ± standard deviations for continuous variables and frequencies and percentages for categorical variables. To compare the differences between groups, Fisher's exact tests were used for categorical variables, and Mann–Whitney *U* tests were used for continuous variables. Statistical analyses were performed using SPSS 23.0 software (Chicago, IL, USA). All tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

From January 2014 to October 2021, a total of 17131 AF-CA procedures were performed, of which 73 (0.4%) were complicated with APT. The clinical and demographic characteristics of all 73 patients are shown in Table 1. Among them, 46 patients received DAT following emergency pericardiocentesis, whereas the other 27 patients did not receive DAT. There were 40 men (54.8%), and 49 paroxysmal AF (67.1%), and the average age was 65.7 ± 9.8. Moreover, 9 patients presented with congestive heart failure (12.3%), 44 with hypertension (60.3%), 8 with diabetes (11.0%), 8 with previous stroke (11.0%), and 15 with coronary artery disease (20.5%). For periprocedural anticoagulation strategy during AF-CA, 9 received uninterrupted warfarin (12.3%), 23 were applied uninterrupted dabigatran (31.5%), and the other 41 received OAC bridging with LMWH (56.2%). Additionally, 2 patients were on treatment with aspirin (2.7%) and 1 with clopidogrel (1.4%) simultaneously. Compared to patients without DAT, a higher incidence of hypertension (69.6 vs. 44.4%) and OAC bridging with LMWH (67.4 vs. 37.0%) was observed in the DAT group (Table 1).

Pericardial tamponade, pericardiocentesis, and direct autotransfusion

During this period, about 50% of patients underwent PVI procedures and the others received more complex procedures. Meanwhile, for all 73 APT patients, 20 patients were performed with PVI only, which is less than those with more complex procedures (53 cases). A sudden onset of APT in the electrophysiological laboratory (EP-lab) was significantly more common in patients with DAT than without DAT (38/46 vs. 9/27). Subsequently, all 73 patients successfully received pericardiocentesis when APT was diagnosed for the first time. There was no significant difference in the application of reversal medications during rescue between two groups (DAT vs. without DAT): vitamin K (3 vs. 1), prothrombin complex (1 vs. 0), and idarucizumab (4 vs. 3), respectively. In addition, more application of protamine sulfate (41 vs. 10), larger volumes of pericardial drainage (611.9 ± 532.7 vs. 262.0 ± 98.4 ml), and higher rates of procedure incompletion (32/46 vs. 25/27) and surgical repair (6 vs. 0) were observed in DAT group (Table 2). It was more frequent in wards of APT patients without DAT, which might be responsible for the less application of protamine.

For all 46 cases with DAT, 7 cases were confirmed to be caused by catheter mechanical operation (15.2%), 8 patients were related to intraoperative steam pop (17.4%), and cumulative ablation effects might be responsible for the other 31 cases. There were 6 (13.0%), 15 (32.6%), and 23 (50.0%) patients with DAT volume >500, >1,000, and <300 ml, respectively (Table 3).

Perioperative adverse event

In the DAT group, 8 patients suffered from infection, and 3 patients developed deep venous thrombosis (DVT) of the lower limbs following the procedure. However, There was no significant difference in major adverse events (death, DIC/MODS/clinical thrombosis) (0/0/1/0 vs. 1/0/0/0), other complications potentially relevant to DAT (fever, infection, and deep venous thrombosis) (8/5/2 vs. 5/3/1), and length of hospital stay (11.4 ± 11.6 vs. 8.3 ± 4.7 d) between two groups (DAT vs. without DAT). Unfortunately, even if pericardiocentesis was successfully performed, 1 patient died of brain death in a group without DAT (Table 3).

Discussion

To the best of our knowledge, the present study represented the largest single-center series referring to the feasibility and safety of DAT in the management of APT during the AF-CA procedure. We observed larger volumes of drained blood reinfused and more need for surgical repair in patients with DAT. Although several complications were recorded, there was no significance in major adverse events and other potential DAT-related complications between patients with and without DAT. Our study demonstrated that DAT might be not perfect, but a feasible, effective/efficient, and safe method in the management of APT during the AF-CA procedure.

APT is one of the most serious complications during AF-CA and may occur at any time for a variety of reasons, including steam pop, excessive radiofrequency energy, mechanical perforation, or transseptal puncture. Moreover, systemic anticoagulation during perioperative AF-CA is also an important risk factor for pericardial tamponade. In the past few years, with AF-CA procedures gradually extending to low-volume centers, the overall incidence of APT had shown an increasing trend: from 0.74% in 2000 to 2.24% in 2010 (14).

In recent years, new catheter, technology, and concept for AF-CA and perioperative anticoagulation strategies had been innovated, including CF-sensing catheter, intracardiac ultrasound catheter, high-power ablation, ablation index (15), Near-Zero X-ray technology (16) and uninterrupted oral anticoagulation. Although the Smart AF Trial (17) showed a high incidence of APT in AF-CA procedure (2.5%, 4/161 patients) with CF-sensing catheter. Toccastar trial (18) demonstrated that the APT incidence when using CF-sensing catheters was lower; however, there was no difference compared to non-sensing catheters (0.66 vs. 0.70%). Performing left atrial

mapping, ICE, and CF-sensing catheter is expected to reduce the rate of APT; however, applying aggressive ablation strategy, increasing ablation intensity, and gradual expansion of AF-CA to low-volume centers may increase the possibility of APT. So herein, the advance of technologies, catheter, and strategies has not reduced the incidence of APT while coping with more complex procedures and improving the success rate of AF-CA.

It is crucial to identify pericardial hemorrhage as soon as possible, which facilitates the prevention of the progression from effusion to tamponade and reverses this fatal complication. The cessation of spontaneous pericardial hemorrhage is unpredictable and depends on a variety of factors, including the size and site of the perforation, pericardial pressure, perforation properties, and perioperative anticoagulation condition (19). Emergency surgical repair is inevitable if bleeding continues after pericardiocentesis, reversal of anticoagulation, and blood transfusion. When APT developed, following emergency pericardiocentesis, rescuing measures including blood transfusion are usually performed in the first place to stabilize hemodynamics and buy time for surgical repair.

Blood-cell salvage system can separate red blood cells from cell debris, fat particles, activated cytokines, clotting factors, and platelets, which may reduce autotransfusion-related complications (20, 21). Current data concerning salvage autotransfusion mainly came from surgical operations, such as cardiac surgery and traumatic surgery (22). Due to the potential risks of thromboembolism and infection, several blood filtering methods reducing the potential complications had been established (23–25). However, the extensive use of cell salvage (especially for retransfused blood >1,500 ml) might lead to a critical loss of coagulation factors and platelets, resulting in a bleeding diathesis (9, 26, 27). To sum up, the results of clinical trials had shown controversial clinical benefits of the cell-salvage system during the intraoperative period (20, 22, 25). For AF-CA, Venkatachalam et al. (28) reported 9 cases of APT successfully treated with autologous blood transfusion via cell-salvage system. Nevertheless, a cell-salvage system usually required more time to prepare and was not available in all institutions, especially in low-volume centers, which might make a difference in this fatal complication.

DAT is a timely and accessible method of reinjecting pericardial blood directly back to the body through vein access. Pericardiocentesis combined with DAT can quickly stabilize hemodynamic status, reduce allogeneic blood transfusion, and more importantly, buy time for patients who ultimately require surgical repair (9, 27). Theoretically, DAT will be effective in the treatment of APT for it can be initiated immediately and with minimal preparation. However, DAT has not been routinely adopted by most interventional electrophysiologists due to its potential risks of thrombotic and infective events. Recently, two studies (10, 11) preliminary investigated the feasibility of DAT in APT during the perioperative period of EP procedures and revealed that DAT reduced the need for allotransfusion and surgical repair without increasing major complications. However, among different EP procedures, only a few (<10) AF patients were enrolled in either study, therefore, their conclusions cannot be completely applicable for AF-CA and need to be further explored. Our present study involving 46 patients with DAT in AF-CA procedures showed a lower incidence of surgical repair (13%) without major adverse events. Despite several cases of infection and DVT being recorded, there were no statistical differences between patients with and without DAT. In our opinion, such complications might be attributed to multiple factors, for instance: pericardial tamponade itself, pericardiocentesis, stress response, extended postoperative bed rest, and surgical operations, instead of the DAT part.

However, several differences in terms of autotransfusion in different scenarios (surgery or EP procedures) should be noted. Firstly, when traditional surgical procedures are performed, the cell-salvage system is usually prepared in advance or in the preparation operation room. However, APT during the EP procedures is usually emergent and unpredictable to prepare a cell-salvage instrument. Secondly, surgical procedures are usually accompanied by massive tissue damage, and the restored blood flow may be rich in tissue/cell debris, small embolism, and/or contaminants. However, catheter-based cardiac procedures usually lead to local hemorrhage, which generates little tissue/cell debris. Moreover, as a closed cavity, the pericardium is basically not involved in bacterial infections. Lastly, for atria are low-pressure cavities, pericardial hemorrhage in AF-CA is usually slower and less in amount than other types of cardiac interventional procedures (such as transcatheter aortic valve implantation and percutaneous coronary intervention), which means that it is not easy to form thrombi in aspirated blood due to the fibrinolytic property of the pericardium. Therefore, DAT may not increase clinical complications including embolism, especially when the transfusion volume is relatively small.

Limitations

Several limitations should be considered. First, although more cases were enrolled, our present study was still a retrospective single-center study. The safety of DAT needs to be further validated by randomized trials and pathophysiological studies on blood. Besides, only 50% of patients had a reinjected blood volume >300 ml, which might lead to a bias. However, as an emergent and fatal complication, APT is usually unpredictable and needs to be treated with close observation.

Conclusion

Our present study showed that direct autotransfusion of pericardial drainage blood in the management of APT during AF-CA procedure could be a safe, efficient, and feasible method.

Although DAT might not be a perfect method for APT, when the primary risk is immediate death, any life-saving measures should be worth considering. In the clinical practice of dealing with APT, DAT could be safely applied, especially for patients with the expected large amount of bleeding and unstable hemodynamics and hemorrhage difficult to judge, which limits the need for transfusions and buy the time for cardiac surgical repair.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Beijing Anzhen Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

D-yL, R-bT, R-HY, and C-hS defined the theme of review. XZ and J-fL wrote the manuscript. XS, NL, C-xJ, X-yG, WW, S-nL, and SZ took part in preparing the manuscript. XZ, J-fL, J-zD, and C-sM prepared and reviewed the manuscript before publication. All authors confirmed that they have read and approved the manuscript and they have met the criteria for authorship.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Left atrial appendage function and structure predictors of recurrent atrial fibrillation after catheter ablation: A meta-analysis of observational studies

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Background: The results of studies evaluating the left atrial appendage (LAA) function and structure as predictors of atrial fibrillation (AF) recurrence after catheter ablation (CA) are contradictory. Therefore, we performed a meta-analysis to assess whether the LAA function and structure can predict the recurrence of AF after CA.

Methods: The PubMed, EMBASE, Web of Science, and Cochrane library databases were used to conduct a comprehensive literature search. Finally, 37 studies encompassing 11 LAA parameters were included in this meta-analysis.

Results: Compared with those in the non-recurrence group, the recurrence group had increased LAA volume (SMD 0.53, 95% CI [0.36, 0.71] $p < 0.00001$), LAA volume index, LAA orifice area, and LAA orifice short/long axis and decreased LAA emptying flow velocity (SMD -0.54, 95% CI [-0.68, -0.40], $P < 0.00001$), LAA filling flow velocity, and LAA ejection fraction, while there was no significant difference in LAA morphology or LAA depth.

Conclusion: Large LAA structure of pre-ablation (LAA volume, orifice area, orifice long/short axis, and volume index) and decreased LAA function of pre-ablation (LAA emptying flow velocity, filling flow velocity, ejection fraction, and LASEC) increase the odds of AF recurrence after CA.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/], identifier [CRD42022324533].

KEYWORDS

atrial fibrillation, atrial fibrillation recurrence, catheter ablation, meta-analysis, left atrial appendage structure, left atrial appendage function

Introduction

The most prevalent chronic cardiac arrhythmia, atrial fibrillation (AF), causes increased morbidity and death (1, 2). AF, especially persistent AF, still has a high recurrence rate, despite the use of catheter ablation (CA) as a medical therapy for it (3). Many individuals with pulmonary vein reconnection do not experience AF recurrence after pulmonary vein isolation, which implies that there are complicated underlying mechanisms beyond pulmonary vein triggers that incite AF recurrence (4, 5). Therefore, assessing the patients' risk of AF recurrence is critical for increasing the benefits of CA and preventing the complications of multiple ablations. The presence of left atrial dilatation and impaired function has been linked to a high AF recurrence rate (6–8). However, the left atrial appendage (LAA), which plays an important role as an AF trigger, is poorly understood (9, 10). Di Biase et al. found that the LAA is an important site of triggers in 27% of 987 patients with repeated ablations (11). A meta-analysis has shown that LAA electrical isolation can achieve a higher rate of improvement in freedom from AF recurrence compared to standard ablation alone in patients with non-paroxysmal AF (12). LAA flow velocity has been used as surrogates of left atri reservoir and contractile function (13). In addition, the LAA also plays an important role in predicting cardioembolic stroke (14, 15).

However, there is disagreement on the LAA structure and function in predicting AF recurrence after CA (16–18). Therefore, this meta-analysis was conducted to determine whether LAA structure and function can predict the recurrence of AF after CA in daily clinical practice.

Methods

Search strategy and selection criteria

We systematically searched the PubMed, Cochrane Library, EMBASE, and Web of Science databases without language restriction until August 25, 2022. Simultaneously, a manual search of related references was conducted, and unpublished documents are sought on clinicaltrials.gov. The search terms were "atrial fibrillation," "left atrial appendage," "catheter ablation," "left atrial appendage electrical isolation" and "recurrence." Search details can be seen in the **Supplementary material**. The criteria for inclusion were as follows: (i) surgical ablation of AF compared to CA, the study subjects were very different; to minimize variability among study patients, we selected only patients with CA; (ii) AF recurrence after CA was measured as an outcome; (iii) 12-lead ECG or Holter ECG confirmation of AF, atrial flutter, or atrial tachycardia; and (iv) the recurrence and non-recurrence groups' means and standard deviations of LAA parameters were provided or could be converted from the medians and ranges (19). The criteria for exclusion were as follows: (i) animal research; (ii) conference abstracts, review articles, case reports, and letters/reports, (iii) studies that included LAA parameters that had been explored in fewer than three studies. (iv) follow-up less than 3 months. The review protocol has been registered in the PROSPERO (registration number: CRD42022324533).

Data extraction and quality appraisal

The following information was gathered from eligible studies: (i) name of the first author, publication year, and design of the research; (ii) detection strategies for AF recurrence, ablation details, and blanking period; (iii) mean follow-up time and baseline characteristics; and (iv) baseline characteristics of LAA. Two reviewers independently assessed the quality of each study by using the Newcastle-Ottawa Scale (**Supplementary Table 1**). Disagreements between the two reviewers were worked out through dialog and consultation of a third reviewer if necessary.

Statistical analysis

Categorical variables are reported as a pooled risk ratio (RR). Continuous variables are expressed via standardized mean difference (SMD). For all outcomes, overall estimate with the 95% confidence interval (CI) was calculated. Cochran's Q test and I^2 statistics were used to assess heterogeneity. I^2 statistics $>25\%$, 50–75%, and $>75\%$ indicated low, moderate, or high heterogeneity, respectively. The random-effects model was used when the heterogeneity was obvious; otherwise, the fixed-effects model was used. A sensitivity analysis or subgroup analysis was performed when necessary. Subgroup analysis was used to investigate the cause of heterogeneity. R programming language (version 4.1.2, R Foundation) was used to assess publication bias by using funnel plots and Egger's test. Review Manager Version 5.3 software (The Nordic Cochrane Centre) was used to conduct overall effect analysis and subgroup analysis.

Results

We retrieved 343 articles from PubMed, 49 articles from the Cochrane Library, 800 articles from EMBASE, and 643 articles from the Web of Science. 926 duplicate articles were removed from the list. Furthermore, 863 studies were excluded after reading the titles and abstracts. For the second round of selection, the entire texts of the remaining 110 studies were read: 3 articles were excluded due to

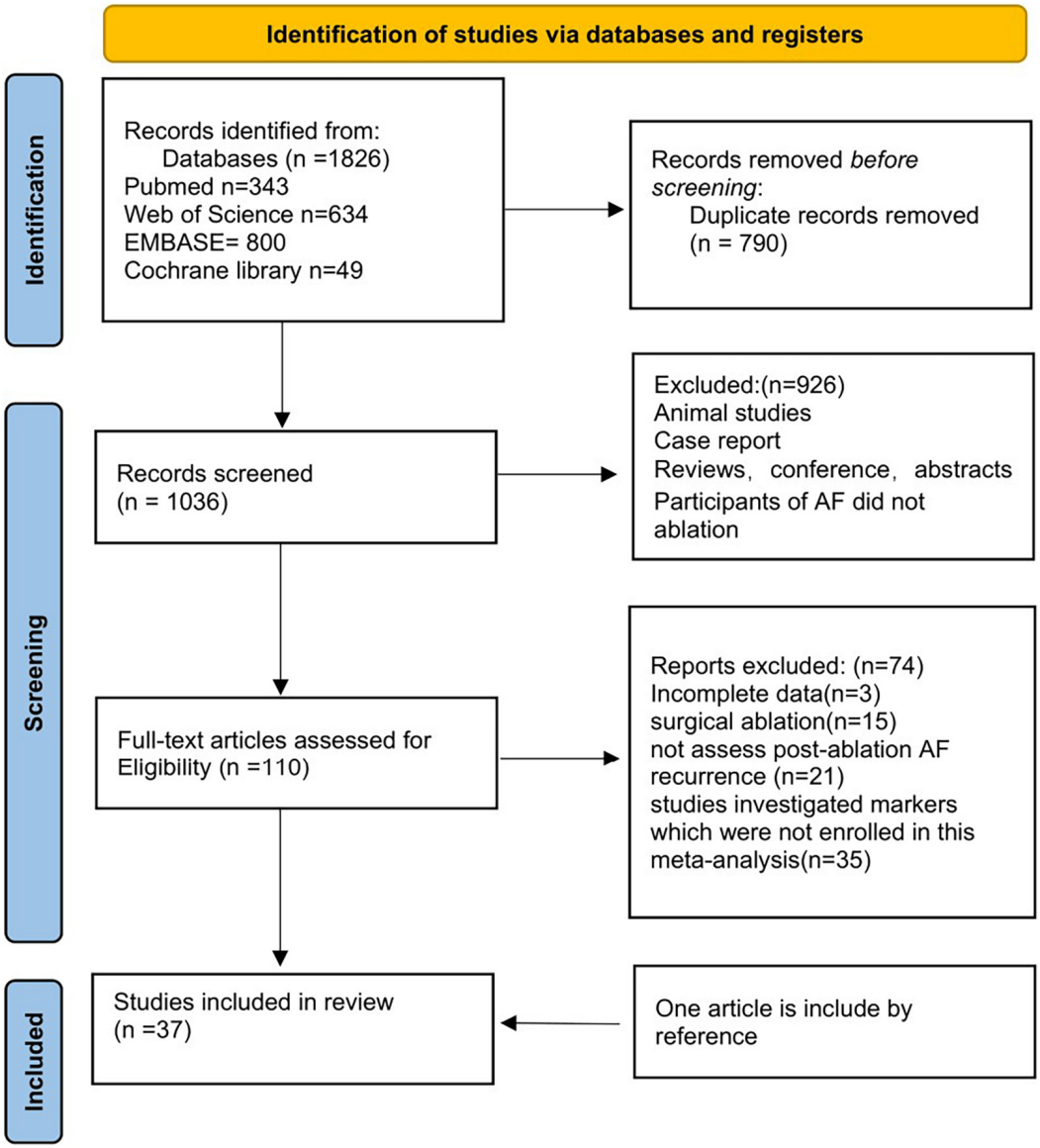

FIGURE 1
Summary of electronic search and included/excluded studies.

incomplete data; 15 articles were excluded due to surgical ablation; 21 articles didn't assess post-ablation AF recurrence; 35 studies didn't investigate markers which we need in this meta-analysis. One article included was obtained from the references. **Figure 1** shows a flow chart of the article screening process.

Finally, 37 observational studies were included after the application of the inclusion and exclusion criteria. The following 11 LAA parameters were covered: LAA emptying flow velocity, LAA volume, LAA filling flow velocity, LAA depth, LAA orifice long/short axis, LAA orifice area, LAA morphology, LAA volume index, LAA ejection fraction (LAAEF), and left atrial spontaneous echo contrast (LASEC). The detailed characteristics of our included patients are depicted in **Supplementary Tables 2**, **3**.

Left atrial appendage morphology and atrial fibrillation recurrence post-radiofrequency catheter ablation

Six studies (17, 20–24) divide LAA morphology into chicken wing (CW) and no chicken wing (NCW), we did not find a statistically significant relationship between pre-ablation LAA morphology (CW vs. NCW) and post-ablation AF recurrence (**Figure 2**, RR 1.23, 95% CI [0.89, 1.68] P = 0.21). The tests

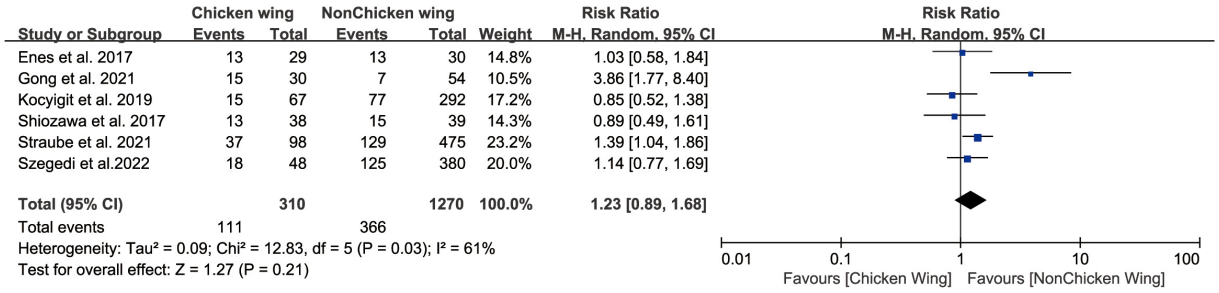

FIGURE 2
Forest plot showing the no difference in LAA morphology (chicken vs. non-chicken) between patients with and without AF recurrence after catheter ablation.

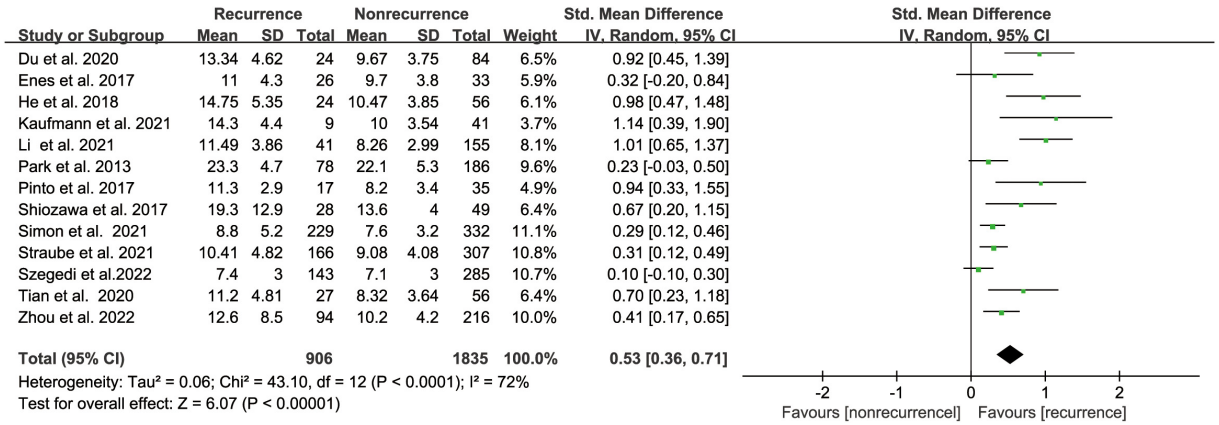

FIGURE 3
Forest plot showing the difference in LAA volume between patients with and without AF recurrence after catheter ablation.

for heterogeneity showed moderate heterogeneity (I^2 = 61). Five studies divided the LAA into chicken wing, cauliflower, cactus, and windsock. Based on the above classification results, we found that the risk of recurrence did not differ between CW patients and windsock (**Supplementary Figure 1A**, RR 1.17, 95% CI[0.79, 1.72] P = 0.44), cactus (**Supplementary Figure 1B**, RR 1.04, 95% CI[0.76, 1.41] P = 0.81), or cauliflower (**Supplementary Figure 1C**, RR 1.10, 95% CI [0.85, 1.41] P = 0.48), patients.

Left atrial appendage volume and atrial fibrillation recurrence catheter ablation

The meta-analysis comprised thirteen (17, 18, 20, 22, 24–32) studies that evaluated the risk of AF recurrence following CA based on LAA volume in 2741 people. LAA volume was assessed using computed tomography (CT) in most studies while one study used transesophageal echocardiography (TEE). The AF recurrence group had an increased LAA volume compared with the non-recurrence group, according to our meta-analysis. (SMD 0.53, 95% CI [0.36, 0.71] p < 0.00001, **Figure 3**). But the heterogeneity was significant with I^2 = 72% (P < 0.00001). After subgroup analysis by follow-up time, AF type, region, and sample size (**Supplementary Figure 2**); we found low heterogeneity after excluding paroxysmal AF. We performed a sensitivity analysis to see determine how each study affected the results by removing one trial at a time. However, we found no source of heterogeneity.

Left atrial appendage emptying flow velocity and atrial fibrillation recurrence after catheter ablation

Twenty-five studies (16, 17, 20, 23, 27, 33–52) with 8945 subjects about pre-ablation LAA emptying flow velocity and AF recurrence after ablation recurrence were included. LAA emptying flow velocity was assessed using TEE in most studies while one study used intracardiac echocardiogram (ICE). The recurrence group showed a lower LAA emptying flow velocity

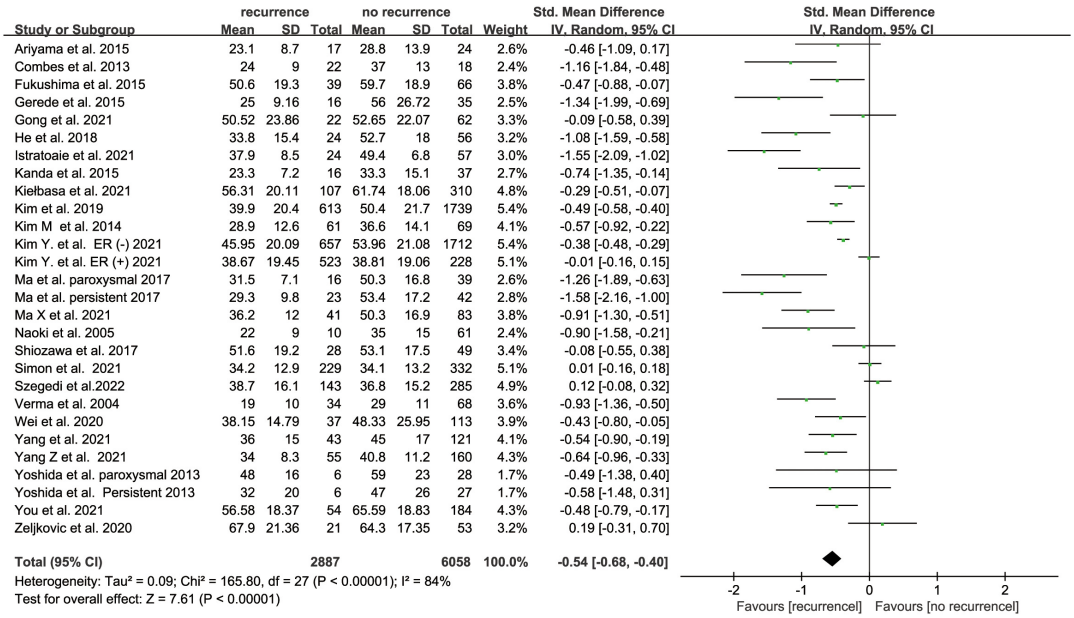

FIGURE 4
Forest plot showing the difference in LAA emptying flow velocity between patients with and without AF recurrence after catheter ablation.

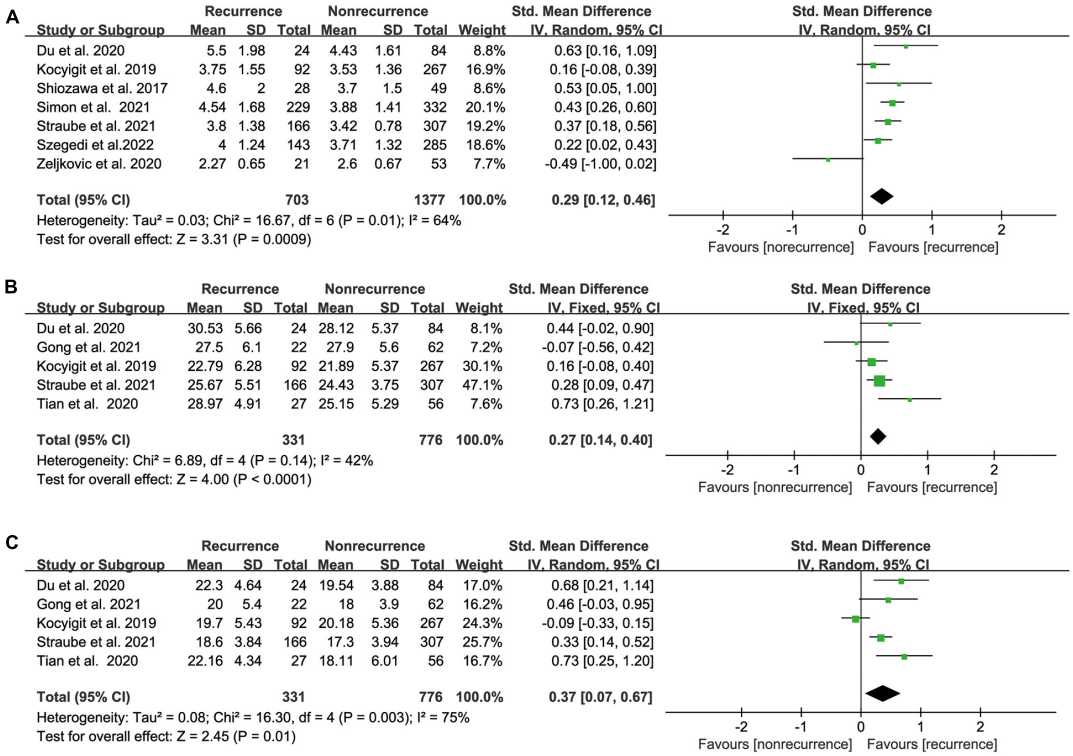

FIGURE 5
(A) Forest plot showing the difference in LAA orifice area between patients with and without AF recurrence after catheter ablation. **(B)** Forest plot showing the difference in LAA orifice long axis between patients with and without AF recurrence after catheter ablation. **(C)** Forest plot showing the difference in LAA orifice short axis between patients with and without AF recurrence after catheter ablation.

than the non-recurrence group, according to our findings (SMD -0.54 95% CI [-0.68, -0.40], $P < 0.00001$; **Figure 4**). The heterogeneity test revealed that I^2 is 84%; we performed the subgroup analysis by size of the sample, follow-up time, AF type, and study region (**Supplementary Figure 3**), but the heterogeneity didn't decrease. We performed a sensitivity analysis to see determine how each study affected the results by removing one trial at a time. However, we found no studies that led to heterogeneity.

Left atrial appendage orifice area or orifice long/short axis and atrial fibrillation recurrence after catheter ablation

Our meta-analysis demonstrated a significant link between pre-ablation LAA orifice area and post-ablation AF recurrence based on the results of seven relevant studies (17, 18, 20–22, 30, 51) that included 2080 participants (SMD 0.29 95% CI [0.12, 0.46] $P = 0.01$; **Figure 5A**). The heterogeneity was significant ($I^2 = 64\%$). Our outcome was unaffected by sensitivity analysis, and heterogeneity was low after excluding Zeljkovic et al., who measured LAA orifice area by TEE, while other studies used CT to measure LAA orifice area.

Based on the findings of the five relevant studies (18, 21–23, 28), we found that the recurrence group had a longer LAA orifice long/short axis than the non-recurrence group, with pooled SMD of 0.27 and 0.37 (95% CI [0.14, 0.40] $P < 0.0001$ **Figure 5B**; 95% CI [0.07, 0.67] $p = 0.01$ **Figure 5C**), respectively. The heterogeneity test showed I^2 values of 42% and 75%, respectively.

Other left atrial appendage parameters and atrial fibrillation recurrence after catheter ablation

As is shown in **Table 1**, we also involved the other five parameters (**Supplementary Figures 5A–E**). Brief descriptions were as follows: pre-ablation LASEC, LAA ejection fraction, decreased LAA filling flow velocity, and increased LAA volume index were associated with AF after catheter ablation while LAA depth was not.

Publication bias analysis

We performed publication bias analysis when >10 studies were included. The funnel plots of LAA emptying flow velocity and volume were both asymmetrical with $P < 0.05$ for Egger's test, which suggested that publication bias was evident. Therefore, we evaluated our results by the trim-and-fill method. After filling the studies, the adjusted results were still statistically significant for both the LAA emptying flow velocity and volume. The analysis results are shown in **Supplementary Figures 6, 7**.

Discussion

This meta-analysis of observational studies assessed whether LAA structure and function could predict the recurrence of AF after CA. The main conclusions were as follows:

(i) LAA structure of pre-ablation (LAA volume, orifice area, orifice long/short axis, and volume index) was larger in the AF recurrence group compared than in the no recurrence group after CA.
(ii) LAA function of pre-ablation (LAA emptying flow velocity, filling flow velocity, ejection fraction, and LASEC) were reduced in patients with AF recurrence patients after CA compared with those without recurrence.
(iii) We found no statistically significant association between pre-ablation LAA morphology (CW vs. NCW, CW vs. cactus, CW vs. cauliflower, CW vs. windsock) and LAA depth.

Notably, this is the first meta-analysis to report the role of LAA function and structure in predicting AF recurrence following CA.

Left atrial appendage (LAA) emptying flow velocity is a commonly used indicator of evaluation LAA function. Previous studies have found that many factors can affect LAA velocity, including AF type, left atrium diameter, left atrium volume, LAA structure, and heart rhythm (52–55). The size of the left atrium is a predictor of AF recurrence after ablation in some meta-analyses (6, 7, 56). Reduced LAA flow velocity has been linked to increased left atrial size (14, 55), which could lead to a higher risk of AF recurrence due to atrial fibrosis and remodeling. Furthermore, new research suggests that left atrial dysfunction, rather than left atrial size, is a more sensitive predictor of AF recurrence (37). In addition, the LAA can play a considerable role in hemodynamics by modifying left atrial pressure-volume relationships because of its increased distensibility (57). The LAA works as a reservoir during excessive volume loading in the beating heart, acting as a barrier to keep the left atrial pressure from increasing too high (58). Therefore, LAA flow velocity was found to be a reliable indicator of contractile and reservoir function in the left atrium.

Moreover, our findings suggest a link between LAA volume and AF recurrence after ablation. Shirani et al' s study found that AF patients have a considerably greater LAA volume than non-AF patients (59). The increased LAA volume may be similar to that of the left atrium, and both of are closely related to myocardial remodeling (22). With fibrosis and

TABLE 1 Analysis of the association of left atrial appendage (LAA) parameters with the post-ablation atrial fibrillation (AF) recurrence.

LAA parameters	No. ofstudies	Participants	P value	Effect estimate(95% CI)	I^2
LAA morphology, (CW vs. NCW)	6	1580	0.21	1.23 (0.89, 1.68)	61
LAA morphology, (CW vs. Windsock)	5	890	0.44	1.17 (0.79, 1.72)	65
LAA morphology, (CW vs. Cactus)	5	398	0.81	1.04 (0.76, 1.41)	0
LAA morphology, (CW vs. Cauliflower)	5	685	0.48	1.10 (0.85, 1.41)	0
LA/LAA spontaneous echo contrast	5	5622	0.0002	1.95 (1.38, 2.75)	90
LAA emptying flow velocity	25	8932	< 0.00001	−0.54 (−0.68, −0.40)	84
LAA filling flow velocity	5	2687	< 0.00001	−0.47 (−0.56, −0.39)	0
LAA ejection fraction	5	519	0.0001	−0.94 (−1.42, −0.46)	80
LAA volume	13	2741	< 0.00001	0.53 (0.36, 0.71)	72
LAA volume index	3	1101	0.02	0.47 (0.09, 0.85)	57
LAA orifice area	7	2080	0.0009	0.29 (0.12, 0.46)	64
LAA orifice long axis	5	1107	< 0.0001	0.27 (0.14, 0.40)	42
LAA orifice short axis	5	1107	0.01	0.37 (0.07, 0.67)	75
LAA depth	5	1375	0.09	0.20 (−0.03, 0.42)	70

LAA, Left atrial appendage; CW, chicken wing; NCW, no chicken wing.

arrhythmogenicity of the LAA, the volume of the LAA can be used as a proxy for the link between left atrial volume and arrhythmogenicity (26). LAA structural alterations, in terms of both function and morphology, which precede left atrial remodeling, have been found to predict AF recurrence (60). LAA may be a far more sensitive criterion than left atrial structure or functional for predicting AF recurrence after CA (16). In addition, paroxysmal AF is typically in the early phases of left atrial remodeling. Therefore, LAA is a more sensitive marker for evaluating AF recurrence after ablation than left atrium in patients with paroxysmal AF (16, 37).

Although the changes in the LAA are closely related to the left atrium, LAA function and structure proved to be strong predictors of AF recurrence after controlling for left atrial structure and related clinical factors in our included study (29, 61). The tissue characteristics of the LAA differ from those of the left atrium and there is a large amount of pectinate muscle that can speed up atrial beats, resulting in faulty electrophysiological features between the LAA and left atrium (62, 63). These findings might indicate that remodeling of the LAA, which differ from the left atrium, plays distinct roles in AF recurrence after CA.

Fukushima et al found that morphology of the LAA is a major factor in the reduced in LAA emptying flow velocity (53). Only Gong et al. and Kocyigit et al. found that the morphology of the LAA is correlated with a higher likelihood of AF recurrence after CA among our six included studies (21, 23). Finally, we found that LAA morphology was not associated with recurrence of AF post ablation, similar to most of the studies we included. Further research may be needed to clarify the relevant mechanism.

These studies which our included suggested that LAA is an essential factor for the recurrence of AF after CA and our meta-analysis confirmed that LAA structure and function can influence AF recurrence. The LAA is viewed as an inconsequential auxiliary structure during the AF. But as the study goes on, we learn more and more in-depth things about the LAA. The LAA has a complicated architecture with large pectinate muscles and extremely varied muscle bundle orientation, which may allow slow conduction and block, as well as the development of re-entry, in contrast to the left atrium (64, 65). It is widely acknowledged that cardiovascular comorbidities like obesity and hypertension have a significant impact on left atrial remodeling and enlargement (26). Because the LAA differs from the left atrium in terms of its embryology, anatomy, and histology, it is unclear what causes it to grow larger (64, 65). This may explain why some patients may have very large LAA with small or moderately sized left atrium (26). We think that the first reason is that the LAA's contraction and extension are more powerful than the left atrium, and it acts as a buffer to lower left atrial pressure (23). Second, the primary conduction channels for atrial electrical activity are the Marshall ligament and Bachmann beam close to the LAA. The normal electrophysiological activity of the LAA must be maintained by the efferent fibers of the sympathetic and vagus nerves. Distinct LAA architectures might result in different electrophysiological activity in the left atrium.

In our included literature, different imaging modalities were used. LAA flow velocity was measured using ultrasound, including TEE or ICE. Measurement of LAA structure, including cardiac CT and TEE. We have not found any studies comparing ICE and TEE measurements of LAA flow velocity. Anter et al. found that TEE can be replaced by ICE

imaging during CA procedures (66). While TEE is the gold standard for perioperative imaging with LAA occlusion, a meta-analysis concluded that ICE is a viable and safe option (67). However, there is currently no accurate method for assessing LAA flow velocity using cardiac CT. For the measurement of the LAA structure, including cardiac CT and TEE. Study demonstrated intraobserver and interobserver reproducibility of TEE and CT measurements of LAA were also good (68). However, LAA measurements derived from TEE were smaller compared with those obtained by CT (68). Xu et al. found that the CTmax of the LAA ostium was substantially connected with the final deployed occluder size (Spearman's rho: 0.81, $p < 0.001$), but the TEEmax of the LAA ostium was only moderately correlated with the occluder size (Spearman's rho: 0.61, $p < 0.001$) (69). However, TEE can provide real-time three-dimensional views of the LAA, allowing it to play a key role for intraprocedural monitoring (70). When these two approaches are used to evaluate LAA size and shape, there may be additional benefits.

Clinical implications

Catheter ablation is a well-established effective therapeutic option for AF. The success rate decreased to 55–65% for paroxysmal AF and 40–50% for persistent AF at five years after CA (71). Our study concluded that decreased LAA function (LAA emptying flow velocity, filling flow velocity, ejection fraction, and LASEC) and enlarged LAA size (LAA volume, orifice area, orifice long/short axis, and volume index) can predict AF recurrence after ablation. The LAA's arrhythmogenic involvement in AF is becoming more widely understood and some researchers have proposed that, in addition to pulmonary vein isolation, the LAA may also be a target during CA for AF (62, 72). A meta-analysis concluded LAA electrical isolation led to a significantly higher improvement in freedom from all-atrial arrhythmia recurrence compared to standard ablation alone in individuals with non-paroxysmal AF (12). Therefore, evaluation of the LAA structure and function before ablation may help physicians make better choices for ablation strategies.

Limitations

We must acknowledge that there are certain limitations of our review. First, our study presented publication bias, which we corrected for using the trim-and-fill method. After filling the studies, the adjusted results were still statistically significant for both the LAA emptying flow velocity and volume. We think the publication bias may be related to some negative results which weren't reported. Second, the specific methods for the measurement of some parameters may not have been provided, which affects the final results in the studies we included. For example, the rhythm of the heart can significantly affect the flow velocity of the LAA. However, data on cardiac rhythm during TEE was not available. Third, there was moderate to high heterogeneity among studies on LAA flow velocity, LAA volume, and LAA orifice area. AF type, follow-up period, geographic location, and sample size were among the study parameters included in our subgroup analyses. Other clinical characteristics, such as comorbidities, gender, and various assessments of AF recurrence, might also contribute to heterogeneity. However, because several studies lacked relevant data, we were unable to do additional subgroup analyses. In addition, different imaging modalities may also lead to significant sources of heterogeneity. Finally, we have to admit that, like our similar type of meta-analysis, our study did not provide ROC-based cut-off values for LAA volume and emptying flow velocity.

Conclusion

Our meta-analysis concluded that large LAA structure of pre-ablation (LAA volume, orifice area, orifice long/short axis, and volume index) and decreased LAA function of pre-ablation (LAA emptying flow velocity, filling flow velocity, ejection fraction, and LASEC) increase the odds of AF recurrence after CA. Pre-ablation assessment LAA function and structure might aid in physicians to improve treatment strategies.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

SH and ML conceived the review. SH drafted and wrote the manuscript. RJ, ZC, RG, and GL revised and edited all the version of the manuscript. KC revised the sections. All authors contributed to the manuscript revision and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1009494/full#supplementary-material

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Performance of the ABC-bleeding risk score for assessing major bleeding risk in Chinese patients with atrial fibrillation on oral anticoagulation therapy: A real-world study

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Objective: To evaluate performance of the ABC (Age, Biomarkers, Clinical history)-bleeding risk score in estimating major bleeding risk in Chinese patients with atrial fibrillation (AF) on oral anticoagulation (OAC) therapy in real-world practice.

Methods: Data were collected from the Chinese Atrial Fibrillation Registry study (CAFR). Patients were stratified into low-, medium-, and high-risk groups based on ABC-bleeding risk score with 1-year major bleeding risk (<1%, 1–2%, and > 2%) and modified HAS-BLED score (≤1, 2, and > 2 points). Cox proportional-hazards (Cox-PH) models were used to determine the association of major bleeding incidence with bleeding scores. Harrell's C-index of the two scores were compared. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) at 1 year were employed to evaluate the reclassification capacity. The calibration curve was plotted to compare the predicted major bleeding risk using ABC-bleeding risk score with the observed annualized event rate. The decision analysis curves (DCA) were performed to show the clinical utilization of two scores in identifying major bleeding events.

Results: The study included 2,892 AF patients on OAC therapy. After the follow-up of 3.0 years, 48 patients had major bleeding events; the incidence of a bleeding event in the low-, medium-, and high-risk groups according to ABC-bleeding risk score was 0.31% (reference group, HR = 1.00),0.51%

(HR = 1.83, 95%CI: 0.91–3.69, P = 0.09), and 1.49% (HR = 4.92, 95%CI: 2.34–10.30, $P < 0.001$), respectively. Major bleeding incidence had an independent association with growth differentiation factor 15 (GDF-15) level (HR = 2.16, 95%CI: 1.27–3.68, P = 0.005) after adjusting components of the HAS-BLED score and cTnT-hs level. The ABC-bleeding score showed a Harrell's C-index of 0.67 (95%CI: 0.60–0.75) in estimating major bleeding risk, which was non-significant compared to the modified HAS-BLED score (0.67 vs. 0.63; P = 0.38). NRI and IDI also revealed comparable reclassification capacity of ABC-bleeding risk score compared with HAS-BLED score (14.6%, 95%CI: −10.2%, 39.4%, P = 0.25; 0.2%, 95%CI −0.1 to 0.9%, P = 0.64). Cross-tabulation of the two scores showed that the ABC-bleeding score outperformed the HAS-BLED score in identifying patients with a high risk of major bleeding. The calibration curve showed that the ABC-bleeding risk score overestimated the observed major bleeding risk. DCA did not show any difference in net benefit when using either of the scores.

Conclusion: This study verified the value of the ABC-bleeding risk score in assessing major bleeding risk in Chinese patients with AF on OAC therapy in real-world practice. Despite the overestimation of major bleeding risk, ABC-bleeding score performed better in stratifying patients with a high risk than the modified HAS-BLED score. Combining the two scores could be a clinically practical strategy for precisely stratifying AF patients, especially those at a high risk of major bleeding, and further supporting the optimization of OAC treatment.

KEYWORDS

atrial fibrillation, ABC-bleeding risk score, HAS-BLED score, major bleeding, anticoagulation, real-world study, GDF-15

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in China with a weighted prevalence of 1.8% [95% confidence interval (CI): 1.7–1.9] (1). Patients with AF have an approximately fivefold increased risk of ischemic stroke, and international guidelines recommend oral anticoagulation (OAC) therapy for stroke prevention (2, 3). However, anticoagulation might result in major bleeding events, which sometimes are even fatal. Therefore, the development of bleeding risk assessment tools is of great importance for decisions making in anticoagulation treatment.

The HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly] score was developed and validated to assess major bleeding risk in patients with AF on OAC therapy (4–6). The 2020 European Society of Cardiology (ESC) AF guidelines recommended the HAS-BLED score to assess major bleeding risk (3). However, as based solely on clinical factors, the HAS-BLED score has only a modest predictive ability for high-risk patients (5).

Recently, several biomarkers have shown the potential to reflect cardiovascular and renal physiology, coagulation, and inflammatory activity, which can determine AF prognosis (7–9).

Growth differentiation factor 15 (GDF-15), secreted by a broad range of cells upon hypoxia and oxidative stress, is a marker of cellular aging and inflammatory activity, as well as a major risk indicator of hemorrhages in patients with AF treated with OAC, even adjusted by the clinical components of HAS-BLED score and other biomarkers (10, 11). In 2016, Hijazi et al. reported a novel biomarker-based tool, the ABC (Age, Biomarkers, Clinical History)-bleeding risk score. The components of the ABC-bleeding risk score include age, GDF-15, high-sensitive cardiac troponin T (cTnT-hs), hemoglobin, and history of bleeding (12). The ABC-bleeding risk score was externally validated and calibrated through several large AF clinical trials (13), and thus is considered more favorable in evaluating major bleeding risk than the HAS-BLED risk score owing to its higher Harrell's C-index suggesting better predictive performance (12, 14). However, a real-world investigation raised a contrary conclusion that the HAS-BLED score outperformed the ABC-bleeding score in estimating major bleeding events (15). Therefore, it is still debatable whether the ABC-bleeding

score is better than the HAS-BLED score for predicting major bleeding, and more evidence from real-world practice is required for further confirmation.

Considering the large population of patients with AF on OAC therapy in China, we aimed to validate the predictive value of the ABC-bleeding risk score and assess how it compared to the HAS-BLED score in Chinese patients with AF receiving OAC based on real-world evidence.

Materials and methods

Our study enrolled patients between 2014 and 2018 from the Chinese Atrial Fibrillation Registry study (CAFR), a prospective, multicenter, hospital-based, ongoing registry study that includes Chinese patients with AF (16). CAFR consecutively enrolled patients with AF from 31 tertiary and non-tertiary hospitals in Beijing, China, with regular follow-ups every 6 months. Data related to AF, including demographics, medical history, symptoms and signs, comorbidities, medical treatment, physical examination, and biochemical tests, were collected. A specialized follow-up team independently recorded clinical events such as major bleeding, stroke, myocardial infarction, and other cardiovascular events.

This study was approved by the Human Research Ethics Committee of Beijing Anzhen Hospital and conducted in accordance with the Declaration of Helsinki.

Study population

A total of 2,892 patients were included in the study and observed with a mean follow-up of 3 years. Patients aged ≥ 18 years who had received OAC treatment lasting at least 3 months were enrolled. Patients were excluded if they met any of the following criteria: valvular AF, including any mechanical valves, or moderate to severe mitral stenosis; unstable conditions: onset of acute coronary syndrome, acute heart failure, stroke, transient ischemic attacks (TIA), and major bleeding events within the 6 months before baseline; data missing during follow-up.

Data collection

Baseline data were collected, including demographic characteristics, comorbidities, OAC treatment received, and biomarker measurements. Major bleeding risk was evaluated by the ABC-bleeding risk and the modified HAS-BLED scores that international normalized ratio (INR) lability was not included as time in therapeutic range (TTR) data were unavailable in this study. Based on the ABC-bleeding risk score predicting 1-year major bleeding risk, patients were stratified into three groups: low-risk (<1%), medium-risk (1–2%), and high-risk (>2%). The modified HAS-BLED score was also calculated to stratify patients into three risk groups: low (0–1 point), medium (2 points), and high (>2 points).

Biochemical samples and laboratory analysis

Three biomarkers were measured in the ABC-bleeding risk score (GDF-15, cTnT-hs, and hemoglobin). EDTA-anticoagulated blood samples were collected from the enrolled patients. Plasma samples were obtained following centrifugation and stored at −70°C until being analyzed centrally. GDF-15 level was analyzed using the Elecsys® GDF-15 assay (Roche Diagnostics International Ltd., Rotkreuz, Switzerland) with the same standardization as other routine reagents on cobas® e 801 analytical unit (Roche Diagnostics International Ltd., Rotkreuz, Switzerland). Other biomarkers included in the ABC-bleeding risk score were measured using the previously published method (10, 11). All analyses were conducted according to manufacturer instructions.

Clinical outcomes

The primary endpoint of this study was major bleeding events defined according to the 2005 International Society on Thrombosis and Hemostasis criteria: fatal bleeding or symptomatic bleeding in a critical anatomical site (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a fall in hemoglobin ≥ 20 g/L, or transfusion of ≥ 2 units of whole blood or red blood cells (17).

Statistical analysis

Baseline characteristics were described and stratified into the three ABC-bleeding risk score levels. Continuous variables were described as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the data distribution.

Cox-proportional hazard (Cox-PH) regression models were conducted to assess the association between the risk levels identified by the ABC-bleeding risk and the modified HAS-BLED scores and major bleeding incidence. Kaplan-Meier (K-M) curves showing the probability of major bleeding in each ABC-bleeding 1-year and modified HAS-BLED risk level were plotted. Log-rank test was conducted to compare the survival distributions between groups. Harrell's C-index was calculated to evaluate the discriminatory performance of the ABC-bleeding risk and the modified HAS-BLED scores. Net reclassification improvement (NRI),

and integrated discrimination improvement (IDI) at 1 year, the positive value of which can indicate an improvement in risk prediction (18), were used to assess the reclassification performance of the ABC-bleeding risk score in predicting 1-year major bleeding risk compared with the modified HAS-BLED score. The calibration curve of ABC-bleeding risk score was plotted by comparing the predicted one-year risk with observed annualized event rate. The decision curves analysis (DCA) was employed to evaluate the net benefit of using one score to identify major bleeding events. Sensitivity analysis was further conducted according to the anticoagulation types and by the exclusion of those with antiplatelet therapy.

In this study, a one-side P-value of < 0.025 was considered statistically significant for the Cox-PH regression model, and $P < 0.05$ was considered statistically significant for all other analyses. All analyses were conducted using R 4.0.0 and SAS 9.4 statistical software.

Results

Baseline characteristics

Demographic and baseline characteristics of the three patient groups stratified by ABC-bleeding risk score are summarized in Table 1. In total, 2,892 patients were included in the cohort, with a mean age of 59.9 (SD: 10.70) years and 68.0% male. The mean age of patients decreased from 72.72 (SD: 8.21) years in the high-risk group to 53.18 (SD: 8.66) years in the low-risk group. Paroxysmal AF was the most common type of AF, present in over 60%

TABLE 1 Demographic and baseline characteristics stratified by the ABC-bleeding risk score.

	Risk level		
	High (N = 301)	**Medium (N = 1,084)**	**Low (N = 1,507)**
Demographics			
Mean age, years, (SD)	72.72 (8.21)	65.79 (6.29)	53.18 (8.66)
Male, *n* (%)	166 (55.1)	664 (61.3)	1,136 (75.4)
Mean BMI, kg/m^2, (SD)	25.23 (3.70)	25.46 (3.46)	26.06 (3.57)
AF type, *n* (%)			
New onset	1 (0.3)	4 (0.4)	2 (0.1)
Paroxysmal	197 (65.4)	713 (65.8)	970 (64.4)
Persistent/permanent	103 (34.2)	367 (33.9)	535 (35.5)
Mean eGFR (CKD-EPI), mL/min/1.73 m^2, (SD)	73.76 (18.59)	83.74 (13.92)	94.54 (13.58)
Current smoking, *n* (%)	24 (8.0)	97 (8.9)	205 (13.6)
Current alcohol consumption, *n* (%)	20 (6.6)	101 (9.3)	211 (14.0)
Comorbidities, *n* (%)			
Coronary artery disease	61 (20.3)	175 (16.1)	119 (7.9)
Peripheral arterial disease	6 (2.0)	7 (0.6)	4 (0.3)
Hypertension	221 (73.4)	726 (67.0)	715 (47.4)
Heart failure	31 (10.3)	62 (5.7)	52 (3.5)
Ischemic stroke or TIA	53 (17.6)	154 (14.2)	88 (5.8)
Diabetes mellitus	79 (26.2)	291 (26.8)	215 (14.3)
Previous bleeding	33 (11.0)	65 (5.8)	49 (3.3)
Medication, *n* (%)			
OAC therapy			
Warfarin	136 (45.2)	371 (34.2)	443 (29.4)
NOAC	165 (54.8)	713 (65.8)	1,064 (70.6)
Antiplatelet therapy	47 (15.6%)	171 (15.8%)	160 (10.6%)
Biomarker levels			
GDF-15, ng/L, medium (IQR)	2075.00 [1532.00, 2773.00]	1281.50 [1061.75, 1602.75]	783.00 [619.00, 983.50]
cTnT-hs, ng/L, median (IQR)	15.60 [11.80, 24.20]	9.54 [7.85, 12.10]	6.56 [5.27, 8.11]
Hemoglobin, g/L, median, (IQR)	136.83 (16.38)	144.75 (13.83)	152.05 (13.72)
CHA_2DS_2-VASc, mean ± SD	3.39 (1.47)	2.44 (1.40)	1.12 (1.05)
HAS-BLED, mean ± SD	2.04 (0.91)	1.57 (0.90)	0.92 (0.80)

AF, atrial fibrillation; BMI, body mass index; cTnT-hs, high-sensitive cardiac troponin T; eGFR (CKD-EPI), estimated glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration equation; GDF-15, growth differentiation factor 15; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulants, which includes three drugs: rivaroxaban, apixaban, and dabigatran; OAC, oral anticoagulation; SD, standard deviation; TIA, transient ischemic attack.

of patients in each group. Compared with patients in the medium- and low-risk groups, high-risk patients had a lower estimated glomerular filtration rate and were more likely to suffer from multiple cardiovascular comorbidities, particularly hypertension, coronary artery disease, and heart failure. Non-vitamin K antagonist oral anticoagulants (NOACs) were the most common anticoagulation therapies that were used to treat 50–70% of patients across the three groups. Median GDF-15 level increased from 783.00 ng/L (IQR: 619.00, 983.50) in the low-risk group to 2,075.00 ng/L (IQR: 1532.00, 2773.00) in the high-risk group. The CHA_2DS_2-VASc (a clinical prediction rule used for estimating the risk of stroke in patients with AF) and the modified HAS-BLED scores in each group showed the same trend of increasing with a higher risk level based on the ABC-bleeding risk score.

Association of ABC-bleeding risk score with major bleeding incidence

The follow-up lasted at least 3 months with a median of 3.0 years. The medium treatment period for patients on warfarin was 293 (IQR: 93, 815) days and 265 (IQR: 98, 447) days for those on NOACs.

In total, 48 major bleeding events occurred during the follow-up. The incidence rate of major bleeding events was 0.51 per 100 person-year. Cox-PH models showed a statistically significant association between major bleeding events and $\log_2$(GDF-15) [hazard ratio (HR) 2.72, 95% CI: 1.68–4.41, $P < 0.001$; **Supplementary Table 1**], even after adjusted using the components of HAS-BLED score and level of cTnT-hs (HR 2.16, 95% CI: 1.27-3.68, $P = 0.005$, **Supplementary Table 1**).

Risk stratification by ABC-bleeding risk score and how it compares with the modified HAS-BLED score

The 48 major bleeding events were classified into subgroups based on risk levels identified by the ABC-bleeding risk and the modified HAS-BLED scores. The incidence of major bleeding in each group was summarized in **Table 2**. Specifically, 1,507 (52.11%), 1,084 (37.48%), and 301 (10.41%) patients were identified as low-, medium-, and high-risk, respectively, by the ABC-bleeding risk score, with an increasing incidence of major bleeding from 0.31 (15/48), 0.51 (18/48) to 1.49 (15/48) per 100 person-years, respectively. The Cox-PH regression model showed that the high-risk group identified by the ABC-bleeding risk score had a statistically significant higher major bleeding risk than the low-risk group (HR 4.92, 95% CI: 2.34–10.30, $P < 0.001$). In contrast, the association of risk level with the major bleeding incidence in the medium-risk group failed to reach statistical significance (HR 1.83, 95% CI 0.91–3.69, $P = 0.09$). For patient groups stratified by the modified HAS-BLED score, the Cox-PH regression model revealed that the actual major bleeding risk level was statistically significant in the medium-risk (HR 2.58, 95% CI: 1.32–5.05, $P = 0.005$) and the high-risk groups (HR 3.70, 95% CI 1.67–8.30, $P = 0.001$). Kaplan-Meier curves showed a significant difference in the cumulative incidence rate of major bleeding among the three risk levels stratified by ABC-bleeding and the modified HAS-BLED scores ($P < 0.001$ and $P = 0.001$, respectively, **Figure 1**). However, cumulative incidence rate curves and log-rank test between each two risk level groups by the modified HAS-BLED score showed that the survival distribution between the median- and high-risk groups did not reach a significant difference ($P = 0.35$, **Supplementary Figure 1**).

To further evaluate the discriminatory ability of the ABC-bleeding risk score to identify high-risk patients, the low- and medium-risk groups determined by the ABC-bleeding risk score were combined and analyzed using a Cox-PH regression model. Using the combined low + medium risk level as the reference, the high-risk level identified by the ABC-bleeding risk score showed a significantly higher major bleeding risk (HR 3.68, 95% CI: 1.96–6.90, $P < 0.001$). A similar but lower risk was also observed between the high-risk level and low + medium risk level stratified by the modified HAS-BLED score (HR 2.42, 95% CI: 1.20–4.89, $P = 0.01$) (**Supplementary Table 2**). Corresponding Kaplan-Meier curves also suggested a better performance of the ABC-bleeding risk score than the modified HAS-BLED score in differentiating high-risk patients (**Supplementary Figure 2**).

Performance of ABC-bleeding risk score in major bleeding risk and how it compares with the modified HAS-BLED score

As summarized in **Table 3**, the Harrell's C-index of the ABC-bleeding risk score was non-significantly higher than that of the modified HAS-BLED score [0.67 (95% CI: 0.60–0.75) vs. 0.63 (95% CI: 0.56–0.70), $P = 0.38$]. The NRI and IDI value at 1-year follow-up for the ABC-bleeding risk score revealed comparable reclassification capacity compared with the modified HAS-BLED score (14.6%, 95%CI: −10.2 to 39.4%, $P = 0.25$; 0.2% 95%CI −0.1 to 0.9%, $P = 0.64$).

To find the underlying relationship between the two scores, the major bleeding incidence in nine patient subgroups cross-tabulated by ABC-bleeding 1-year and the modified HAS-BLED risk levels was shown in **Figure 2**. ABC-bleeding risk score could further discriminate low-risk patients defined by the modified HAS-BLED score into low-, medium-, and high-risk subgroups with corresponding major bleeding incidences of 0.16, 0.39, and

TABLE 2 Major bleeding incidence and Cox proportional-hazards regression analysis of risk levels stratified by the ABC-bleeding and the modified HAS-BLED scores.

	ABC-bleeding score risk level			Modified HAS-BLED score risk level		
	Low	Medium	High	Low	Medium	High
N (%)	1,507	1,084	301	1,717	874	301
No. of events	15	18	15	15	23	10
Incidence (per 100 person-years)	0.31	0.51	1.49	0.27	0.78	0.97
HR (95% CI)*	–	1.83 (0.91–3.69)	4.92 (2.34–10.30)	–	2.58 (1.32–5.05)	3.70 (1.67–8.30)
P-value	–	0.09	<0.001	–	0.005	0.001

CI, confidence interval; HR, hazard ratio.
*HR vs. the low-risk group.

1.44 per 100 person-years, respectively. Meanwhile, the HAS-BLED score could also stratify low-risk patients determined by the ABC-bleeding score into three different risk levels, with an incidence rate of 0.16, 0.74, and 1.03 per 100 person-years, respectively. Notably, the incidence rate of the three high-risk subgroups stratified by ABC-bleeding score was all higher than 1.4 per 100 person-years, which implied better discrimination of high-risk patients by ABC-bleeding score.

The calibration curve is shown in **Figure 3**. The ABC-bleeding risk score overestimated the major bleeding risk when comparing the predicted risk with the observed annulized event rate. DCA showed no difference in net benefit of ABC-bleeding risk score in identifying more major bleeding events without increasing the false positive rate compared with HAS-BLED score (**Figure 4**).

Sensitivity analysis

In subgroups stratified by anticoagulation types, the incidence rate of major bleeding events in the warfarin subgroup was significantly higher than that in the NOAC subgroup (0.67%, 95%CI 0.44–0.98% $p < 0.001$ vs. 0.40%, 95%CI 0.25–0.60%, $P < 0.001$), the performance of the ABC-bleeding risk score was comparable with that of the modified HAS-BLED score [0.65 (95% CI: 0.53–0.76) vs. 0.64 (95% CI: 0.55–0.74), $P = 0.93$ for warfarin; 0.69 (95% CI: 0.58–0.80) vs. 0.62 (95% CI: 0.52–0.72), $P = 0.28$ for NOACs], as presented in **Supplementary Table 3**.

We further investigated the performance of ABC-bleeding risk and HAS-BLED scores by excluding the patients on antiplatelet therapy ($n = 378$, 13.1%), and the results were similar to our main findings (**Supplementary Table 4**). Discriminative performance of ABC-bleeding score was comparable with that of HAS-BLED score (0.69 vs. 0.64, $P = 0.41$); NRI also showed similar reclassification capacity of ABC-bleeding score compared with HAS-BLED score (15.5%, 95%CI −11.0–42.0%, $P = 0.25$); Although the IDI reached the significant threshold, it showed modest improvement when comparing ABC-bleeding score with HAS-BLED score (0.4%, 95%CI 0–0.8%, $P = 0.02$).

Discussion

This observational study represented the first real-world Chinese-patient-specific study to validate the ABC-bleeding risk score in assessing major bleeding in patients with AF on OAC therapy. The GDF-15 level, an important variable included in the ABC-bleeding risk score, showed a significant association with major bleeding risk. Although we observed no significant difference in the C-index and reclassification capacity when comparing ABC-bleeding risk and the modified HAS-BLED scores, the further cross-table analysis suggested that these two scores were complementary and can cross-identified high-risk patients from the other's low-risk group. Despite the overestimation of major bleeding risk, the ABC-bleeding score performed better in differentiating high-risk patients. Overall, we suggest that the ABC-bleeding risk score is an important tool in estimating major bleeding risk in Chinese patients with AF on OAC therapy, especially those at high risk. The two scores can complement one another to identify patients with a high risk of major bleeding for the further optimization of OAC therapy.

AF patients on OACs frequently develop bleeding events, the most severe of which can be fatal. Several factors, including age, uncontrolled hypertension, and renal failure, can enhance the patients' risk of major bleeding. However, previous studies have demonstrated that the predictive performance of the risk assessing scores and tools based solely on clinical criteria is just moderate, especially for identifying individuals with a high risk of bleeding. Several biomarkers have been investigated as the subject for quantitatively assessing major bleeding risk. cTnT-hs, a biomarker reflecting cardiovascular endothelial integrity, was associated with an increased risk of major bleeding regardless of OACs patterns in the ARISTOTLE trial (19), and this association remained significant after adjusted cTnT-hs level by the components of the HAS-BELD score in the ENGAGE AF-TIMI 48 trial (14). However, the comparable predictive ability of cTnT-hs toward stroke makes it less specific in assessing bleeding risk. GDF-15, a marker of tissue hypoxia and oxidative stress, has received great attention in predicting major bleeding in patients on OAC (20). It has been observed in clinical trials

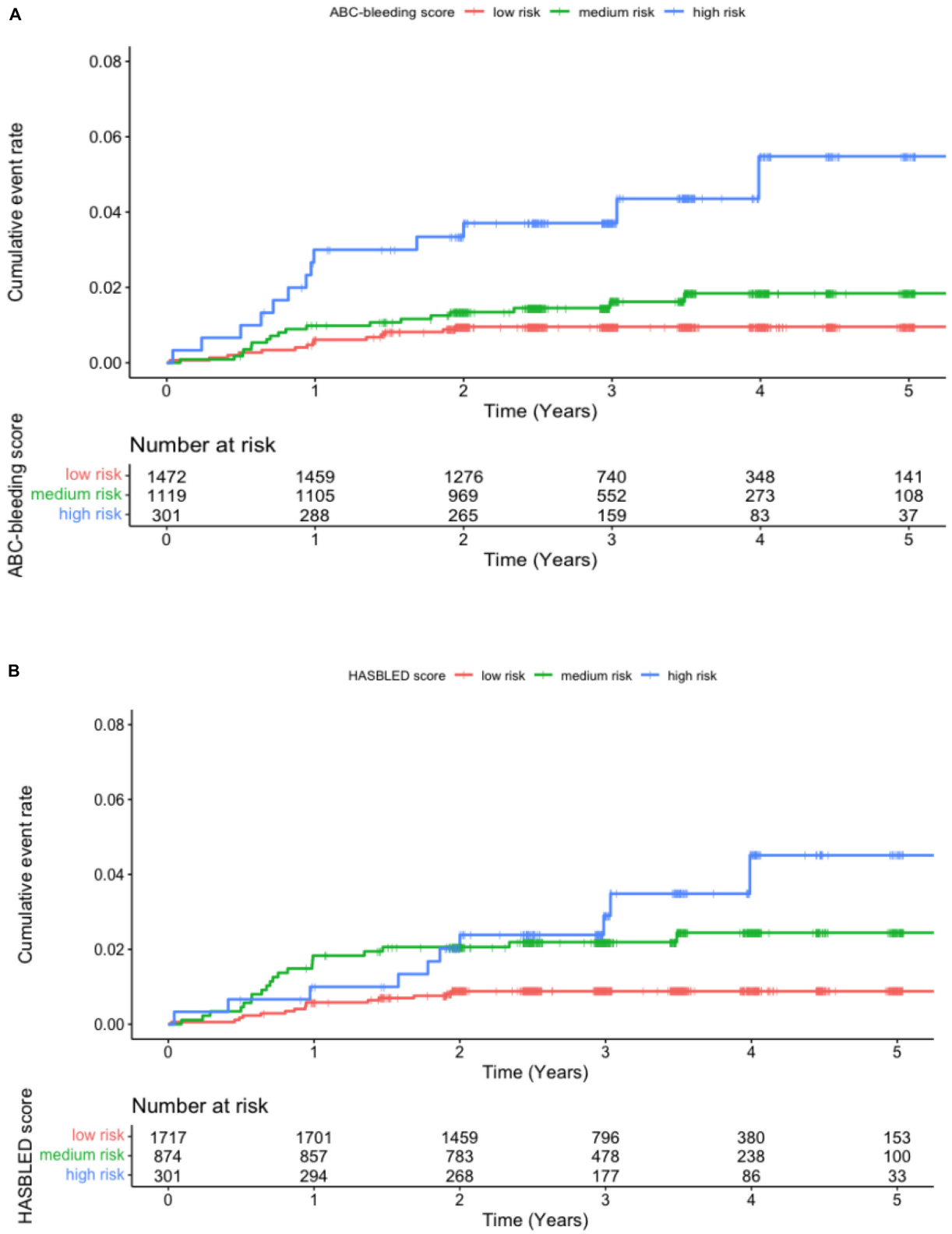

FIGURE 1
Kaplan-Meier curve for major bleeding in patients at low, medium, and high risk stratified by **(A)** the ABC-bleeding risk and **(B)** the modified HAS-BLED scores.

TABLE 3 Discrimination and reclassification analysis of the ABC-bleeding risk and the modified HAS-BLED scores.

	C-index	95% CI	*P*-value*	NRI at 1 year	*P*-value	IDI at 1 year	*P*-value
ABC-bleeding risk score	0.67	0.60–0.75	0.38	14.6% (−10.2%, 39.4%)	0.25	0.2% (−0.1 to 0.9%)	0.64
Modified HAS-BLED score	0.63	0.56–0.70					

CI, confidence interval; IDI, integrated discrimination improvements; NRI, net reclassification improvement.
**P*-value for comparison of ABC-bleeding score with the modified HAS-BLED score.

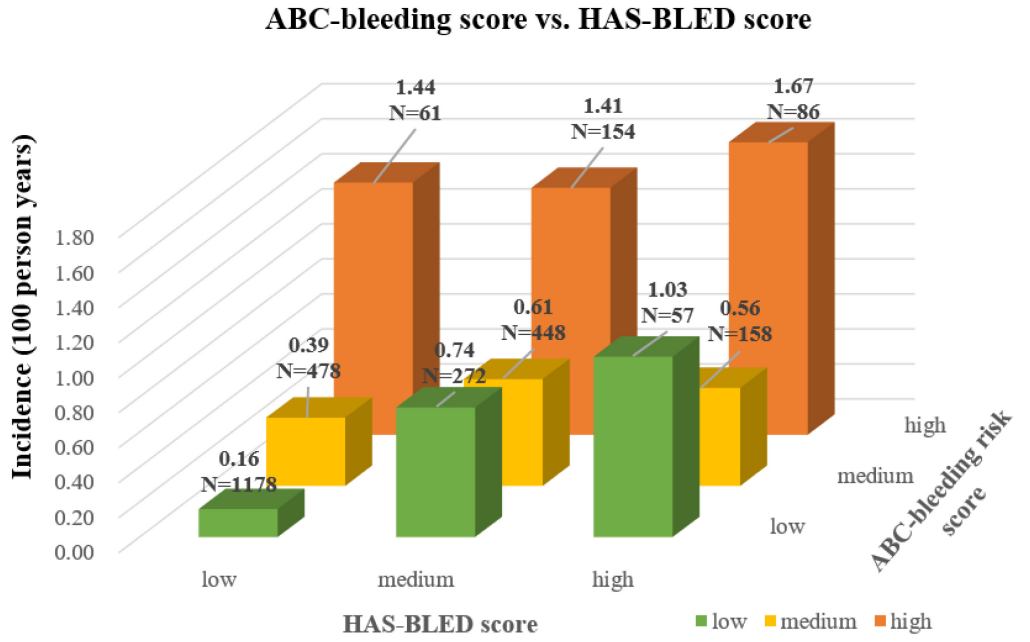

FIGURE 2
Cross-tabulation showing major bleeding incidence stratified by the ABC-bleeding risk and the modified HAS-BLED scores. The risk level shown by the color of column was assigned based on the modified HAS-BLED score.

that after controlling components in the HAS-BLED score and other biomarkers, including cTnT-hs and NT-proBNP, GDF-15 was highly related to the risk of major bleeding (10, 14). In our study, the significant association of GDF-15 with major bleeding risk was also recognized, regardless of adjusting the Cox-PH model using the components in the HAS-BLED score and cTnT-hs level. This observation further supports the previous studies in clinical trials and suggests the value of GDF-15 in indicating major bleeding risk.

Combining clinical factors and biomarkers related with major bleeding risk, a novel biomarker-based score, the ABC—bleeding risk score, was developed and utilized in estimating bleeding risk of patients with AF in the ARISTOTLE trial (12). Afterward, the outperformance of ABC-bleeding score compared to HAS-BELD score in patients receiving anticoagulation was externally validated in RE-LY and ENGAGE AF-TIMI 48 trials (14, 20). However, it should be noted that a previously reported real-world study concluded that the HAS-BLED score performed significantly better than the ABC-bleeding risk score, with a higher Harrell's C-index (0.583 vs. 0.518) and positive NRI. This weaken in the predictive performance of the ABC-bleeding risk score in the established real-world study compare to in clinical trials may be attributed to several factors: Firstly, the differences in study design, demographic characteristics, and uncontrolled factors may lead to the variation in performance of the ABC-bleeding risk score; Secondly, the validation study in clinical trials implied that the risk discrimination performance of ABC-bleeding score was much better for AF patients on NOAC than on warfarin therapy, while at the baseline of the real-world study, patients only received warfarin therapy (21). Therefore, the performance of the ABC-bleeding score might be underestimated in the real-world study due to its unicity of OAC therapy; Thirdly, in the established real-world study, GDF-15 level was replaced by creatinine clearance estimated by the CKD-EPI equation, which might also weaken the performance of the ABC-bleeding risk score in predicting major bleeding events.

Unlikely the aforementioned studies in clinical trials and the real-world situation that both stating one score is significantly

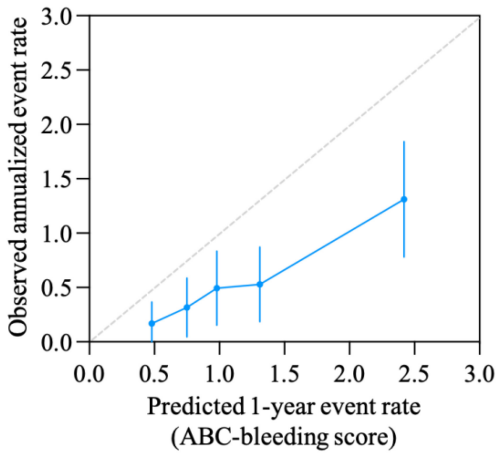

FIGURE 3
Calibration curve for ABC-bleeding risk score. Calibration was evaluated by comparison of the ABC-bleeding risk score-predicted event rate and the observed annualized events rate.

better than the other, a recent meta-analysis demonstrated that the HAS-BELD score is as least non-inferior to the ABC-bleeding score with a comparable c-index value (0.61 vs. 0.65, $P > 0.05$) (22), while further analyses investigating the discriminative ability of these two scores were limited. In addition, another network meta-analysis suggested that the HAS-BLED score has an optimal balance of sensitivity and specificity, while the ABC-bleeding score had comparatively higher sensitivity, defined as the ratio between the number of major bleeding events in high-risk stratification and the total number of bleeding events, suggesting that the ABC-bleeding score has its own strength in stratifying high-risk patients (23). Similar to these two meta-analyses, our real-world study suggested that the two scores did not perform significantly different in assessing major bleeding risk, and our further analysis revealed a better discrimination of the ABC-bleeding score to patients with a high risk of major bleeding. It should be recognized that several high risk patients could be further stratified by the HAS-BELD score from the groups with low-risk level identified by the ABC-bleeding score, and this might explain the non-significant difference between the two scores. Considering the validation of the two scores and the observed complementary effect in identifying high risk patients, a combination of the two scores might optimize the identification of patients with different risk levels.

Our study showed the potential clinical implications of ABC-bleeding score in real-world practice. When assessing the major bleeding risk of AF patients on OAC, physicians could use a combination of the ABC-bleeding risk score and the international guidelines recommended HAS-BELD score to recognize AF patients with a high risk of major bleeding. For the high-risk patients stratified by the two scores, international guidelines suggested that their high bleeding risk score should

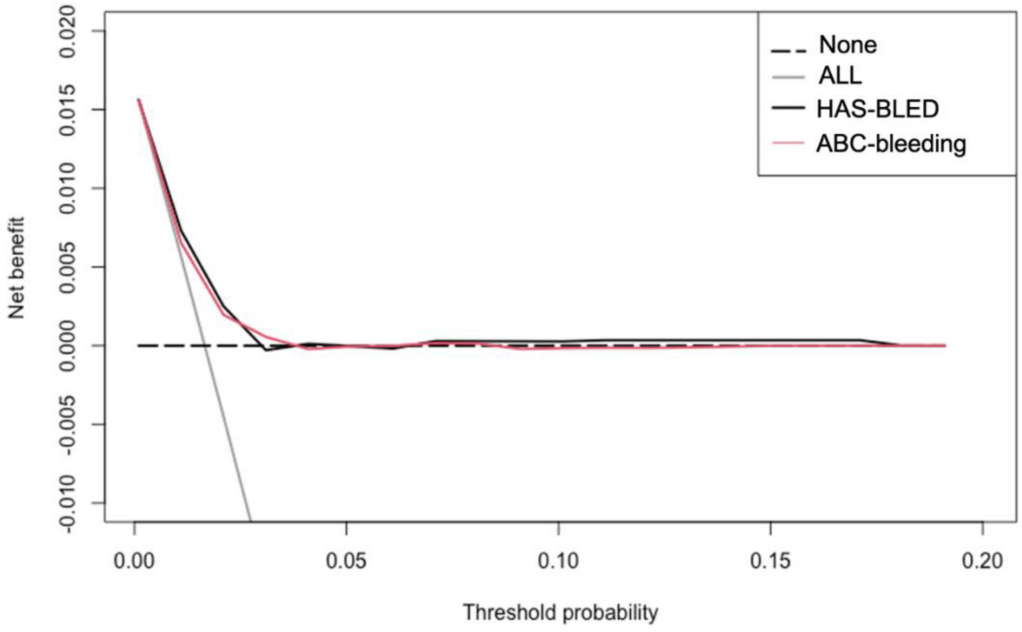

FIGURE 4
Decision curves for ABC-bleeding risk and HAS-BLED scores. This analysis shows the clinical usefulness of each score based on a continuum of potential thresholds for major bleeding events (*x*-axis) and the net benefit of using the score to stratify patients at risk (*y*-axis) comparing to assuming that no patient will suffer from major bleeding risk.

not lead to the withholding of OAC as the net benefit of OAC is even greater amongst such patients (3). However, the OAC treatment pattern of these patients will need careful management and active monitoring to prevent potential major bleeding events. GDF-15 and other biomarkers could also be used to monitor changes in risk indicators and could contribute to altering OAC therapy in AF treatment over time. In conclusion, we endorse that combining the ABC-bleeding risk and the modified HAS-BLED scores, as a comprehensive consideration of biomarkers and clinical information, could well recognize patients with a high risk of major bleeding and optimize the net benefit of OAC therapy in clinical practice.

Limitations

The limitations of this study should be addressed. As a prospective observational study, baseline characteristics could be diverse among different bleeding risk levels in real-world situations, which might lead to bias in our results. Another limitation is that INR lability was not included in the calculation of the modified HAS-BLED score, as the TTR data for patients on warfarin were not available in our cohort. Although most patients were prescribed NOACs in our study, the absence of INR lability might cause a bias in assessing the predictive value of the HAS-BLED score. Moreover, as the cohort represents the Chinese population with AF on OAC, extrapolating the findings in this study to other ethnic groups requires further investigation. Finally, as the ABC-bleeding risk score overestimated the major bleeding risk due to the relatively lower event rate than previous studies, recalibration for better utilization requires further investigation.

Conclusion

This observational study represented the first real-world validation of the ABC-bleeding risk score in China to assess major bleeding risk in patients with AF on OAC treatment. The predictive performance of the ABC-bleeding scores was not significantly different from the modified HAS-BLED score, and the ABC-bleeding risk score overestimated the major bleeding risk. but the ABC-bleeding score categories revealed a better capability in identifying high-risk patients. As the modified HAS-BLED score could stratify high-risk patients from the low-risk groups determined by the ABC-bleeding risk score, we endorse that combining the two risk scores would be a clinically practical strategy yielding a more comprehensive understanding of patients with different risk levels of major bleeding, especially for those at a high-risk level, and improving decision-making in OAC treatment.

Data availability statement

The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Human Research Ethics Committee of Beijing Anzhen Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Y-FW undertook study design and data analysis under the guidance of the MDs. Y-FW wrote this manuscript under the guidance of the corresponding author. All authors revised the article and approved the submitted version.

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Conflict of interest

This study was sponsored by Roche Diagnostics (Shanghai). Roche Diagnostics (Shanghai) Limited was allowed to review the study protocol and comment on the final version of the

manuscript as well as contributed to the design, conducting, and statistical analysis of the study. Under the authors' direction, medical writing support was provided by Xue Wu of Roche Diagnostics (Shanghai) Limited.

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Publisher's note

Supplementary material

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Effect of angiotensin receptor-neprilysin inhibitor on atrial electrical instability in atrial fibrillation

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Background and objective: Around 33.5 million patients suffered from atrial fibrillation (AF), causing complications and increasing mortality and disability rate. Upstream treatment for AF is getting more popular in clinical practice in recent years. The angiotensin receptor-neprilysin inhibitor (ARNI) is one of the potential treatment options. Our study aimed to investigate the effect of ARNI on atrial electrical instability and structural remodeling in AF.

Methods: Our research consisted of two parts – a retrospective real-world clinical study and an animal experiment on calmness to verify the retrospective founding. In the retrospective study, we reviewed all patients (n = 110) who had undergone the first AF ablation from 1 August 2018 to 1 March 2022. Patients with ARNI (n = 36) or angiotensin II receptor antagonist (ARB) (n = 35) treatment were enrolled. Their clinical data, ultrasound cardiogram (UCG) and Holter parameters were collected before radiofrequency catheter ablation (RFCA) as baseline and at 24-week follow-up. Univariate and multivariate logistic regression analysis were performed. In the animal experiment, we established an AF model (n = 18) on canines by rapid atrial pacing. After the successful procedure of pacing, all the 15 alive beagles were equally and randomly assigned to three groups (n = 5 each): Control group, ARB group, and ARNI group. UCG was performed before the pacing as baseline. Physiological biopsy, UCG, and electrophysiological study (EPS) were performed at 8-week.

Results: Clinical data showed that the atrial arrhythmia rate at 24-week was significantly lower in ARNI group compared to ARB group ($P < 0.01$), and ARNI was independently associated with a lower atrial arrhythmia rate ($P < 0.05$) at 24-week in multivariate regression logistic analysis. In the animal experiment, ARNI group had a higher atrial electrical stability score and a shorter AF duration in the EPS compared to Control and ARB group ($P < 0.05$). In the left atrium voltage mapping, ARNI group showed less low voltage and disordered zone compared to Control and ARB group. Compared to Control group, right

atrium diameter (RAD), left ventricle end-diastolic volume index (LVEDVI), E/A, and E/E′ were lower in ARNI group ($P < 0.05$) at the 8-weeks follow-up, while left atrium ejection fraction (LAEF) and left ventricle ejection fraction (LVEF) were higher ($P < 0.01$). Compared to ARB group, LVEF was higher in ARNI group at the 8-week follow-up ($P < 0.05$). ARB and ARNI group had a lower ratio of fibrotic lesions in the left atrium tissues compared to Control group ($P < 0.01$), but no difference was found between the ARB and the ARNI group.

Conclusion: ARNI could reduce atrial electrical instability in AF in comparison with ARB in both retrospective study and animal experiment.

KEYWORDS

ARNI, RFCA, atrial fibrillation, atrial electrical instability, structural remodeling

Introduction

Atrial fibrillation (AF) is defined as a tachyarrhythmia with uncoordinated atrial activation and ineffective atrial contraction (1). With 33.5 million patients worldwide, AF is the most common type of cardiac arrhythmia (2), leading to complication such as cerebral strokes and heart failure. It caused an increasing mortality and disability rate, leading to a higher health related economic burden (3).

More effective treatment for AF needs to be explored, especially for persistent AF. Most patients had a high risk of AF recurrence after cardioversion by classic anti-arrhythmic drugs (4). With the development of technology, radiofrequency catheter ablation (RFCA) was gradually becoming an effective treatment for AF, but the recurrence rate was still around 30% in the long-term (5). Considering the unsatisfactory results of classic antiarrhythmic drugs and RFCA (6), increasing attention was paid to the upstream treatment of AF, which could mechanically counter the atrial remodeling and therefore theoretically inhibit the initiation, maintenance, and progression of AF (7).

Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor antagonist (ARB) were observed in experimental studies to be able to prevent the electrical and structural remodeling in AF (8, 9). In clinical practice, however, ACEI/ARB often played a role in primary prevention to reduce the incidence of new AF in patients with heart failure (10). Among patients already with AF, ACEI/ARB did not seem to be an effective treatment in secondary prevention in face of a recurrence rate with no statistical difference (11).

Valsartan/sacubitril, an angiotensin receptor-neprilysin inhibitor (ARNI), had gained increasing interest in the treatment of AF in recent years. In addition to the ARB effect with valsartan, ARNI also contains sacubitril, a neprilysin increasing the half-life of A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), which in turn results in a natriuretic, diuretic, vasodilatory, and antifibrotic effect (12). ARNI had been recognized as having superior effects to ACEI/ARB in the treatment of heart failure with the greatest mortality reduction (13). Several studies suggested that ARNI could decrease the atrial remodeling in heart failure and play a potential role in AF prevention (14). Dong et al. found ARNI was associated with a lower risk of AF recurrence compared to ACEI after RFCA in a propensity-matched cohort study (15). However, it was difficult to find whether it was the ARB or ARNI as a whole that resulted in a superior therapeutic effect to ACEI after the RFCA, given that ARB was one of the components of ARNI. There were few studies comparing the effects of ARNI and ARB on AF, especially from both clinical and experimental animal perspectives. Herein, we investigated the effects of ARNI in comparison with ARB on atrial electrical instability and structural remodeling in AF through retrospective clinical studies and canine animal experiments.

Materials and methods

Clinical data review

We retrospectively reviewed all patients who had undergone first AF ablation from 1 August 2018 to 1 March 2022 in the Heart Center of Peking University International Hospital. The data included the information below: (1) Basic information, including age, gender, height, weight, body mass index, and current smoker or drinker. (2) Medical history, including persistent atrial fibrillation (persistent AF), hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure (CHF), myocardial infarction (MI), revascularization, peripheral vascular disease (PVD), stroke/transient ischemia attack (TIA), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), obstructive sleep apnea-hypopnea syndrome (OSAHS), and CHA2DS2-VASc score. (3) Perioperative medications that may affect the results. (4) Baseline clinical data at hospitalization before AF ablation,

including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin, serum creatinine, estimated glomerular filtration rate (eGFR), and serum potassium. (5) Ultrasound cardiogram (UCG) parameters at hospitalization before RFCA (baseline) and 24-week follow-up, including left atrium diameter (LAD), right atrium diameter (RAD), left ventricle end-diastolic diameter (LVEDD), right ventricle end-diastolic diameter (RVEDD), and left ventricle ejection fraction (LVEF). (6) Clinical data at 24-week follow-up, including AF recurrence or other atrial arrhythmia in Holter, all cause rehospitalization and all cause death.

The data was mainly collected by reviewing outpatient and inpatient medical history. For patients from provincial cities who were not able to be followed up in outpatient clinics, we used telephone follow-up to obtain information.

In this study, persistent AF was defined as AF lasting more than 7 days. AF early recurrence at 24-week follow-up was defined as AF sustained more than 30 s detected on Holter. Atrial arrhythmia at 24-week follow-up was defined as AF/flutter/tachycardia lasting longer than 3 beats or premature atrial contraction more than 1,000 beats per day on Holter.

Exclusion criteria: patients who did not take ARB or ARNI; patients we lost contact with. Patients treated with ARNI were selected to the ARNI group, and patients treated with ARB were selected to the ARB group (**Figure 1**).

The research was in compliance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Peking University International Hospital.

Radiofrequency catheter ablation strategy

At baseline, electrocardiogram (ECG), Holter, and UCG were routinely performed for all patients. The AF was confirmed by ECG or Holter (AF on at least one ECG, or AF lasting more than 30 s on Holter). Anticoagulant such as Rivaroxaban or Dabigatran was routinely given to all patients before the RFCA for at least 3 weeks. Anti-arrhythmic drugs were discontinued for at least 5 half-lives before the RFCA. Transesophageal echocardiography was performed before the RFCA to rule out the embolism in left atrium (LA).

The ablation was performed under general anesthesia. After the successful punctures on bilateral femoral veins, the first dose of heparin was given (50 IU/kg). The decapolar catheter was placed in coronary sinus *via* the left femoral vein for electro-anatomical reference and stimulation. The LA access was established by an atrial septal puncture. After the successful atrial septal puncture, the second dose of heparin (50 IU/kg) was administered to maintain an activated clotting time at 250–350 s.

The Pentaray catheter (Pentaray Nav eco High-Density Mapping Catheter, Biosense Webster, CA, USA) was placed in the pulmonary veins (PVs) *via* the right femoral vein. The 3D mapping of LA was performed by CARTO system (CARTO 3, Biosense Webster, Yokneam, Israel). After the 3D mapping, the diagnostic/ablation deflectable tip catheter (THERMOCOOL SMARTTOUCH Catheter, Biosense Webster, Yokneam, Israel) was switched into the place for the subsequential ablations.

The PV antrum isolation was performed to block the atrial-PV bidirectional electrical conduction with a maximum power at 30–40 W, a maximum temperature at 43°C, an irrigation rate at 17–30 ml/min, and a minimum distance from the PV Ostia at 5 mm. If a non-PV trigger was present, such as LA posterior wall or superior vena cava, an additional isolation would be performed after the PV isolation. If there was an AF lasting more than 5 min after the isolations above, an additional ablation would be performed at the discretion of operator, such as LA linear (LA roofline and mitral isthmus line), cavotricuspid isthmus, and complex fractionated atrial electrogram (CFAE) ablation. An external electrical cardioversion would be performed to get the sinus rhythm if there was still an AF after all the ablations above.

Anticoagulants was continued after ablation. Anti-arrhythmic drugs such as Propafenone or Amiodarone were routinely administered within 3 months after RFCA if there was no contraindication. (Briefly: Propafenone for patients without heart failure and structural heart disease; Amiodarone for patients without hyperthyroidism, abnormal liver function and pulmonary fibrosis). Patients would be treated with only β-blocker because of the contraindications of both Propafenone and Amiodarone. No anti-arrhythmic drugs would be used if there was a bradycardia after RFCA, with the consent of operator.

Establishing atrial fibrillation animal model

Eighteen male beagles (10–15 kg) were obtained from Nongnong Biotechnology Co., Ltd. (Beijing, China) (**Supplementary material 1**). ECG and UCG were performed to collect the baseline data. Canines with existing AF or low LVEF would be excluded. The canine model of AF was established in the same protocol as previously reported (16). All procedures were performed after sterile thoracotomy on the fifth intercostal space of the right chest under mechanical ventilation. The pacemaker was obtained from Xiamen Liqi Technology Co., LTD. (Fujian, China). The electrode was attached to the right atrium during the procedure. Then the pacemaker was inserted into a subcutaneous pocket on the back of canines. ECG was used to confirm the successful pacing. The pacemakers were initially turned off for the first week to give the canines a recovery time. Then we set an atrial rapid pacing at 500 beats per minute with 5 V square wave and 0.8 ms duration for 8 weeks (AOO mode).

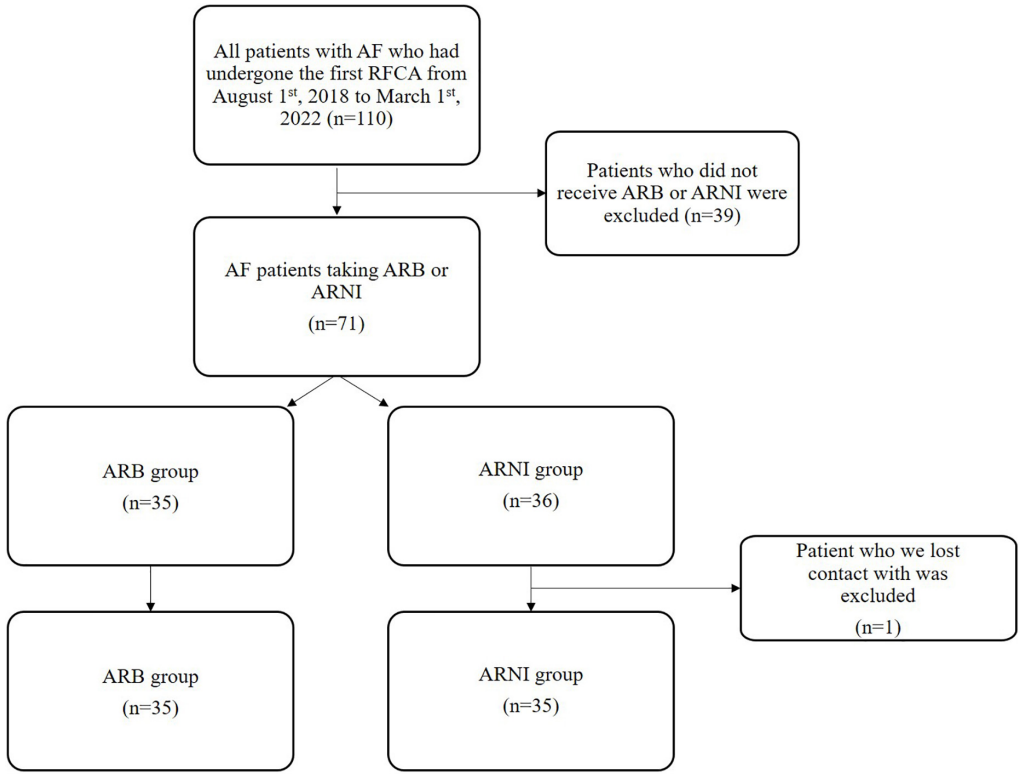

FIGURE 1
Flowchart of clinical retrospective study. AF, atrial fibrillation; RFCA, radio frequency catheter ablation.

The canines were randomly divided into three groups as follows: Control group treated with placebo control (sausage without medication), ARB group treated with Valsartan (p.o. at a dose of 30 mg/kg/day, inserted into sausage; Novartis Pharma Schweiz AG, Switzerland), and ARNI group treated with Sacubitril/Valsartan (p.o. at a dose of 60 mg/kg/day, inserted into sausage; Novartis Pharma Schweiz AG, Switzerland). All medications were bought from the pharmacy of Peking University International Hospital. After 8 weeks of pacing, ECG was used to confirm the function of pacemaker. Canines that deceased and those with malfunction pacemaker would be excluded. The canines were anesthetized with 3% pentobarbital sodium (1 ml/kg) during the establishment of AF model, the echocardiography and the electrophysiological study (EPS).

Electrophysiological study

After 8 weeks of continuous pacing, EPS was measured using DF-5A cardiac electrophysiological programmed stimulator (Dongfang Electronic Instrument Factory, Jiangsu, China) under the guidance of 3D electrophysiological navigation system (Biosense Webster, CA, USA). The electrode catheter was introduced into the right atrium *via* the right femoral vein. The LA voltage mapping was measured after the atrial septal puncture.

Atrial fibrillation was induced by eight S1S1 electrical stimuli at a pacing cycle length of 200, 170, and 150 ms, three times each in sequence. AF was defined as irregular atrial rates faster than 500 bpm associated with irregular AV conduction lasting more than 1,000 ms. The atrial electrical stability score was defined as the number of the first stimuli to induce AF, if there was no AF at the end of nine times electrical stimuli (three times in each pacing cycle length), the atrial electrical stability score would be 10 points at the final. The AF duration was defined as the time from the end of the stimuli to the first sinus P wave. If the AF was persistent, the AF duration was recorded as 60 s.

Echocardiography

Ultrasound cardiogram parameters were measured at the baseline and 8 weeks after continuous pacing, using a GE video E9 ultrasonic diagnostic instrument, s5-1 probe, probe frequency 2.5–3.5 mhz. The experimental canines were placed in the horizontal position, connected with the electrocardiogram, and each parameter was measured and averaged after three cardiac cycles.

The 2D parameters are routinely measured. The left atrial anteroposterior diameter (LAD) and left ventricular end-diastolic diameter (LVEDD) were measured on the parasternal left ventricular long axis view. The RAD was measured on the four-chamber view. The left atrium volume (LAV) was measured by area length method in four-chamber and two-chamber view. The maximum left atrial volume (LAVmax) was measured when the mitral valve was about to open, the minimum left atrial volume (LAVmin) was measured at the peak of the R wave. Body surface area (BSA) = $10.1 \times \text{Weight}^{2/3} \times 10^{-4}$. Left atrium volume index (LAVI) = LAVmax / BSA. Left atrial ejection fraction (LVEF) = (LAVmax − LAVmin) / LAVmax × 100%. Simpson's method was used to measure left ventricular end-diastolic volume (LVEDV) and left ventricular ejection fraction (LVEF). Left ventricular end-diastolic volume index (LVEDVI) = LVEDV/BSA. Pulsed Doppler was used to measure mitral orifice velocities E and A in the four-chamber view. Tissue Doppler was used to measure E′ on the left-ventricular side of the mitral annulus. The E/A and E/E′ were automatically calculated by the machine.

Pathological staining

The experimental canines were euthanized after electrophysiological examination. The LA tissues were rapidly separated and preserved in formalin solution. The LA tissues were fixed in 10% formalin, dehydrated conventionally, embedded in paraffin, and sliced into 4 μm thick sections. The specimens were stained with Masson's stain (Biotopped, Beijing, China) and examined under a light microscope (4 × 10 magnification). The ratio of fibrotic lesions was measured by ImageJ 1.8.0 (National Institutes of Health, Bethesda, MD, USA).

Data and statistical analysis

Data are presented as mean ± standard deviation (SD) or mean ± standard error of the mean (SEM) for continuous variables and as frequency and percentages for nominal variables. Normally distributed continuous variables were compared using the Student's *t*-test. The Pearson χ^2 test was applied to all categorical variables. Logistic regression analysis was performed to evaluate the relation between ARNI and atrial arrhythmia at 24-week follow-up. A *P*-value of <0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS v22.0 statistical software (SPSS, Chicago, IL, USA) and Prism 8.0 (GraphPad, San Diego, CA, USA).

Results

Baseline patient characteristics

A total of 110 patients' data was retrospectively reviewed (**Figure 1**). Those who had neither ARNI or ARB were excluded (n = 39). The remaining 71 patients were enrolled for two groups: ARNI (n = 36) or ARB (n = 35). One patient we lost contact with in ARNI group was excluded. The basic information, the medical history and the clinical data at hospitalization before RFCA had no statistical difference between two groups (**Table 1**).

All medications that may affect AF outcomes were recorded (**Table 1**). Patients in these two groups were initially prescribed with ARB or ARNI, and did not change their treatment after the RFCA. All patients followed the anti-arrhythmic drugs strategy mentioned above, Amiodarone and Propafenone would be switched to the β-blocker 3 months after RFCA if there was no contraindication. The preoperative and postoperative anti-arrhythmic drugs were recorded in the **Table 1**. All these medications had no statistical difference between two groups, except for Spironolactone (ARB 1/35 vs. ARNI 9/35, $P = 0.009$).

At the baseline UCG data (**Table 2**), there were a significantly larger LVEDD (ARB 46.03 ± 5.37 mm vs. ARNI 50.09 ± 6.91 mm, $P = 0.008$) and a significantly lower LVEF (ARB 64.28 ± 1.34% vs. ARNI 56.05 ± 13.37%, $P = 0.003$) in ARNI group compared to ARB group. But LAD, RAD, and RVEDD shares no statistical difference between two groups.

Ultrasound cardiogram changes in patients

The UCG parameters were comparable between ARB and ARNI group (**Table 2**). At the 24-week follow-up, there was no difference in LAD, RAD, LVEDD, and RVEDD between the two groups. However, the LVEF was still significantly lower in ARNI group compared to ARB group (ARB 65.21 ± 6.73% vs. ARNI 59.87 ± 8.31%, $P = 0.005$). Compared to the baseline, both ARB group and ARNI group had a significantly lower RAD (ARB baseline 37.80 ± 6.18 mm vs. 24-week 34.91 ± 3.88 mm, $P = 0.012$; ARNI baseline 39.43 ± 6.93 mm vs. 24-week 34.83 ± 4.48 mm, $P < 0.001$) and RVEDD (ARB baseline 35.43 ± 4.08 mm vs. 24-week 32.03 ± 4.95 mm, $P = 0.001$; ARNI baseline 34.71 ± 5.29 mm vs. 24-week 31.71 ± 4.34 mm, $P = 0.010$) at the 24-week follow-up. Meanwhile, ARNI group also had significantly lower LAD (ARNI baseline 44.00 ± 6.83 mm vs. 24-week 40.13 ± 5.64 mm, $P < 0.001$) and larger LVEF (ARNI baseline 56.05 ± 13.37% vs. 24-week 59.87 ± 8.31%, $P = 0.021$) at the follow-up. Because of the differences in baseline UCG data between the two groups, it is possible that simply comparing the follow-up UCG data could not show the true picture. Therefore, we used the UCG

TABLE 1 Baseline clinical data.

Baseline data	ARNI	ARB	Differences between ARNI and ARB
Basic information			
Age	67.26 ± 11.97	65.2 ± 9.79	$P = 0.434$
Male gender	22/35	22/35	$P > 0.999$
Height (cm)	166.03 ± 8.48	166.89 ± 9.44	$P = 0.691$
Weight (kg)	70.46 ± 12.34	72.16 ± 13.47	$P = 0.584$
BMI (kg/m^2)	25.47 ± 3.56	25.78 ± 3.38	$P = 0.716$
Current smoker	16/35	20/35	$P = 0.339$
Current drinker	15/35	18/35	$P = 0.473$
Perioperative medications			
Statin	18/35	20/35	$P = 0.631$
SGLT-2i	6/35	4/35	$P = 0.495$
Spironolactone	9/35	1/35	$P = 0.006$
Preoperative anti-arrhythmic drugs			
β-Blocker	21/35	17/35	$P = 0.337$
Amiodarone	2/35	3/35	$P = 0.643$
Postoperative anti-arrhythmic drugs			
β-Blocker	1/35	1/35	$P > 0.999$
Amiodarone	32/35	29/35	$P = 0.284$
Propafenone	2/35	5/35	$P = 0.232$
Medical history			
Persistent AF	16/35	10/35	$P = 0.138$
Hypertension	31/35	33/35	$P = 0.393$
Diabetes mellitus	16/35	19/35	$P = 0.473$
Hyperlipidemia	24/35	27/35	$P = 0.420$
CHF	16/35	14/35	$P = 0.809$
MI	3/35	2/35	$P = 0.643$
Revascularization	8/35	3/35	$P = 0.101$
PVD	4/35	2/35	$P = 0.393$
Stroke/TIA	14/35	11/35	$P = 0.454$
COPD	5/35	3/35	$P = 0.452$
CKD	4/35	3/35	$P = 0.690$
OSAHS	1/35	3/35	$P = 0.303$
CHA2DS2-VASc	3.54 ± 1.74	3.20 ± 1.53	$P = 0.384$
Baseline clinical data			
HR (beats per minute)	83.14 ± 20.34	80.03 ± 15.75	$P = 0.476$
SBP (mmHg)	131.49 ± 16.54	133.91 ± 15.66	$P = 0.530$
DBP (mmHg)	76.74 ± 15.88	73.77 ± 14.10	$P = 0.411$
Hemoglobin (g/L)	137.54 ± 18.48	139.43 ± 18.81	$P = 0.674$
Serum creatinine (μmol/L)	88.49 ± 38.97	76.66 ± 16.52	$P = 0.103$
eGFR (ml/min/1.73 m^2)	77.11 ± 23.21	84.31 ± 14.54	$P = 0.126$
Serum potassium (mmol/L)	3.98 ± 0.30	4.11 ± 0.37	$P = 0.108$

Baseline characters had no statistical difference between two groups, except for usage of spironolactone.

BMI, body mass index; SGLT-2i, sodium-dependent glucose transporters inhibitor; AF, atrial fibrillation; CHF, congestive heart failure; MI, myocardial infarction; PVD, peripheral vascular; TIA, transient ischemia attack; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; OSAHS, obstructive sleep apnea-hypopnea syndrome; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; RFCA, radiofrequency catheter ablation.

change ratio [("follow-up data" − "baseline data") / "baseline data" × 100%] to describe the cardiac structural changes in these two groups. In ARNI group, the UCG change ratio showed a significant decrease in LAD (ARB −2.80 ± 11.29% vs. ARNI −8.05 ± 10.16%, $P = 0.046$) and LVEDD (ARB +3.51 ± 11.40% vs. ARNI −2.30 ± 8.43%, $P = 0.019$).

Rhythm and major clinical events in different patient groups

The Holter was routinely measured at 24-week follow-up in all patients (Table 3). The atrial arrhythmias were significantly less in ARNI group (ARB 15/35 vs. ARNI 4/35, $P = 0.003$). Meanwhile, the AF early recurrence rate (ARB 4/35 vs. ARNI 2/35, $P = 0.673$) was lower in ARNI group with no statistical significance compared to ARB group. Besides, the rate of all cause rehospitalization and all cause death had no difference between the two groups (Table 3).

As there were differences at baseline data between ARB and ARNI groups such as LVEF, LVEDD, and preoperative medication, we performed a univariate logistic regression analysis for the presence of atrial arrhythmias at 24-week follow-up (Supplementary material 2). Factors with $P < 0.2$ in the univariate logistic regression analysis (ARNI and Statins in perioperative medications; Amiodarone in preoperative anti-arrhythmic drugs; persistent AF, diabetes mellitus, and stroke/TIA in medical history; SBP and serum potassium in baseline clinical data), factors that differed between the two groups at baseline (Spironolactone in perioperative medications; LVEF and LVEDD in baseline UCG data), and factors commonly considered to be associated with atrial electrical instability in clinic (LAD in baseline UCG data) were included in the multivariate logistic regression analysis (Table 4). The application of ARNI ($P = 0.014$, OR = 0.109) and Statins ($P = 0.039$, OR = 0.200) was independently associated with the atrial arrhythmia rate at 24-week follow-up.

Baseline animal characteristics

A total of 18 beagles were entered into the experiment, and one was excluded at the beginning due to AF and low LVEF. The rest 17 canines underwent the right atrium pacing, and two of them deceased within 1 week after the procedure. A total of 15 canines were randomly divided into three groups. During 8 weeks of rapid pacing, one canine with malfunction pacemaker was excluded in ARNI group, and there was one deceased canine excluded in each of Control and ARB group. There were four canines in each group in the end (Supplementary material 1). All canines had similar length and weight in three groups (Supplementary material 3). All UCG data at baseline, including LAD, RAD, LAVI, LVEF, LVEDVI, LVEF, E/A, and E/E′, had no difference between all the groups (Table 5).

TABLE 2 Ultrasound cardiogram parameters at baseline and 24-week follow-up.

UCG parameters	ARB			
	Baseline	24-week	Differences between baseline and 24-week	Change ratio
LAD (mm)	43.40 ± 6.05	41.74 ± 5.20	$P = 0.105$	−2.80 ± 11.29%
RAD (mm)	37.80 ± 6.18	34.91 ± 3.88	$P = 0.012$	−5.26 ± 12.45%
LVEDD (mm)	46.03 ± 5.37	47.11 ± 4.61	$P = 0.164$	+3.51 ± 11.40%
RVEDD (mm)	35.43 ± 4.08	32.03 ± 4.95	$P = 0.001$	−8.78 ± 14.39%
LVEF (%)	64.28 ± 1.34	65.21 ± 6.73	$P = 0.647$	+2.28 ± 13.78%
	ARNI			
	Baseline	24-week	Differences between baseline and 24-week	Change ratio
LAD (mm)	44.00 ± 6.83	40.13 ± 5.64	$P < 0.001$	−8.05 ± 10.16%
RAD (mm)	39.43 ± 6.93	34.83 ± 4.48	$P < 0.001$	−10.38 ± 11.67%
LVEDD (mm)	50.09 ± 6.91	48.70 ± 6.16	$P = 0.064$	−2.30 ± 8.43%
RVEDD (mm)	34.71 ± 5.29	31.71 ± 4.34	$P = 0.010$	−7.09 ± 16.15%
LVEF (%)	56.05 ± 13.37	59.87 ± 8.31	$P = 0.021$	+11.49 ± 24.65%
	Differences between ARB and ARNI			
	Baseline	24-week	Change ratio	
LAD (mm)	$P = 0.699$	$P = 0.223$	$P = 0.046$	
RAD (mm)	$P = 0.303$	$P = 0.889$	$P = 0.083$	
LVEDD (mm)	$P = 0.008$	$P = 0.232$	$P = 0.019$	
RVEDD (mm)	$P = 0.529$	$P = 0.779$	$P = 0.648$	
LVEF (%)	$P = 0.003$	$P = 0.005$	$P = 0.061$	

ARNI group had a significant larger LVEDD and lower LVEF at the baseline compared to ARB group. At the 24-week, the LVEF was still lower in ARNI group. LAD and LVEDD change ratios were higher in ARNI group.
LAD, left atrium diameter; RAD, right atrium diameter; LVEDD, left ventricle end-diastolic diameter; RVEDD, right ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction. Change ratio = ("24-week" − "baseline") / "baseline" × 100%.

TABLE 3 Differences in rhythm and clinical events between groups.

	ARB	ARNI	Differences between ARB and ARNI
Rhythm			
AF early recurrence	4/35	2/35	$P = 0.673$
Atrial arrhythmia	15/35	4/35	$P = 0.003$
Clinical event			
All cause hospitalization	2/35	1/35	$P = 0.555$
All cause death	0/35	0/35	–

ARNI group had a significantly lower rate for atrial arrhythmia compared to ARB group. There was no difference in all cause hospitalization and all cause death between groups.
AF, atrial fibrillation.

Ultrasound cardiogram changes in animals

At 8-week UCG data (Table 5), LAD was lower in both ARB and ARNI groups compared to Control group, but was only statistically significant in ARB group (Control 24.39 ± 4.11 mm vs. ARB 18.39 ± 2.18 mm, $P = 0.042$). There was no statistical difference between ARB group and ARNI group. RAD was significantly lower in both ARB group and ARNI group compared to Control group (Control 23.96 ± 1.16 mm vs. ARB 19.72 ± 2.88 mm, $P = 0.034$; Control 23.96 ± 1.16 mm vs. ARNI 17.28 ± 4.29 mm, $P = 0.024$). However, there was still no significant difference between ARB and ARNI group. The similar characteristics were apparent in the left atrium ejection fraction (LAEF) and E/A. Compared to Control group, LAEF was significantly larger in both ARB and ARNI groups (Control 34.63 ± 7.96% vs. ARB 47.79 ± 5.69%, $P = 0.036$; Control 34.63 ± 7.96% vs. ARNI 52.09 ± 2.97%, $P = 0.006$), while E/A was significantly lower at the same time (Control 1.89 ± 0.10 vs. ARB 1.59 ± 0.20, $P = 0.036$; Control 1.89 ± 0.10 vs. ARNI 1.34 ± 0.13, $P = 0.076$), with no statistical difference between ARB and ARNI group. LVEF had no difference between Control and ARB group, but was significantly larger in ARNI group (Control 55.47 ± 4.39% vs. ARNI 65.09 ± 2.56%, $P = 0.009$; ARB 54.06 ± 6.60% vs. ARNI 65.09 ± 2.56%, $P = 0.021$). LVEDVI (Control 54.29 ± 3.27 ml/m^2 vs. ARNI

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TABLE 4 Multivariate logistic regression analysis for the presence of atrial arrhythmia at 24-week follow-up.

Multivariate logistic regression analysis for atrial arrhythmia rate			
Factors	***P*-value**	**OR**	**95% CI for OR**
Perioperative medications			
ARNI	$P = 0.014$	0.109	0.019–0.635
Statin	$P = 0.039$	0.200	0.044–0.919
Preoperative anti-arrhythmic drugs			
Amiodarone	$P = 0.174$	8.341	0.392–177.276
Medical history			
Persistent AF	$P = 0.417$	2.127	0.344–13.161
Diabetes mellitus	$P = 0.601$	0.666	0.145–3.056
Stroke/TIA	$P = 0.441$	0.491	0.081–2.998
Baseline clinical data			
SBP (mmHg)	$P = 0.287$	1.027	0.978–1.079
Serum potassium (mmol/L)	$P = 0.136$	4.976	0.605–40.939
Baseline UCG			
LAD (mm)	$P = 0.565$	0.955	0.816–1.117
LVEDD (mm)	$P = 0.670$	1.032	0.894–1.190
LVEF (%)	$P = 0.847$	0.992	0.917–1.073

Factors with $P < 0.2$ in the univariate logistic regression analysis, factors that differed between the two groups at baseline and factors commonly considered to be associated with atrial electrical instability in clinic were included in the multivariate logistic regression analysis. ARNI and Statins were independently associated with the presence of atrial arrhythmia at 24-week follow-up ($P < 0.05$) in multivariate logistic regression analysis.
OR, odd ratio; CI, confidence interval; AF, atrial fibrillation; TIA, transient ischemia attack; SBP, systolic blood pressure; LAD, left atrium diameter; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction.

44.62 ± 6.30 ml/m^2, $P = 0.034$) and E/E′ (Control 12.55 ± 0.78 vs. ARNI 7.63 ± 2.08, $P = 0.004$) were also significantly lower in ARNI group compared to Control group, but had no difference between ARB and ARNI group.

Histological changes in animals

In the pathological staining results (Figure 2A), Control group had more fibrotic lesions compared to ARB and ARNI group in LA tissues. The ratio of fibrotic lesions (Figure 2B) was lower in both ARB (Control 10.15 ± 1.57% vs. ARB 2.36 ± 0.40%, $P = 0.003$) and ARNI group (Control 10.15 ± 1.57% vs. ARNI 1.31 ± 0.25%, $P = 0.001$) compared to Control group. There was no statistical difference between ARB and ARNI group (ARB 2.36 ± 0.40% vs. ARNI 1.31 ± 0.25%, $P = 0.066$), although ARNI group had a trend of a lower ratio of fibrotic lesions.

Electrophysiological study in animals

In the LA voltage mapping (Figure 3A), LA in ARNI group had less low voltage zone with red color and less disordered voltage zone with heterogeneous colors compared to ARB and Control groups, indicating a more stable atrial electrical activity. In the EPS, all canines did not have spontaneous AF. After the electrical stimuli, ARNI group showed a significantly higher atrial electrical stability score (Control 2.5 ± 1.29 pts vs. ARNI 9.75 ± 0.50 pts, $P < 0.001$; ARB 5 ± 2.16 pts vs. ARNI 9.75 ± 0.50 pts, $P = 0.005$) and shorter AF duration (Control 47.25 ± 25.5 s vs. ARNI 0.50 ± 1.00 s, $P = 0.011$; ARB 9.50 ± 3.11 s vs. ARNI 0.50 ± 1.00 s, $P = 0.001$) compared to ARB group and Control group (Figure 3B).

Discussion

Our study investigated the effect of ARNI compared to ARB on atrial electrical instability and structural remodeling. We found the application of ARNI was independently associated with a lower atrial electrical instability in both retrospective study and canine AF model, while the difference of structural remodeling was only significant in the 24-week follow-up clinical study but not in the 8-week animal study.

In recent years, RFCA was gradually becoming the first-choice treatment for AF because of its advantages over classic antiarrhythmic drug therapy in all-cause mortality, HF hospitalization, LVEF, and quality of life (17). We therefore chose patients who had undergone RFCA, rather than those treated with classic antiarrhythmic drugs, for our retrospective study.

In our study, patients in ARNI group had worse structural parameters at baseline, including a larger left ventricle and a lower ejection fraction, which usually leads to a higher AF recurrence rate and a higher atrial electrical instability (18). However, patients in ARNI group had a lower rate of atrial arrhythmia at 24-week follow-up compared to ARB group in our study, although the AF early recurrence rate had no statistical difference. Besides, the application of ARNI was an independent protective factor for the presence of atrial arrhythmia at the 24-week follow-up in multivariate analysis. It was reasonable to speculate that ARNI performed better than ARB on reducing atrial electrical instability in patients with AF, as the worse cardiac structure at baseline and the lower atrial electrical instability at follow-up were found in ARNI group. Furthermore, ARNI group also had a higher reduction ratio in LAD and LVEDD, suggesting the advantage of ARNI group over ARB group on cardiac structural remodeling.

Atrial structural remodeling, especially atrial fibrosis occurs with disease progression in AF, which is an important cause of atrial electrical instability (19, 20). The role of ACEI/ARB in the inhibition of fibrosis in heart failure was well recognized. In patients with heart failure, ACEI/ARB could reduce the incidence of AF and other types of arrhythmias (21). However, there was a lack of strong evidence of ACEI/ARB in the secondary prevention of AF (22). The application of ARNI

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TABLE 5 Ultrasound cardiogram parameters in all animal groups.

UCG parameter	Control		
	Baseline	8-week follow-up	Differences between baseline and 8-week follow-up
LAD (mm)	19.87 ± 0.80	24.39 ± 4.11	$P = 0.096$
RAD (mm)	19.68 ± 0.92	23.96 ± 1.16	$P = 0.048$
LAVI (ml/m^2)	17.34 ± 0.89	22.76 ± 5.80	$P = 0.206$
LAEF (%)	56.51 ± 3.11	34.63 ± 7.96	$P = 0.016$
LVEDVI (ml/m^2)	46.36 ± 2.73	54.29 ± 3.27	$P = 0.115$
LVEF (%)	63.36 ± 4.38	55.47 ± 4.39	$P < 0.001$
E/A	1.19 ± 0.05	1.89 ± 0.10	$P = 0.018$
E/E′	8.27 ± 0.75	12.55 ± 0.78	$P < 0.001$
	ARB		
	Baseline	8-week follow-up	Differences between baseline and 8-week follow-up
LAD (mm)	19.98 ± 0.91	18.39 ± 2.18	$P = 0.180$
RAD (mm)	18.77 ± 0.97	19.72 ± 2.88	$P = 0.392$
LAVI (ml/m^2)	14.20 ± 1.14	18.55 ± 2.87	$P = 0.065$
LAEF (%)	56.06 ± 3.90	47.79 ± 5.69	$P = 0.055$
LVEDVI (ml/m^2)	46.30 ± 2.04	52.96 ± 15.72	$P = 0.403$
LVEF (%)	64.57 ± 3.58	54.06 ± 6.60	$P < 0.001$
E/A	1.13 ± 0.11	1.59 ± 0.20	$P = 0.430$
E/E′	6.64 ± 1.17	9.31 ± 2.79	$P = 0.012$
	ARNI		
	Baseline	8-week follow-up	Differences between baseline and 8-week follow-up
LAD (mm)	21.33 ± 2.25	20.57 ± 5.18	$P = 0.523$
RAD (mm)	19.12 ± 1.10	17.28 ± 4.29	$P = 0.332$
LAVI (ml/m^2)	14.71 ± 1.66	18.59 ± 3.85	$P = 0.016$
LAEF (%)	57.05 ± 2.50	52.09 ± 2.97	$P = 0.030$
LVEDVI (ml/m^2)	43.73 ± 2.61	44.62 ± 6.30	$P = 0.837$
LVEF (%)	64.26 ± 4.26	65.09 ± 2.56	$P < 0.001$
E/A	1.12 ± 0.11	1.34 ± 0.13	$P = 0.419$
E/E′	9.73 ± 1.66	7.63 ± 2.08	$P = 0.008$
	Differences at baseline between all groups	Differences at 8-week follow-up	
		Control vs. ARB	Control vs. ARNI	ARB vs. ARNI
LAD (mm)	$P = 0.745$	$P = 0.042$	$P = 0.291$	$P = 0.468$
RAD (mm)	$P = 0.810$	$P = 0.034$	$P = 0.024$	$P = 0.380$
LAVI (ml/m^2)	$P = 0.227$	$P = 0.240$	$P = 0.275$	$P = 0.987$
LAEF (%)	$P = 0.977$	$P = 0.036$	$P = 0.006$	$P = 0.228$
LVEDVI (ml/m^2)	$P = 0.703$	$P = 0.874$	$P = 0.034$	$P = 0.362$
LVEF (%)	$P = 0.977$	$P = 0.735$	$P = 0.009$	$P = 0.021$
E/A	$P = 0.849$	$P = 0.036$	$P = 0.001$	$P = 0.076$
E/E′	$P = 0.267$	$P = 0.066$	$P = 0.004$	$P = 0.369$

There was no statistical difference at baseline between all groups. At 8-week follow-up, only LVEF was significantly larger in ARNI group compared to ARB group.
UCG, ultrasound cardiogram; LAD, left atrium diameter; RAD, right atrium diameter; LAVI, left atrium volume index; LAEF, left atrium ejection fraction; LVEDVI, left ventricle end-diastolic volume index; LVEF, left ventricle ejection fraction.

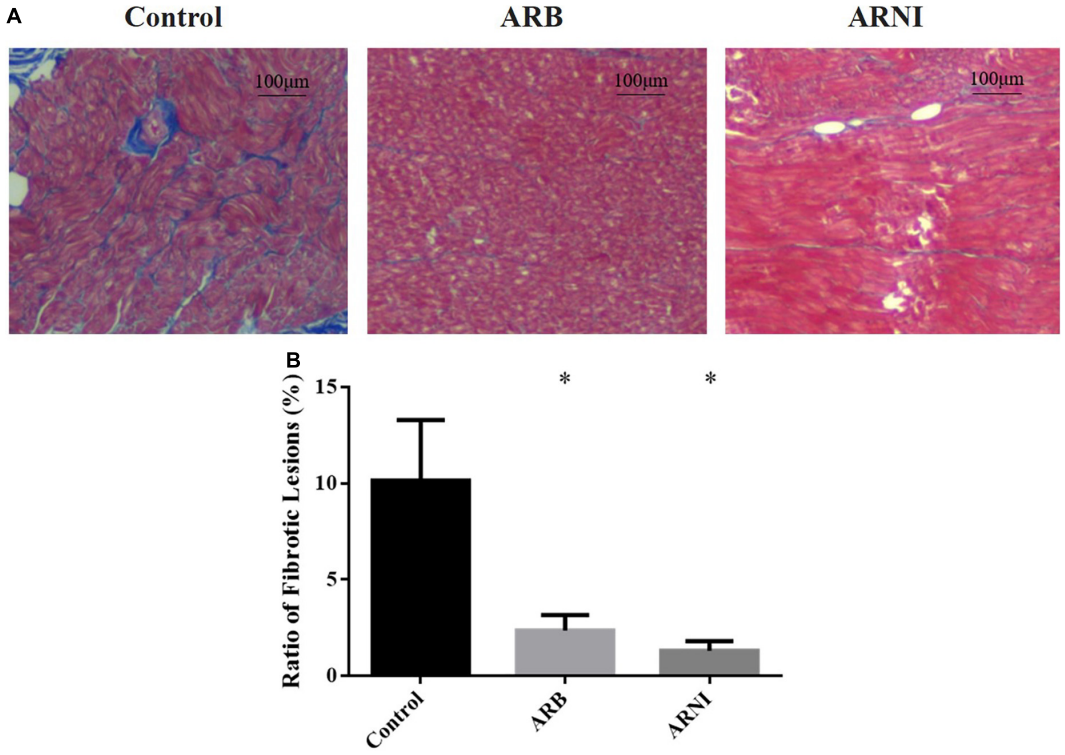

FIGURE 2
Pathological staining of left atrium. **(A)** Masson staining (4 × 10 magnification) renders myocardial cells red and collagen blue. The left atrium tissue in Control group had more fibrotic area compared to the other groups. **(B)** Ratio of fibrotic lesions in left atrium. *$P < 0.05$ compared to the Control group.

in patients with heart failure could lead to better clinical outcome than ACEI/ARB (23, 24). ARNI could attenuate cardiac remodeling after MI through a superior inhibition on fibrosis and hypertrophy than ARB (25). Russo et al. found that ARNI could reduce atrial and ventricular arrhythmias in patients with reduced ejection fraction and implantable cardiac defibrillator, indicating the potential effect in primary prevention of AF in patients with heart failure (26). Yang et al. found that LAD and RAD were lower in ARNI group patients compared to ARB group at the 24-week follow-up after AF ablation, indicating that ARNI is superior to ARB in attenuating atrial structural remodeling in RFCA-treated AF patients (27). Wang et al. found patients in ARNI group had a lower AF recurrence rate at 1-year follow-up after persistent AF catheter ablation compared to ARB group (28).

To sum up, there were scarce clinical studies on ARNI application in AF treatment as previous studies had mainly demonstrated a unilateral benefit of ARNI in electrical or structural terms. Our study demonstrated an extra clinical benefit of ARNI on both structural remodeling and atrial electrical instability in AF patients.

To further understand the mechanism by which ARNI benefits AF patients, we performed the animal experiment on canines to get data of UCG, EPS, and pathological staining. Our study found that ARNI group had a higher atrial electrical stability score and a shorter AF duration compared to ARB and Control group, indicating a superior protective effect on atrial electrical instability. The LA voltage mapping confirmed this conclusion, with less LA low voltage and disordered voltage zone in ARNI group.

Li et al. found that ARNI could ameliorate the atrial fibrosis and elevate the AF inducibility in rabbit AF models (29). Li et al. found ARNI could inhibit angiotensin II induced atrial fibrosis and therefore had a better effect than ARB in decreasing the AF susceptibility in rat AF model (30). Our animal experiment on canines was consistent with these studies regarding its influence on atrial electrical instability in AF. Nevertheless, previous animal studies had suggested that ARNI could reduce the atrial electrical instability through inhibition of atrial structural remodeling, but our animal experiments on canines had shown a different result.

In ARNI group, although RAD and LVEDVI was significantly lower at 8-week follow-up compared to Control group, all structural parameters such as LAD, RAD, LAVI, and LVEDVI had no statistical difference compared to ARB group. The pathological staining results were consistent with these UCG results, with a lower ratio of fibrotic lesions in ARNI group compared to Control group but no statistical difference when

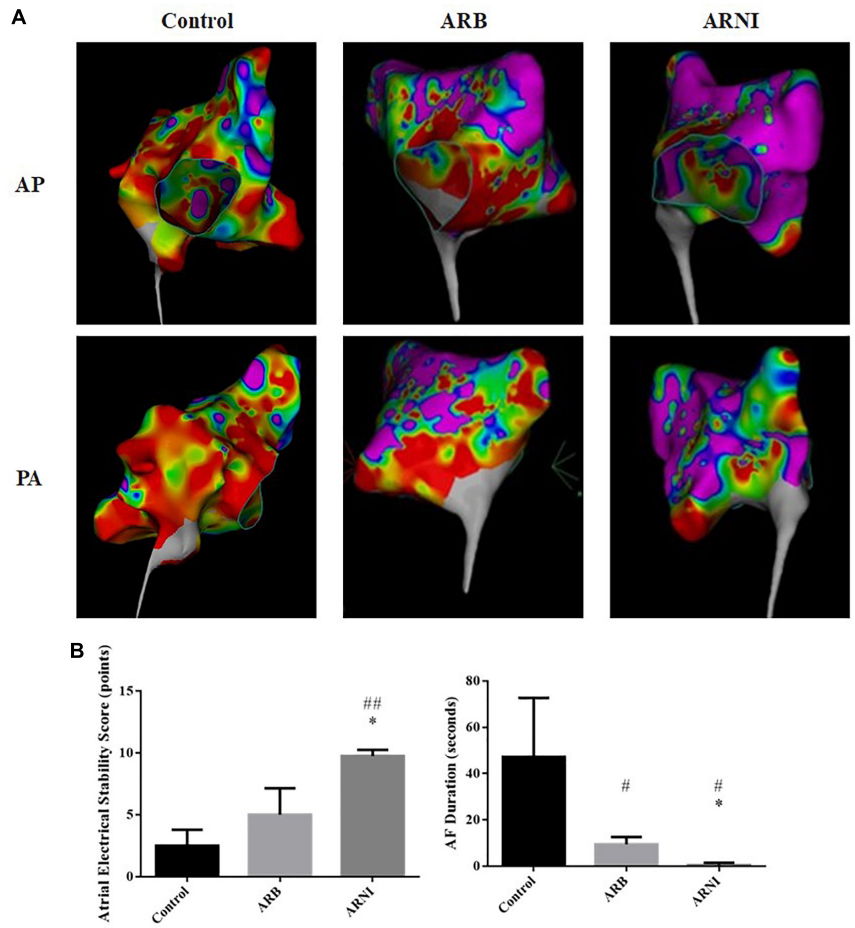

FIGURE 3
Electrophysiological study data. **(A)** LA voltage mapping in sinus rhythm in chest PA and AP views. Red area represents a low LA voltage zone with bipolar peak-to-peak electrogram voltage <0.50 mv. Purple area represents bipolar peak-to-peak electrogram voltage >3.0 mv. ARNI group had less low voltage and disordered voltage zone in left atrium. **(B)** Data after electrical stimuli. ARNI group had a higher atrial electrical stability score and a shorter AF duration. $^{\#}P < 0.05$ compared to Control group; $^{\#\#}P < 0.01$ compared to the Control group; $^{*}P < 0.01$ compared to ARB group. AF, atrial fibrillation; LA, left atrium; AP, anteroposterior; PA, posteroanterior.

comparing to ARB group. In clinical practice, the additional effect of ARNI to reverse cardiac structural remodeling may take 6–12 months to occur (31). Therefore, it is possible that the difference in structural remodeling between ARNI and ARB group was not found in this 8-week canine experiments. Obviously, ARNI could attenuate cardiac structural remodeling in AF, but its superior effect over ARB on atrial electrical instability was not only contributed by the inhibition of cardiac structural remodeling in our experimental study. Similar results were reported in a study with left atrial appendage closure rabbit model (32), Cheng et al. found that ARNI could suppress the atrial arrhythmogenicity by increasing the level of ANP, even though the fibrosis between groups had no statistical difference.

Besides the inhibition of cardiac structural remodeling, the improvement in cardiac function by ARNI was thought to have potential anti-arrhythmic effects (14). De Vecchis et al. found that ARNI group had a higher increase of the peak atrial longitudinal strain and a lower risk of AF recurrence compared to the conventional therapy group in patients with heart failure and at least one episode of AF in the history (33). Suo et al. found that ARNI could lead to a superior improvement in left atrial function than ARB in both AF patients and pressure overload mouse model (34).

In our animal experiment, at 8-week follow-up, E/A and E/E′ were significantly lower, while LAEF was significantly higher in ARNI group compared to Control group. Besides, LVEF was significantly higher in ARNI group in compared with both ARB and Control group. Also, there was a trend towards higher LAEF in ARNI group compared to ARB group. These results indicated a better atrial and ventricular function in ARNI group. In the absence of significant difference between ARNI and ARB group in cardiac structural remodeling, it was a plausible explanation that ARNI could reduce atrial electrical instability by improving cardiac function. This phenomenon

demonstrated that the effect of reducing atrial electrical instability after ARNI administration may occur rapidly with the protection of cardiac function, rather than until after the cardiac structural remodeling has taken place.

Calcium handling system of atrial myocytes was also considered to be related to AF (35). Extracellular calcium (Ca^{2+}) enters myoplasm *via* activation of voltage-gated L-type Ca^{2+} channel (LTCC) and sodium-calcium exchanger (NCX) during the cardiac action potential and excitation-contraction coupling. This Ca^{2+} entry activates the ryanodine receptor 2 (RyR2) channel, triggering a larger amount of Ca^{2+} release from the sarcoplasmic reticulum (SR), resulting in myofilament activation. For relaxation, cytosolic Ca^{2+} was uptake back to SR *via* sarco-endoplasmic reticulum calcium ATPase 2a (SERCA2a) and excluded from cytoplasm to extracellular space *via* NCX and plasma membrane calcium ATPase (PMCA), allowing Ca^{2+} to dissociate from the myofilaments (36). High level of SR Ca^{2+} leak triggered by increased RyR2, together with upregulated NCX, could contribute to the pathogenesis of AF (37). Acute upregulation of SERCA2a by doxycycline in the setting of hyperactive RyR2 exacerbates dysregulated myocyte Ca^{2+} handling and arrhythmogenesis in both ventricular and atrial myocardium in rodent model (38). However, overexpression of SERCA2a could suppress ERP shortening and AF induced by rapid pacing atrium in rabbit model (39). The stress kinase c-Jun N-terminal kinase 2 (JNK2), a key factor to activate calmodulin-dependent protein kinase II (CaMKII), could stimulate the SERCA2a activity by regulating CaMKII-dependent arrhythmic SR Ca^{2+} leak and a CaMKII-independent uptake, which in turn exacerbates atrial arrhythmogenicity (40). Previous study had shown that ARNI could reduce the atrial arrhythmogenicity by reversing the remodeling of RyR2 channels and NCX1 channel (32). The Jun N-terminal kinases (JNKs) could be inhibited by ARNI in mice with diabetic cardiomyopathy (41), which may possibly result in a different activity of SERCA2a and CaMKII. The pathways above could be the other potential mechanisms for ARNI to affect atrial electrical instability in AF. This could to be further explored in the future.

Limitations

For patients with AF and hypertension, our Heart Center prefer to use ACEI/ARB/ARNI to attenuate the cardiac remodeling in clinical practice. Therefore, we could not find a sizable control group with AF and hypertension but not taking the above medications for this retrospective real-world study. In clinical practice, ARNI and spironolactone were recommended to add in patients with definite ventricular enlargement and reduced ejection fraction (42), so the differences in LVEF, LVEDD, and spironolactone usage rate at baseline between groups were unavoidable in this retrospective study. The AF recurrence rate at 24-week had no statistical difference between groups, probably due to the short period of follow-up and the small sample size. More studies with longer follow-up period and bigger sample size are still needed to elucidate the role of ARNI in AF.

Conclusion

In summary, the application of ARNI was independently associated with a lower incidence of atrial arrhythmia, which may result from reducing atrial electrical instability, when comparing to ARB for treating AF patients after their first RFCA. Therefore, we believe that ARNI could be a rational treatment in secondary prevention of AF.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University International Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. The animal study was reviewed and approved by the Peking University Institutional Review Board.

Author contributions

TZ: methodology, investigation, data curation, formal analysis, and writing—original draft. WZ: conceptualization, investigation, and resources. QY: investigation, data curation, and validation. NW: investigation and validation. YF and YL: investigation and data curation. GC, LW, XZ, HY, XS, YC, and XW: investigation. XC: methodology, investigation, data curation, resources, and writing—review and editing. XL: supervising, project administration, and foundation acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1048077/full#supplementary-material

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Periodontitis was associated with worse clinical outcomes after catheter ablation for paroxysmal atrial fibrillation

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Background: Periodontitis (PD), a common chronic inflammatory disease, may be associated with the subsequent development of atrial fibrillation (AF) through a mechanism of systemic inflammation. However, little is known about the impact of PD on the recurrence of atrial fibrillation after catheter ablation (CA).

Methods: A total of 132 patients (age 62.2 ± 10.6 years; 72.7% male) who underwent periodontal examinations and the first CA for paroxysmal atrial fibrillation (PAF) were investigated. Clinical periodontal examination was performed by independent trained periodontists, and patients were diagnosed with PD when the maximum periodontal probing depth was equal to or greater than 4 mm and bleeding on probing was evident. Of these, 71 patients (54%) were categorized as those with PD (PD group) and the other 61 (46%) as those without PD (non-PD group). Pulmonary vein isolation was performed in a standard fashion.

Results: Kaplan–Meier curve analysis revealed worse atrial arrhythmia recurrence-free survival probabilities after CA for PAF in the PD group than in the non-PD group (64.8% versus 80.3%, respectively; p = 0.024) during a median follow-up period of 3.0 (interquartile range: 1.1–6.4) years. Cox regression analysis revealed PD as a significant predictor of arrhythmia recurrence (hazard ratio: 2.063, 95% confidence interval: 1.018–4.182), after adjusting for age and gender.

Conclusion: Periodontitis was independently associated with an increased risk of arrhythmia recurrence after the first CA for PAF. Our results may suggest that the periodontal status is potentially a modifiable determinant of the outcomes after PAF ablation, and further prospective studies are warranted.

KEYWORDS

catheter ablation, atrial fibrillation, paroxysmal atrial fibrillation (PAF), arrhythmia recurrence, periodontitis (PD), oral health status

1. Introduction

Periodontitis (PD) is a chronic inflammatory disease primarily initiated by the response to periodontopathic bacteria in the periodontium surrounding and supporting teeth (1). The global burden of severe PD was estimated as 1.1 billion cases worldwide in 2019 (2). Previous epidemiological studies have suggested that PD may be a potential risk factor of a variety of heart diseases, including coronary artery disease (3–5), and atrial fibrillation (AF) (6). AF is the most common type of sustained cardiac arrhythmia in adults, is widely recognized as one of the main causes of stroke and poses a significant burden to patients and to public health systems (7). Paroxysmal AF (PAF) is a subtype of AF defined by a spontaneous or intervened termination within 7 days from onset, which is often targeted by the rhythm control strategy using anti-arrhythmic drugs or catheter ablation (CA). Despite significant advancement in CA technology, the non-negligible proportion of patients with PAF still had arrhythmia recurrence after the procedure (8). Previous studies have suggested various risk factors of recurrent AF after CA, including anatomical factors, comorbidities, and biomarkers. Notably, the inflammatory status, represented by higher levels of inflammatory biomarkers, has been reported to be relevant to the recurrence of arrhythmia (9). As a manifestation of chronic inflammation inducing recurrent arrhythmia, PD was investigated in previous studies (6, 10, 11). A recent study has shown the association between the serum antibodies to the periodontal pathogens and the recurrence of AF (11). Nevertheless, the impact of PD that is clinically diagnosed by periodontal examinations assessing clinical outcomes after AF ablation has not been elucidated. The present study sought to investigate the association between baseline PD evaluated at the time of the first CA for PAF and subsequent recurrence rate after CA.

2. Materials and methods

2.1. Study population

The prospective observational registry for the assessment of the association between cardiovascular disease and periodontal disease was conducted between May 2012 and August 2015 at Tokyo Medical and Dental University Hospital. The registry enrolled 1,000 consecutive patients with written informed consent who were admitted to the Department of Cardiovascular Medicine. The original protocol was approved in March 2012 by the institutional review board (IRB) of the Tokyo Medical and Dental University (MD2000-1165). All participants underwent a periodontal examination during hospitalization to assess their periodontal status. The ancillary protocol, which was additionally approved by the IRB in 2020 (M2020-020), was performed to collect the long-term clinical follow-up data of the participants from the original protocol by reviewing the clinical records in 2020. Of the 1,000 enrolled patients, a total of 135 patients who were hospitalized to undergo first CA for PAF were identified. After excluding three patients in whom the periodontal status was not examined (insufficient number of teeth), 132 patients were investigated in the present study. This study complies with the ethical principles of the Declaration of Helsinki.

2.2. Clinical periodontal examination

Periodontal examinations were performed before CA by three independent periodontists (certified by the Japanese Society of Periodontology) who were blinded to the patients' characteristics and cardiovascular disease statuses. The number of remaining teeth were counted. The probing pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BoP), and Community Periodontal Index (CPI) at six points per tooth (buccal-mesial, mid-buccal, buccal-distal, lingual-mesial, mid-lingual, and lingual-distal) on six representative teeth (an upper right molar, an upper incisor, an upper left molar, a lower right molar, a lower incisor, and a lower left molar) were measured using a manual probe (PCP-UNC 15, Hu-Friedy, Chicago, IL, USA). When the corresponding tooth was missing, the adjacent tooth was used instead. PPD was defined as the distance from the gingival margin to the bottom of the periodontal pocket, CAL was defined as the distance from the cementoenamel junction to the bottom of the periodontal pocket, and BoP was defined as bleeding from the gingiva at the probe tip. CPI is a screening measurement of the

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TABLE 1 Patient characteristics.

	Overall (*n* = 132)	Periodontitis group (*n* = 71)	Non-periodontitis group (*n* = 61)	*p*-value
Age, years	62.2 ± 10.6	63.5 ± 10.4	60.7 ± 10.8	0.124
Female	36 (27.3%)	18 (25.4%)	18 (29.5%)	0.696
BMI, kg/m^2	23.8 ± 3.9	23.9 ± 4.4	23.6 ± 4.4	0.907
Hypertension	65 (49.2%)	40 (56.3%)	25 (41.0%)	0.084
Diabetes mellitus	13 (9.8%)	7 (9.9%)	6 (9.8%)	1.000
Dyslipidemia	53 (40.2%)	23 (32.4%)	30 (49.2%)	0.053
CKD, stage 3 or more	15 (11.4%)	12 (16.9%)	3 (4.9%)	0.051
Heart failure	6 (4.4%)	2 (2.8%)	3 (4.9%)	0.662
Old myocardial infarction	5 (3.8%)	2 (2.8%)	3 (4.9%)	0.662
Stroke, TIA, or prior thromboembolism	8 (6.1%)	3 (4.2%)	5 (8.2%)	0.470
$CHADS_2$ score	1 [0–1]	1 [0–1]	1 [0–1]	0.332
CHA_2DS_2-VASc score	2 [1–2]	2 [1–2]	1 [1–2]	0.595
Drinking	83 (62.9%)	48 (67.6%)	35 (57.4%)	0.279
Smoking				
Current smokers	22 (16.7%)	11 (15.5%)	11 (18.0%)	0.816
Former smokers	56 (42.4%)	30 (42.3%)	26 (42.6%)	1.000
Never smokers	53 (40.2%)	30 (42.3%)	23 (37.7%)	0.722
Medication use				
Warfarin	32 (24.2%)	20 (28.2%)	12 (19.7%)	0.311
DOAC	98 (74.2%)	51 (71.8%)	47 (77.0%)	0.553
Aspirin	9 (6.8%)	5 (7.0%)	4 (6.6%)	1.000
Beta-blocker	34 (25.8%)	16 (22.5%)	18 (29.5%)	0.426
Dihydropyridine CCB	40 (30.3%)	22 (31.0%)	18 (29.5%)	1.000
ACEI/ARB	49 (37.1%)	25 (35.2%)	24 (39.3%)	0.718
Diuretics	10 (7.6%)	6 (8.5%)	4 (6.6%)	0.752
MRA	4 (3.0%)	2 (2.8%)	2 (3.3%)	1.000
Statins	40 (30.3%)	17 (23.9%)	23 (37.7%)	0.092
Laboratory findings				
White blood cells, /μL	5200 [4500–6500]	5300 [4700–6800]	5000 [4400–6200]	0.072
Hemoglobin, g/dL	14.0 ± 1.3	14.0 ± 1.4	14.1 ± 1.3	0.798
Albumin, g/dL	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.4	0.980
Creatinine, mg/dL	0.82 [0.71–0.95]	0.82 [0.74–0.92]	0.83 [0.70–0.97]	0.803
Total cholesterol, mg/dL	200 ± 33	195 ± 30	205 ± 35	0.083
Triglyceride, mg/dL	143 ± 106	126 ± 62	162 ± 138	0.046
HDL-cholesterol, mg/dL	62 ± 16	62 ± 15	62 ± 17	0.835
LDL-cholesterol, mg/dL	120 ± 29	118 ± 27	122 ± 31	0.362
HbA1c, %	5.8 ± 0.7	5.8 ± 0.7	5.8 ± 0.7	0.693
CRP, mg/dL	0.06 [0.03–0.11]	0.05 [0.03–0.14]	0.06 [0.04–0.08]	0.587
CRP ≥ 0.1 mg/dL	36 (27.3%)	25 (35.2%)	11 (18.0%)	0.032

(Continued)

TABLE 1 (Continued)

	Overall (n = 132)	Periodontitis group (n = 71)	Non-periodontitis group (n = 61)	p-value
Brain natriuretic peptide, pg/mL	43.2 [18.0–83.5]	56.7 [24.4–97.5]	32.9 [15.3–59.4]	0.016
Echocardiographic measures				
Left ventricular ejection fraction, %	65.4 ± 8.7	65.1 ± 9.6	65.8 ± 7.6	0.686
Left atrial diameter, mm	38.1 ± 5.3	38.8 ± 5.6	37.3 ± 5.0	0.118

BMI, body mass index; CKD, chronic kidney disease; TIA, transient ischemic attack; $CHADS_2$ score, congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack (2 points) score; CHA_2DS_2-VASc, congestive heart failure, hypertension, age (>65 = 1 point, >75 = 2 points), diabetes, previous stroke/transient ischemic attack (2 points) vascular disease score; DOAC, direct oral anticoagulant; CCB, calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin; CRP, C-reactive protein.

periodontal condition that assesses the presence or absence of periodontal pockets, calculus, and gingival bleeding, and it is scored from 0 to 4. In this study, patients were diagnosed with PD when the maximum PPD was equal to or greater than 4 mm with positive BoP.

2.3. Examination of periodontopathic bacteria

The presence of three major periodontal bacteria (*Porphyromonas gingivalis*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans*) in the periodontal pocket and saliva were evaluated using real-time polymerase chain reaction. Furthermore, the serum immunoglobulin G (IgG) titer against each bacterium was measured.

2.4. Baseline patients' characteristics

The patient's medical history, medications, smoking history, and alcohol consumption were recorded; physical examination was performed on admission. Peripheral blood samples were obtained for a blood cell count and the concentrations of albumin, creatinine, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin A1c, C-reactive protein (CRP), and brain natriuretic peptide (BNP). The left ventricular ejection fraction and left atrial diameter were evaluated by transthoracic echocardiography before CA.

2.5. Ablation procedure

All procedures were performed under moderate or deep sedation and continuous heparinization to maintain the activated clotting time >300 s after the transseptal puncture. All patients in the current study underwent pulmonary vein (PV) isolation with a radiofrequency catheter under the guidance of a three-dimensional mapping system (CARTO-3; Biosense Webster, Diamond Bar, CA, USA), cryoablation (Arctic Front Advance; Medtronic Inc., Minneapolis, MN, USA), or hot balloon (SATAKE HotBalloon; Toray Industries, Inc., Tokyo, Japan) at the operator's discretion. The procedural endpoint was defined as the electrical isolation of the PV. Additionally, a majority of the patients underwent cavotricuspid isthmus ablation, and some patients underwent adjunctive ablation (linear and focal ablation) at the operator's discretion.

2.6. Clinical outcomes

Clinical outcomes after CA were assessed by reviewing the medical records. Atrial arrhythmia recurrence was defined as an episode of AF, atrial flutter, or atrial tachycardia lasting 30 s or longer after a 3-month blanking period, with or without the use of antiarrhythmic drugs. 12-lead electrocardiogram was recorded at every visit to the outpatient clinic, and 24-h Holter monitoring or 1-week event loop recorder was encouraged to be performed at 3- and 6-months and every 6-month thereafter. If patients were symptomatic suggesting atrial arrhythmia recurrence, an electrocardiogram, Holter monitoring, or event loop recorder was performed in addition.

2.7. Statistical analysis

All statistical analyses were performed using R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean ± standard deviation or median with interquartile range (25th–75th percentile) and analyzed using the Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as numbers with percentages and analyzed using the chi-squared test or Fisher's exact test, as appropriate. Kaplan–Meier analysis was performed to compare clinical outcomes between the patients with and without PD. To provide separate descriptions of the short- and long-term risks of recurrences, a landmark analysis with a landmark set at 1 year was performed. Cox proportional hazards model was used to

TABLE 2 Periodontal conditions.

	Overall (n = 132)	Periodontitis group (n = 71)	Non-periodontitis group (n = 61)	p-value
Number of remaining teeth	26 [21–28]	25 [20–28]	26 [22–28]	0.215
Maximum PPD, mm	4.0 [3.0–5.0]	4.0 [4.0–6.5]	3.0 [3.0–3.0]	<0.001
Mean PPD, mm	2.3 [2.1–2.6]	2.6 [2.4–2.9]	2.1 [1.9–2.2]	<0.001
Maximum CAL, mm	5.0 [4.0–6.3]	6.0 [4.0–7.0]	4.0 [3.0–5.0]	<0.001
Mean CAL, mm	2.6 [2.3–3.3]	3.0 [2.7–3.8]	2.3 [2.2–2.6]	<0.001
Positive rate of BoP	0.10 [0.00–0.28]	0.20 [0.08–0.40]	0.00 [0.00–0.08]	<0.001
Maximum CPI	3 [2–3]	3 [3–4]	2 [1–2]	<0.001
Pathogens in the periodontal pocket				
P. gingivalis	88 (67.7%)	55 (78.6%)	33 (55.0%)	0.005
P. intermedia	31 (23.8%)	23 (32.9%)	8 (13.3%)	0.013
A. actinomycetemcomitans	20 (15.4%)	10 (14.3%)	10 (16.7%)	0.809
Pathogens in the saliva				
P. gingivalis	90 (71.4%)	57 (82.6%)	33 (57.9%)	0.003
P. intermedia	40 (31.7%)	29 (42.0%)	11 (19.3%)	0.007
A. actinomycetemcomitans	28 (22.2%)	14 (20.3%)	14 (24.6%)	0.668
Serum antibody titer, U/mL				
P. gingivalis	124 [43–399]	210 [71–548]	94 [21–178]	<0.001
P.intermedia	332 [192–595]	318 [178–519]	386 [199–600]	0.567
A. actinomycetemcomitans	44 [25–91]	45 [25–83]	39 [25–107]	0.886

PPD, probing pocket depth; CAL, clinical attachment level; BoP, bleeding on probing; CPI, Community Periodontal Index; *P. gingivalis*, *Porphyromonas gingivalis*; *P. intermedia*, *Prevotella intermedia*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*.

identify the independent predictors of recurrent arrhythmia after CA. The associated variables showing a p-value < 0.150 in univariate analysis were entered in the multivariate model with patients' age and gender, and stepwise regression was performed using the Akaike information criterion to fit the regression model.

3. Results

3.1. Patient characteristics

Of the 132 patients, 71 patients (54%) were included in the PD group, and 61 (46%) were in the non-PD group. The baseline patient characteristics are shown in Table 1. There were no significant differences between the two groups except lower triglyceride and higher BNP levels in the PD group compared to the non-PD group (triglyceride: 126 ± 62 and 162 ± 138 mg/dL, $p = 0.046$; BNP: 57 [24–98] and 33 [15–59] pg/mL, $p = 0.016$). The patients' age, white blood cell counts, and left atrial diameter showed non-significant trends toward higher values in the PD group than in the non-PD group (age: 63.5 ± 10.4 and 60.7 ± 10.8 years, $p = 0.124$; white blood cell counts: 5300 [4700–6800] and 5000 [4400–6200], $p = 0.072$; left atrial diameter: 38.8 ± 5.6 and 37.3 ± 5.0 mm, $p = 0.118$).

3.2. Periodontal status

The baseline periodontal conditions in the two groups are summarized in Table 2. Patients in the PD group had significantly greater PPD and CAL values, more prevalent BoP-positive teeth, and higher CPI values in comparison with those in the non-PD group, suggesting the worse periodontal status in the PD group. The antigens of *P. gingivalis* and *P. intermedia* were more frequently detected in the periodontal pocket and in the saliva in the PD group than in the non-PD group. The serum IgG titer for *P. gingivalis* was significantly higher in the PD group than in the non-PD group.

3.3. Catheter ablation procedures

The procedures performed on each patient are shown in Table 3. PV isolation was successfully achieved in all patients using a radiofrequency catheter (81.1%), cryoballoon (15.2%), or hot balloon (3.8%). There were no significant differences

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TABLE 3 Ablation procedures.

	Overall (n = 132)	Periodontitis group (n = 71)	Non-periodontitis group (n = 61)	p-value
Energy source for catheter ablation				
Radiofrequency ablation	107 (81.1%)	60 (84.5%)	47 (77.0%)	0.373
Cryoballoon ablation	20 (15.2%)	9 (12.7%)	11 (18.0%)	0.468
Hot balloon ablation	5 (3.8%)	2 (2.8%)	3 (4.9%)	0.662
Ablation strategy				
PVI without adjunctive ablation except CTI block	101 (76.5%)	53 (74.6%)	48 (78.7%)	0.682
PVI with adjunctive ablation except CTI block	31 (23.5%)	18 (25.4%)	13 (21.3%)	0.682
CTI block	113 (85.6%)	62 (87.3%)	51 (83.6%)	0.623
Procedure-related complications				
Stroke/TIA	0	0	0	
Cardiac tamponade	2	2	0	
Congestive heart failure	2	1	1	
Lower respiratory tract infections	4	2	2	
Phrenic nerve palsy	2	1	1	
Pulmonary vein stenosis	1	1	0	
Pericarditis	1	1	0	
Arteriovenous fistula	1	0	1	
Total	12 (9.1%)	8 (11.3%)	4 (6.6%)	0.383
Class I or III antiarrhythmic drugs on discharge	39 (29.5%)	22 (31.0%)	17 (27.9%)	0.707

PVI, pulmonary vein isolation; CTI, cavotricuspid isthmus; TIA, transient ischemic attack.

in procedure strategies and procedure-related complications between the PD and non-PD groups.

3.4. Post-ablation outcomes and predictors of recurrent arrhythmia

A total of 37 (28.0%) arrhythmia recurrences were observed in 132 patients at a median follow-up period of 3.0 (1.1–6.4) years. In the Kaplan–Meier analysis, worse atrial arrhythmia recurrence-free survival rate was observed in the PD group than in the non-PD group (64.8% vs. 80.3%, Log-rank: p = 0.024) (**Figure 1**). In the univariate Cox regression analysis, only PD was significantly associated with recurrence (**Table 4**), while mildly elevated CRP $\geq$ 0.1 mg/dL showed worse recurrent-free survival rate as compared with those without mildly elevated CRP in Log-rank test (p = 0.048) (**Supplementary Figure 1**), which was not statistically significant in Cox regression analysis (**Table 4**). The multivariate Cox regression analysis revealed that PD was a significant predictor of arrhythmia recurrence (hazard ratio: 2.063, 95% confidence interval: 1.018–4.182) after adjusting for the age and gender (**Table 4**). In the landmark analysis, during the initial 1 year, the atrial arrhythmia recurrence-free survival rate was not significantly different between PD and non-PD groups (76.8% vs. 84.6%, Log-rank: p = 0.305). After 1 year, there was a continuous separation of the curves in the Kaplan–Meier analysis, with a significantly worse atrial arrhythmia recurrence-free survival rate in the PD group (Log-rank: p = 0.020) (**Figure 2**). The multivariate Cox regression analysis also revealed PD as a significant predictor of arrhythmia recurrence after 1 year (hazard ratio: 5.677, 95% confidence interval: 1.482–21.74) after adjusting for the age and gender.

4. Discussion

To the best of our knowledge, this is the first study which demonstrates a significant association between PD diagnosed by performing periodontal examinations and the recurrence of arrhythmia after CA. The main finding of this study was that concurrent PD was an independent predictor of recurrent atrial arrhythmia after the first CA for PAF in multivariable Cox regression analysis adjusting for other clinical factors.

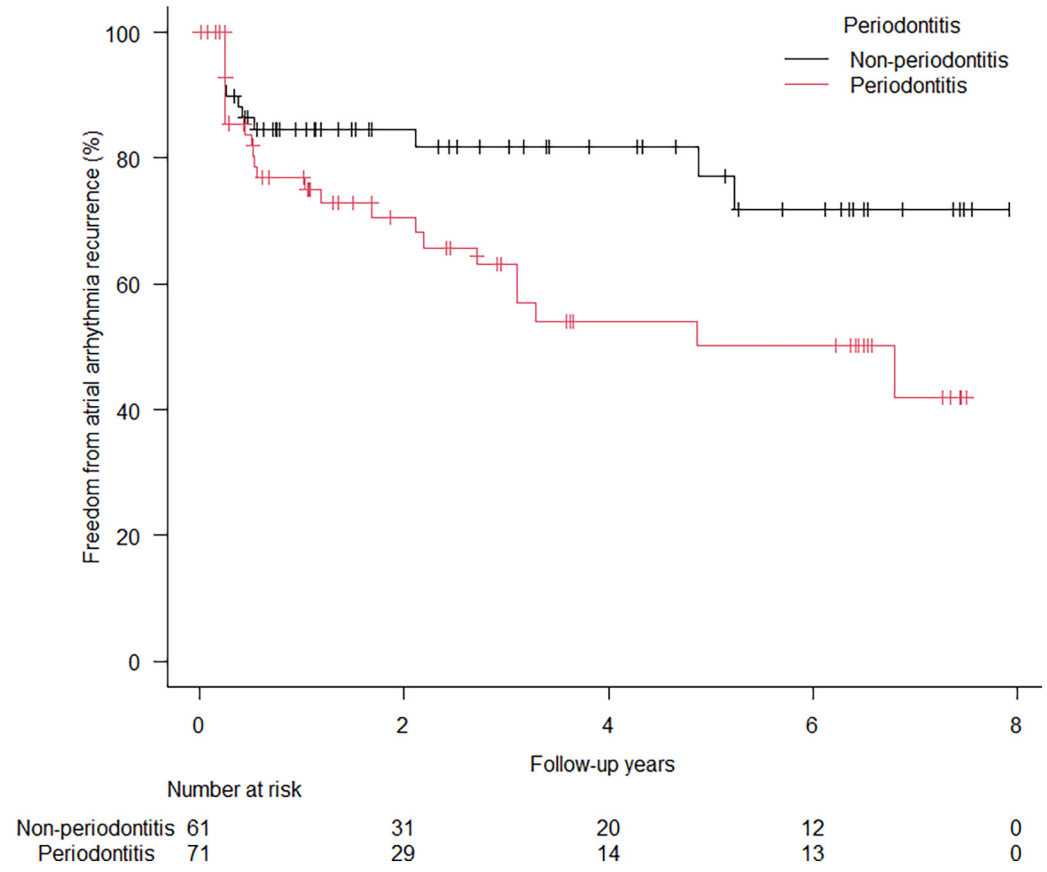

FIGURE 1
Arrhythmia recurrence-free survival in the patients with and without periodontitis. Kaplan–Meier curve analysis showed worse atrial arrhythmia recurrence-free survival probabilities after the first session of catheter ablation for paroxysmal atrial fibrillation in the patients with periodontitis than in those without periodontitis (64.8% vs. 80.3%, respectively: $p = 0.024$).

4.1. PD and systemic inflammation

Periodontitis is a common and well-known chronic oral inflammatory disease. Previous studies reported that subjects with PD are more susceptible than those without PD to the infiltration of periodontal pathogens into the systemic circulation, which potentially causes bacteremia through oral interventions, such as dental treatment or tooth extractions, and even through activities in daily lives, including chewing, biting, toothbrushing, and flossing (12, 13). It is hypothesized that repeated short-time bacteremia activates inflammatory cells, endothelial cells, and other types of cells, leading to the production of systemic inflammatory mediators (14). This is supported by the evidence of elevated plasma CRP (15) and serum interleukin (IL)-6 levels, and lower IL-4 and IL-18 (16) levels in patients with PD compared to healthy controls. Present study, due to a limited sample size, did not show a significant difference in the numerical value of CRP levels between PD and non-PD groups. Nevertheless, the prevalence of mildly elevated CRP levels of ≥0.1 mg/dL was significantly higher in PD group than in non-PD group (**Table 1**).

4.2. Systemic inflammation and AF

A variety of factors, such as the age, other structural heart diseases, the blood pressure, the alcohol intake, obesity, and genetic factors, have been reported to play a role in modifying the electrophysiological substrate of AF (17, 18). Systemic inflammation has also been suggested as one of the modifying factors of AF, which was corroborated by the increased inflammatory markers in the patients with AF (9, 19–22). A case–control study reported that the circulating CRP level was higher in patients with AF than in those without AF (9). A population-based study revealed that the serum CRP level was independently associated with the new occurrence of AF as well as baseline AF (20). Additionally, AF is associated with elevated pro-inflammatory IL-6 levels (19, 21, 22), and left atrial diameters were positively associated with CRP and IL-6 levels, which suggested that the inflammation

TABLE 4 Predictors of recurrent arrhythmia.

	Univariate Cox regression			Multivariate Cox regression		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (per year)	1.014	0.980–1.049	0.425	1.008	0.973–1.044	0.663
Male gender	1.092	0.528–2.260	0.812	1.065	0.499–2.274	0.870
BMI (per kg/m^2)	0.956	0.877–1.042	0.309			
HTN	1.178	0.617–2.248	0.620			
DM	0.469	0.113–1.954	0.299			
DLP	0.835	0.429–1.623	0.594			
CKD	1.206	0.468–3.109	0.699			
LVEF (per%)	1.014	0.975–1.056	0.485			
LA diameter (per mm)	0.990	0.932–1.051	0.732			
CRP (per mg/dL)	1.512	0.562–4.068	0.413			
CRP $\geq$ 0.1 mg/dL	1.889	0.979–3.644	0.057			
BNP (per pg/mL)	1.001	0.999–1.003	0.337			
Periodontitis	2.135	1.072–4.252	0.031	2.063	1.018–4.182	0.045

HR, hazard ratio; CI, confidence interval; BMI, body mass index; CHF, congestive heart failure; HTN, hypertension; DM, diabetes mellitus; DLP, dyslipidemia; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; LA, left atrium; CRP, C-reactive protein; BNP, brain natriuretic peptide.

might promote atrial remodeling (23). A basic research has suggested the interaction between the release of inflammatory cytokines, such as tumor necrosis factor-alpha and IL-6, and the remodeling of the atrial muscle, leading to the development of AF substrates (24). In the present study, although a numerical value of CRP level was not correlated with AF recurrence in Cox proportional hazard models, the patients with mildly elevated CRP $\geq$ 0.1 mg/dL showed a higher recurrence rate than the counterpart (CRP $<$ 0.1 mg/dL) (**Supplementary Figure 1**).

4.3. PD and AF

In animal models, induced PD led to an inflammatory response and remodeling of the atrial myocardium, facilitating AF inducibility (25). In addition, previous studies have reported the presence of periodontal pathogens in human atheromatous lesions and the association of those pathogens with myocardial damage (26, 27), which suggested that periodontal pathogens may infiltrate into arterial wall or myocardium. Thus, the direct infiltration of periodontal bacteria also may be a potential mechanism of atrial remodeling and predisposition to AF. A Taiwanese nationwide population-based cohort study showed an association between PD and the future development of AF or atrial flutter (6). PD was associated with future arrhythmic events, including AF, atrial tachycardia, and atrial premature beat, and thromboembolic events during the long-term follow-up of the patients with AF (10). Nevertheless, the association of PD with arrhythmia recurrence after CA has not been elucidated. A recent study has shown the association between serum antibody levels to one of the periodontal pathogens and the recurrence of AF (11). This study is the first to demonstrate the association between actual oral health conditions examined in detail by periodontists or dentists and arrhythmia recurrence after CA for PAF, which supports the results of previous studies (6, 10, 11). An interesting finding of this study is the recurrence-free rate curves in the Kaplan–Meier analysis of the PD and non-PD groups separated in the long-term (after 1 year) rather than in short-term (**Figures 1**, **2**). A recent study reported that electrical left atrial remodeling and non-PV triggers were more common in long-term recurrence of AF than in short-term recurrence, whereas PV reconnections were dominant in short-term recurrence (28). In other words, short-term recurrence is mainly associated with procedure-related factors while long-term recurrence is more affected by atrial remodeling, which may develop slowly. This may explain how PD and subsequent systemic inflammation may have an impact on long-term recurrence through atrial remodeling rather than on short-term outcomes. Although the present study could not show the association of PD with the evidence of atrial remodeling such as enlarged atrial dimension or greater atrial low voltage area because of the small sample size and lack of 3D imaging data or voltage map, future prospective studies may address the impact of PD on electrophysiological findings in AF.

4.4. Clinical implications

Periodontitis is a common disease worldwide, and at the same time, it is preventable and modifiable with oral health care (29, 30). Previous meta-analyses revealed, with a high sensitivity, that CRP was significantly reduced after periodontal

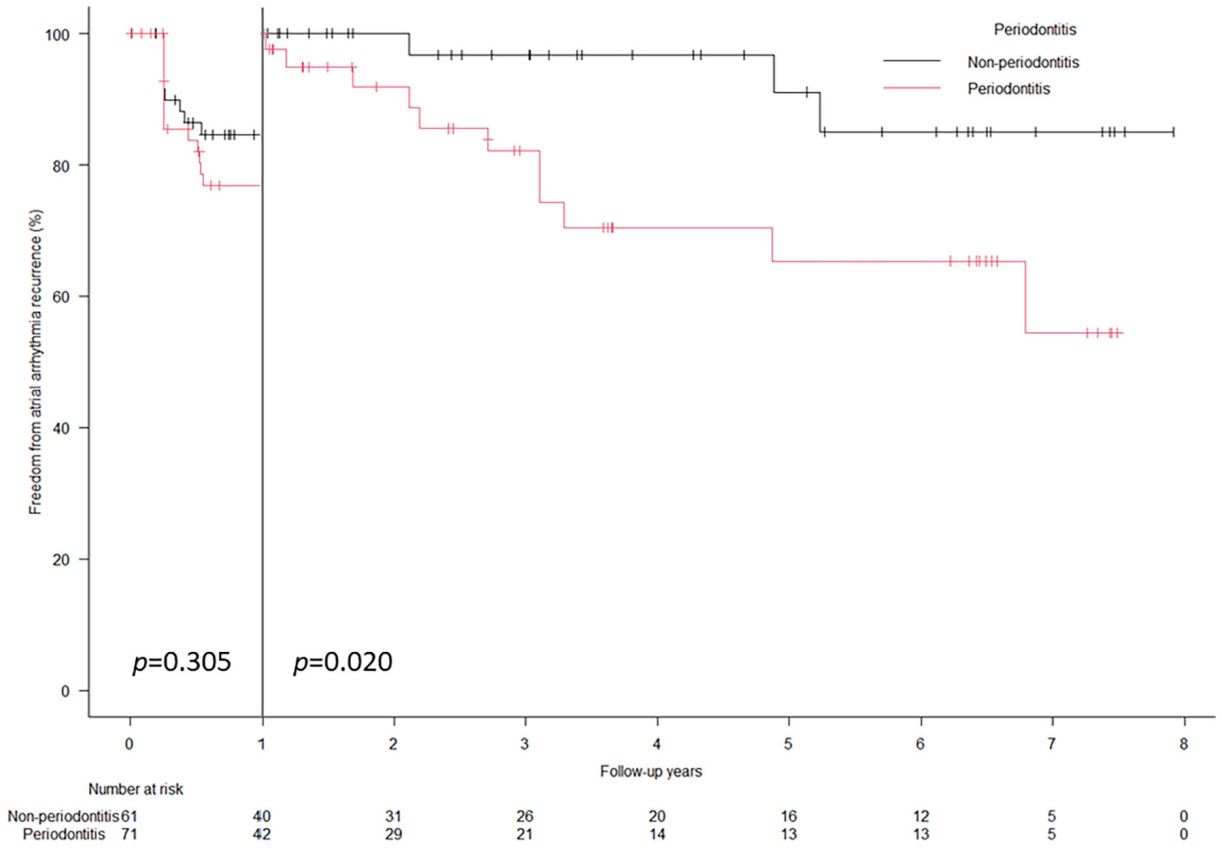

FIGURE 2
Landmark analysis of arrhythmia recurrence-free survival rate. Landmark analysis showed the cumulative atrial arrhythmia recurrence-free survival probabilities was comparable between PD and non-PD groups during the first 1 year (76.8% vs. 84.6%, log-rank: $p = 0.305$). After 1 year, a significantly worse atrial arrhythmia recurrence-free survival probabilities were demonstrated in the PD group (log-rank: $p = 0.020$).

intervention (31). Additionally, a previous randomized study showed a positive effect of the intensive treatment of PD on decreasing serum proinflammatory cytokine levels, including IL-6 (32). Furthermore, the impact of dental scaling on the significant reduction of new-onset AF has also been reported (33). Considering these results, it might be reasonable to posit that dental intervention to maintain periodontal health may reduce AF recurrence after CA. Further prospective studies are required to elucidate the impact of periodontal health care on the outcomes of CA.

4.5. Limitations

There are several limitations in this study. First, this is a single-center observational study. Although consecutive patients were enrolled in the study, potential selection bias cannot be ruled out. Further studies are required to prove a causal relationship between PD and AF. Second, this study comprised relatively small number of patients which precluded the assessment of the impact of each component of periodontal status on the arrhythmia recurrence after CA. In addition, because of limited sample size, it was difficult to determine the interaction and collinearity of PD with other clinical factors related with arrhythmia recurrence. Likewise, relatively small number of cases in our study may not have had sufficient statistical power to demonstrate significant associations of known risk factors with AF recurrence. Future studies will have to prospectively explore collinearity and interaction of PD and known predictors of recurrent AF with sufficient sample size. Third, arrhythmia recurrence after CA was diagnosed based on electrocardiogram documentation or recording of a 24-h Holter or a 1-week event loop recorder. Thus, asymptomatic recurrence may have been missed by examinations, and the recurrence rate might have been underestimated. Fourth, changes in the periodontal status before and after index CA were not assessed, and the information on the periodontal treatment was also lacking, which may have affected the clinical outcomes. Fifth, strategies in CA procedures were left to the operators' discretion, which may have affected the outcomes. Finally, this study excluded patients with persistent AF because of a different recurrence rate from PAF.

5. Conclusion

In this study, we investigated the patients who underwent periodontal examinations during admission for fist CA due to PAF. The presence of PD diagnosed by periodontists at baseline was a significant risk factor for recurrent atrial arrhythmia in long-term follow-up. Future studies are required to confirm whether oral health care may reduce the recurrence of PAF after CA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the IRB of the Tokyo Medical and Dental University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AT was responsible for the data collection, investigation, analysis, and original draft writing. TY participated in the conceptualization and methodology of the work and edited the manuscript. NA, YS-W, and TN contributed to the data collection and investigation. SM, YM, MG, MI, and TI reviewed and edited the manuscript. TS supervised the work. All authors listed have made a substantial contribution to the work and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1061243/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Arrhythmia recurrence-free survival according to the C-reactive protein levels. Kaplan–Meier curve analysis showed worse post-ablation atrial arrhythmia recurrence-free survival probabilities in the patients with CRP $\geq$ 0.1 mg/dL than those with CRP $<$ 0.1 mg/dL (log-rank: $p = 0.048$).

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Efficacy of tolvaptan on the short and mid-term prognosis in elderly patients with acute heart failure coexisting with oliguria: A retrospective cohort study

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Background: In patients with acute heart failure (AHF) coexisting with oliguria, high doses of loop diuretics are often ineffective in increasing urine output and may adversely affect the patient's prognosis, especially in elderly patients. We investigated the efficacy of adding tolvaptan (TLV) on improving the prognosis in elderly patients with AHF coexisting with oliguria.

Methods: All data for this retrospective cohort study were extracted from the electronic medical record system of the Second Medical Center of Chinese PLA General Hospital from January 2018 to December 2020. Patients diagnosed with AHF coexisting with oliguria were enrolled in this study and were divided into TLV and non-TLV groups based on the use of TLV. The primary outcome was all-cause mortality at 7 and 90-day. The secondary outcomes were the remission of AHF within 7 and 30 days or continued progression of AHF, and new-onset chronic kidney disease (CKD) after 90 days. Cox proportional hazards regression was used to assess the relationships between all-cause mortality and diuretic regimens, demographics, laboratory parameters, comorbidities, and medications.

Results: A total of 308 patients met the study criteria for the final statistical analysis, and they had a median age of 91 years (88, 95). The results showed that the addition of TLV was associated with a decreased risk of the 7 and 90-day all-cause mortality in patients with AHF with oliguria [adjusted HR, 95% CI: 0.60 (0.37, 0.98), $p = 0.042$; 0.56 (0.41, 0.75), $p < 0.001$, respectively]. Adding TLV significantly increased urine output and decreased N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in 7 days, and alleviated the progression of AHF within 30 days. There were no statistically significant differences between the patients with or without TLV in terms of the occurrence of hypernatremia, the development of hepatic impairment within 30 days, and new-onset CKD after 90 days.

Conclusions: This study demonstrated that the addition of TLV was clinically effective in increasing urine output, and had favorable effects on alleviating AHF progression and may reduce the risk of all-cause mortality at 7 and 90-day in elderly patients with AHF with oliguria, and TLV had a good safety profile.

Trial registration: http://www.chictr.org.cn/showprojen.aspx?proj=148046, identifier: ChiCTR2200055518.

KEYWORDS

tolvaptan, acute heart failure (AHF), oliguria, elderly, prognosis

Introduction

Acute heart failure (AHF) is a frequent cause of hospitalization for patients with heart disease, and patients with AHF, especially older patients, are at high risk of rehospitalization and have worse short- and long-term survival and mortality rates (1, 2). As the population of aging adults increase, the incidence of AHF and its associated health and economic burdens are expected to increase further (3, 4).

Achievement of volume reduction or fluid removal was fundamental to the treatment of AHF. As a result, loop diuretics, such as furosemide, are widely used in high doses in the clinical treatment of AHF (5, 6). This is accompanied by diuretic resistance, activation of the renin-angiotensin-aldosterone system (RAAS), impairment of renal function, and even the occurrence of acute kidney injury (AKI). Diuretic resistance is defined as an impaired sensitivity to diuretics resulting in reduced natriuresis and diuresis limiting the possibility of achieving euvolemia (7). Diuretic resistance is different from oliguria, and patients with diuretic resistance may not meet the criteria of oliguria. The presence of oliguria may mean more severe diuretic resistance which leads to worse prognosis in patients with AHF, especially in elderly patients (8–10). Currently, there is no approved strategy for treating this high-risk subgroup. TLV combined with loop diuretic therapy may have favorable outcomes (11).

Tolvaptan (TLV) is a selective vasopressin V2-receptor antagonist that competes with the antidiuretic hormone vasopressin for the V2 receptor in the renal collecting duct, resulting in inhibition of water resorption by the collecting ducts of the kidney, and increased excretion of free water (12). TLV increases urine output without inducing intravascular volume depletion or activation of the RAAS (13). Moreover, TLV reduces the use of loop diuretics, even in patients who are resistant to loop diuretics, and is clinically effective in relieving congestion and improving renal function in AHF patients (14).

TLV combined with loop diuretics has been shown to be effective in the treatment of diuretic-resistant AHF patients (6, 15, 16). However, there are few reports on whether TLV is equally effective in elderly patients with AHF and oliguria (10, 17). For this reason, in this study, we examined the efficacy and safety of TLV in elderly patients with AHF and oliguria.

Methods

Study design and population

This retrospective, single-center study, was conducted in the Second Medical Center of Chinese PLA General Hospital in Beijing, China. This study was approved by the Ethics Committee of Chinese PLA General Hospital (No. S2022-342-01). Written informed consent was not required for this study because the data were collected anonymously. This study was registered at http://www.chictr.org.cn/showprojen.aspx?proj=148046 (ChiCTR2200055518).

The patients meeting all of the following criteria were included: (1) age $\geq$ 65 years; (2))diagnosis of AHF, as determined by echocardiography showing an ejection fraction $<$50% and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP) $\geq$1800 pg/ml (18, 19), and $\geq$1.5-fold increase in NT-proBNP level from baseline (the baseline level of NT-proBNP defined as the most recent NT-proBNP value measured between 7 and 365 days prior to the onset of oliguria in AHF patients); (3) coexisting oliguria (set as the starting point of this study). In this study, oliguria was defined as a urine output $<$ 0.5 ml/(kg·h) for more than 12 h (20); (4) If patients treated with TLV, the duration of TLV treatment was more than 30 days or until the patient died. The patients meeting at least one of the following criteria were excluded: (1) death within 24 h of the onset of oliguria; (2) accepted renal replacement therapy (RRT), implantation of a mechanical circulatory support (MCS) or ICD, CRT-D; (3) obstructive and non-obstructive type of hypertrophic cardiomyopathy, restrictive cardiomyopathy, cardiac amyloidosis, significant valvular heart disease, acute myocardial infarction, cardiac arrest, massive hemorrhage (bleeding of more than 1000 ml/24 h within 7 days), hemorrhagic stroke; (4) no complete intake and urine volume records after the onset of oliguria; (5) no baseline record of NT-proBNP; (6) no NT-proBNP level available within 7 days and 30 days after the occurrence of oliguria; and 7) missing data or

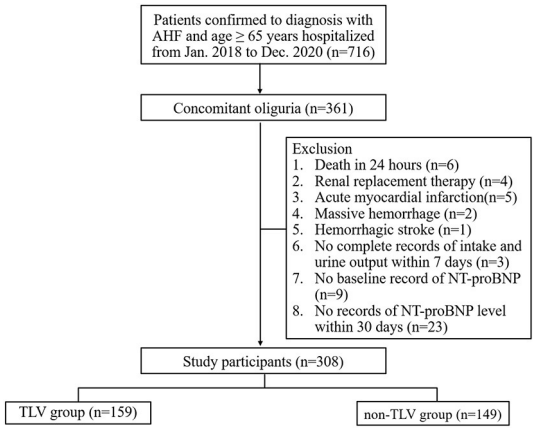

FIGURE 1
Flow chart of patient enrollment in this study. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

clinically unreliable data. The flow chart of this study is shown in Figure 1.

All patients received loop diuretics and standard AHF treatment regimens under the supervision of their physicians. The average intake or urine output was calculated as the average daily intake or urine output over the 7 days after the onset of oliguria. Daily doses of loop diuretics are represented by furosemide, and doses of other loop diuretics were converted into equivalent furosemide doses using the formula: 1 mg bumetanide equivalent to 20 mg torsemide, and equivalent to 40 mg furosemide (21, 22). Depending on whether TLV was used, the patients were divided into two groups: the TLV group and the non-TLV group. The patients in the non-TLV group received 20 to 400 mg equivalent dose of furosemide daily for the treatment of oliguria. The patients in the TLV group received an additional 15 to 45 mg of TLV daily on top of the non-TLV group. TLV was added within 72 h of the onset of oliguria in AHF patients, and the duration of TLV treatment was more than 30 days or until the patient died. The patients were divided into six groups based on the use of equivalent doses of furosemide daily and the additional use of TLV: Group A1: <100 mg/d equivalent doses of furosemide plus TLV; Group A0: <100 mg/d equivalent doses of furosemide only; Group B1: ≥100 and <200 mg/d equivalent doses of furosemide plus TLV; Group B0: ≥100 and <200 mg/d equivalent doses of furosemide only; Group C1: ≥200 mg/d equivalent doses of furosemide plus TLV; and Group C0: ≥200 mg/d equivalent doses of furosemide only.

Clinical data and outcomes

All patients were male because our hospital is a military hospital. Age, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), intake, urine output, laboratory parameters, comorbidities, medications, and outcome data (death or not) were extracted from the Second Medical Center of Chinese PLA General Hospital electronic medical record system from January 2018 to December 2020. All data were entered into a computer database and were cross-checked by two independent physicians (Yang Liu and Yabin Zhang). The principal investigator (Qiangguo Ao) regularly performed randomized group reviews and blinded reviews of the groups.

The primary outcome was all-cause mortality at 7 and 90-day. The secondary outcomes were reversal or continued progression of AHF within 7 and 30 days, and new-onset CKD after 90 days. In this study, reversal of AHF within 7 or 30 days was defined as the NT-proBNP level persistently decreased above 1.5 times the baseline level. Continued progressive AHF was defined as the NT-proBNP level persistently elevated above 1.5 times the baseline level. The new-onset CKD was defined as the patients with eGFR < 60 ml/min/1.73 m^2 after 90 days, expect the history of CKD.

Statistical analysis

We used SPSS software (Version 26.0) to perform data analysis in this study. We evaluated the normality of the distribution of variables using the Kolmogorov–Smirnov test. Continuous variables were reported as the means with standard deviations or medians with interquartile ranges according to normality. The difference between normally distributed continuous variables was tested by the *t*-test or ANOVA, and non-normally distributed data were tested by the Mann–Whitney U test or Kruskal–Wallis test. Categorical variables were presented as numbers (%) and were compared with the chi-square test and Fisher's exact test. The one-way ordered classified variables were compared with the rank sum test. Survival was analyzed by the Kaplan–Meier method. The log rank method was used to compare the survival of two or more groups of patients. Prognostic analysis was performed using Cox regression. All tests were two sided, and a *p*-value < 0.05 was considered statistically significant.

Results

Patient characteristics

From January 2018 to December 2020, 716 patients aged ≥ 65 years were diagnosed with AHF at the Second Medical Center of Chinese PLA General Hospital. Among them, 361 patients developed oliguria. A total of 308 patients were enrolled in this study according to the inclusion and exclusion

TABLE 1 Baseline characteristics of the study population.

Characteristics	Total ($n = 308$)	Tolvaptan[#] ($n = 159$)	Non-tolvaptan ($n = 149$)	p-value
Demographics				
Age, years	91 (88, 95)	92 (88, 95)	91 (87,94)	0.116
Sex, male	308 (100%)	159 (100%)	149 (100%)	
BMI, kg/m^2	23.4 (21.3, 25.6)	23.4 (20.9, 25.6)	23.4 (21.5, 25.7)	1.00
SBP, mmHg	112 (101, 126)	112 (102, 127)	112 (100, 125)	0.544
DBP, mmHg	58 (52, 66)	59 (52, 68)	58 (51, 65)	0.304
MAP, mmHg	77 (69, 86)	77 (70, 87)	76 (68, 84)	0.329
Comorbidities, *n* (%)				
Hypertension	247 (80.2%)	133 (83.6%)	114 (76.5%)	0.116
Diabetes mellitus	166 (53.9%)	85 (53.5%)	81 (54.4%)	0.874
CAD	258 (83.8%)	135 (84.9%)	123 (82.6%)	0.575
Atrial fibrillation	115 (37.3%)	59 (37.1%)	56 (37.6%)	0.931
EF				0.210
EF > 50%	247 (80.2%)	124 (78.0%)	123 (82.6%)	
40%≤EF≤50%	37 (12.0%)	24 (15.1%)	13 (8.7%)	
EF < 40%	24 (7.8%)	11 (6.9%)	13 (8.7%)	
CKD	133 (43.2%)	68 (42.8%)	65 (43.6%)	0.879
Hyperlipidemia	142 (46.1%)	71 (44.7%)	71 (47.7%)	0.598
Hyperuricemia	216 (70.1%)	118 (74.2%)	98 (65.8%)	0.106
Stroke	159 (51.6%)	89 (56.0%)	70 (47.0%)	0.114
COPD	118 (38.3%)	57 (35.8%)	61 (40.9%)	0.358
Non-invasive ventilation	167 (54.2%)	81 (50.9%)	86 (57.7%)	0.233
Infection*	143 (46.4%)	75 (47.2%)	68 (45.6%)	0.788
History of cancer	136 (44.2%)	55 (34.6%)	81 (54.4%)	0.001
Abnormal liver function	130 (42.2%)	67 (42.1%)	63 (42.3%)	0.980
Medications, *n* (%)				
Doses of furosemide, mg	308 (100%)	159 (100%)	149 (100%)	
<100 mg/d	174 (56.5%)	104 (59.8%)	70 (40.2%)	
≥100 mg/d and <200 mg/d	63 (20.5%)	32 (50.8%)	31 (49.2%)	
≥200 mg/d	71 (23.1%)	23 (32.4%)	48 (67.6%)	
Spironolactone	97 (31.5%)	59 (37.1%)	38 (25.5%)	0.028
Hydrochlorothiazide	44 (14.3%)	25 (15.7%)	19 (12.8%)	0.456
ARB/ACEI	97 (31.5%)	52 (32.7%)	45 (30.2%)	0.636
β-Blockers	150 (48.7%)	79 (49.7%)	71 (47.7%)	0.721
Statin	121 (39.3%)	66 (41.5%)	55 (36.9%)	0.409
Nitrates	165 (53.6%)	98 (61.6%)	67 (45.0%)	0.003
Digoxin	34 (11.0%)	16 (10.1%)	18 (12.1%)	0.590
Laboratory parameters				
Hemoglobin, g/L	100 (85, 114)	101 (88, 116)	98 (83, 113)	0.161

(Continued)

TABLE 1 (Continued)

Characteristics	Total ($n = 308$)	Tolvaptan[#] ($n = 159$)	Non-tolvaptan ($n = 149$)	p-value
Albumin, g/L	31.7 (28.6, 35.4)	32.2 (28.8, 35.4)	30.9 (28.1, 35.4)	0.142
Scr, mmol/L	151 (113, 198)	151 (109,193)	151 (116,201)	0.601
eGFR, ml/min/1.73 m^2	34.9 (24.5, 49.2)	35.9 (25.2, 50.8)	34.7 (23.9, 47.2)	0.712
BUN, mmol/L	18.4 (12.5, 27.4)	17.5 (11.9, 23.5)	20.4 (12.8, 31.5)	0.024
Sodium, mmol/L	141 (136, 147)	140 (136, 147)	141 (137, 147)	0.349
Potassium, mmol/L	4.4 (4.0, 4.8)	4.4 (4.0, 4.8)	4.4 (3.9, 4.8)	0.714
TC, mmol/L	3.6 (2.9, 4.4)	3.6 (3.0, 4.4)	3.5 (2.9, 4.4)	0.489
TG, mmol/L	1.4 (0.9, 2.2)	1.2 (0.9, 2.1)	1.5 (1.0, 2.4)	0.074
HDL, mmol/L	0.82 (0.6, 1.1)	0.8 (0.6, 1.2)	0.8 (0.6, 1.1)	0.190
LDL, mmol/L	2.0 (1.5, 2.6)	2.1 (1.6, 2.5)	2.0 (1.4, 2.6)	0.299
Serum uric acid, mmol/L	406 (309, 525)	405 (304, 525)	407 (320, 528)	0.589
Baseline NT-proBNP	1,176 (470, 2986)	1,555 (490, 3283)	967 (439, 2755)	0.181

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; Scr, Serum creatinine; eGFR, estimated glomerular filtration rate; TC, cholesterol; TG, triglyceride; HDL, high density lipoprotein cholesterol; LDL low density lipoprotein cholesterol; CAD, coronary atherosclerotic heart disease; EF, ejection fraction; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ARB/ACEI, angiotensin receptor blocker /angiotensin-converting enzyme inhibitor.
*Infection including: respiratory tract infection, gastrointestinal infection, urinary tract infection, skin and soft tissue infection, and fever of unknown origin.
#Tolvaptan dose and duration: 15 to 45 mg/d, more than 30 days or until death.

criteria. Of these, 159 (51.6%) patients belonged to the TLV group with a median age of 92 years (88, 95), and 149 (48.4%) patients belonged to the non-TLV group with a median age of 91 years (87, 94). The median MAP level was 77 mmHg (69, 86), and the median eGFR was 34.9 ml/min/1.73 m^2 (24.5, 49.2) in all enrolled patients. There was no significant difference in baseline renal function between the two groups [TLV group: eGFR 35.9 (25.2, 50.8) vs. non-TLV group: eGFR 34.7 (23.9, 47.2), ml/min/1.73 m^2, $p = 0.712$]. Compared with the non-TLV group, the patients in the TLV group had lower BUN levels [17.50 (11.90, 23.50) vs. 20.39 (12.83, 31.54), mmol/L, $p = 0.024$] and were more likely to be taking spironolactone [59 (37.1%) vs. 38 (25.5%), $p = 0.028$], and the difference was statistically significant. Table 1 showed that there were no significant differences between the two groups regarding the proportion of patients with comorbidities (hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, atrial fibrillation), the relevant laboratory parameters (hemoglobin, serum albumin, and sodium), and the proportion of patients who took concomitant medications (hydrochlorothiazide, ARB/ACEI, β-blocker). The baseline characteristics of the patients in each group are shown in Table 1.

Changes in urine output and NT-proBNP level

There was no difference in the average volume intake between the TLV and non-TLV groups in 7 days. The addition of TLV significantly increased the median urine output of the patients in 7 days, and the difference between the two groups was statistically significant. The patients in the TLV group showed a gradual decrease in their NT-proBNP levels in 7 and 30 days after TLV administration. However, the patients in the non-TLV group showed a gradual increase from baseline level of NT-proBNP to the 30 days level of NT-proBNP. Compared with the non-TLV group, the TLV group had significantly lower NT-proBNP levels in 30 days, and the ratio of NT-proBNP to baseline NT-proBNP was significantly lower (Table 2).

Cox proportional hazards regression analysis

We have adjusted regarding demographics (BMI), comorbidities (diabetes mellitus, coronary artery disease, atrial fibrillation, EF, hyperlipidemia, hyperuricemia, stroke, COPD, non-invasive ventilation and infection), laboratory parameters (hemoglobin, albumin, eGFR, BUN, sodium, potassium, baseline NT-proBNP), and medications (spironolactone, hydrochlorothiazide, ARB/ACEI, statin, digoxin) for multivariate analysis of 7-day mortality (Figure 2). We have adjusted regarding demographics (age, BMI), comorbidities (diabetes mellitus, coronary artery disease, atrial fibrillation, EF, hyperlipidemia, hyperuricemia, stroke, COPD, non-invasive ventilation and infection), laboratory parameters (hemoglobin, eGFR, sodium, potassium, baseline NT-proBNP), and medications (hydrochlorothiazide, ARB/ACEI, β-Blockers,

TABLE 2 Changes of urine output and NT-proBNP level.

Characteristics	Tolvaptan	Non-tolvaptan	*p*-value
Number of patients	159	149	
Average intake in 7 days, L	2.44 (2.17, 2.72)	2.32(1.97, 2.77)	0.086
Average urine output in 7 days, L	1.45 (1.11, 1.76)	0.85 (0.39, 1.21)	0.001
Baseline NT-proBNP level, pg/ml	1,554 (490, 3,283)	967 (439, 2,755)	0.181
NT-proBNP level in 0 day, pg/ml	5,538 (2,091, 1,2581)	4,369 (1,885, 9,981)	0.084
NT-proBNP level in 7 days, pg/ml	4,035 (1,572, 11432)	4,704 (1,978, 10,065)	0.771
NT-proBNP level in 30 days, pg/ml	3,108 (1,157, 7,821)	6,307 (1,407, 15,303)	0.007
NT-proBNP level in 7 days / Baseline NT-proBNP level	1.42 (0.26, 5.60)	2.30 (0.52, 9.20)	0.063
NT-proBNP level in 30 days / Baseline NT-proBNP level	0.81 (−0.02, 3.92)	2.86 (0.22, 12.39)	0.001

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

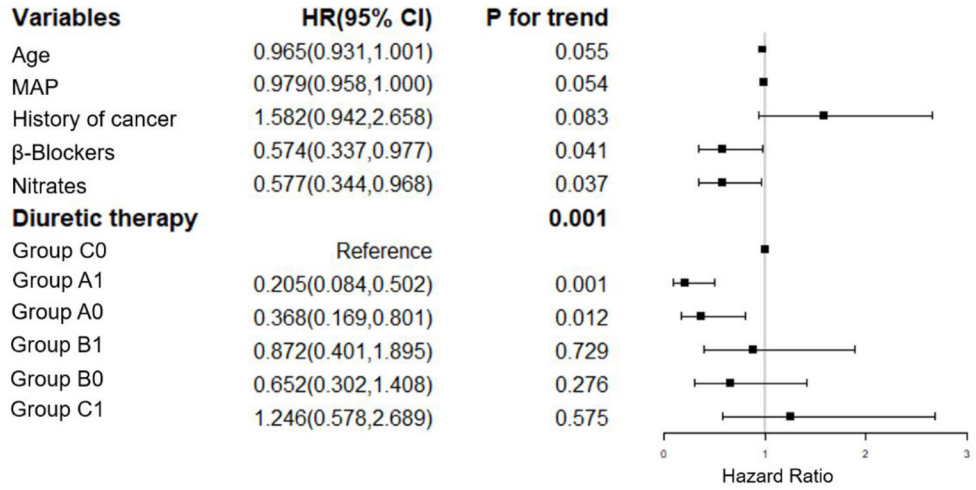

FIGURE 2
Cox regression analysis of the associations between 7-day cumulative mortality and the clinical findings. MAP, mean arterial pressure; Group A1: <100 mg/d equivalent doses of furosemide plus TLV; Group A0: <100 mg/d equivalent doses of furosemide only; Group B1: ≥100 and <200 mg/d equivalent doses of furosemide plus TLV; Group B0: ≥100 and <200 mg/d equivalent doses of furosemide only; Group C1: ≥200 mg/d equivalent doses of furosemide plus TLV; Group C0: ≥200 mg/d equivalent doses of furosemide only.

statin, digoxin) for the multivariate analysis of 90-day mortality (Figure 3). There were significant protective factors of β-blocker ($p = 0.041$) and nitrate ($p = 0.037$) use for 7-day all-cause mortality. The levels of MAP ($p = 0.013$), albumin ($p = 0.003$), and the use of spironolactone ($p = 0.031$) were significant protective factors for 90-day all-cause mortality. BUN level ($p = 0.001$) and cancer history ($p = 0.022$) were associated with an increased risk of 90-day all-cause mortality. The use of <100 mg equivalent furosemide daily only (Group A0) or the addition of TLV on this basis (Group A1) were protective factors for both 7-day all-cause mortality and 90-day all-cause mortality (Figures 2, 3).

Primary outcome and subgroup analysis

The addition of TLV had favorable effects on improving the 7 and 90-day all-cause mortality in elderly patients with AHF combined with oliguria [adjusted HR, 95% CI: 0.60 (0.37, 0.98), $p = 0.042$; 0.56 (0.41, 0.75), $p < 0.001$, respectively; Figures 4A, B]. A subgroup analysis showed that the use of more than 100 mg equivalent doses of furosemide daily was associated with an increased risk of all-cause mortality at 7 and 90-day [group A0 vs. group B0, $p < 0.001$; group A0 vs. group C0, $p < 0.001$; Figures 4E, F]. The difference in all-cause mortality between group B0 (patients on ≥100 and <200 mg/d equivalent doses of furosemide only) and group C0

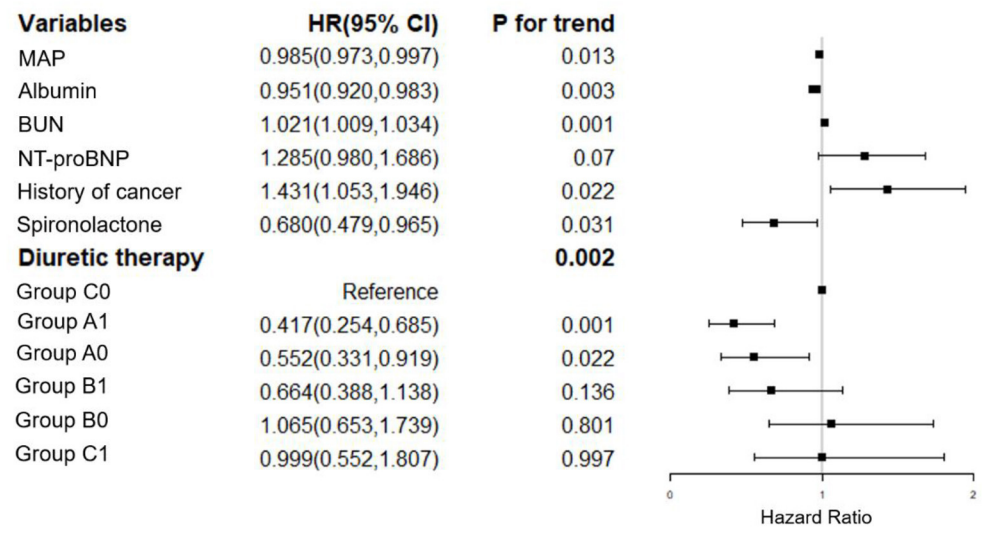

FIGURE 3
Cox regression analysis of the associations between 90-day cumulative mortality and the clinical findings. MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide. Group A1: <100 mg/d equivalent doses of furosemide plus TLV; Group A0: <100 mg/d equivalent doses of furosemide only; Group B1: ≥100 and <200 mg/d equivalent doses of furosemide plus TLV; Group B0: ≥100 and <200 mg/d equivalent doses of furosemide only; Group C1: ≥200 mg/d equivalent doses of furosemide plus TLV; Group C0: ≥200 mg/d equivalent doses of furosemide only.

(patients on ≥200 mg/d equivalent doses of furosemide only) was not statistically significant. However, the addition of TLV was associated with a decreased risk of all-cause mortality at 7 and 90-day when using ≥100 and <200 mg/d equivalent doses of furosemide.

Secondary outcomes and safety analysis

The addition of TLV significantly decreased the NT-proBNP levels and alleviated the progression of AHF within 30 days. However, the use of TLV did not have a statistically significant effect on the alleviation of AHF progression within 7 days and new-onset CKD after 90 days. Compared with the non-TLV group, there were no statistically significant differences in hypernatremia, hyponatremia, or hepatic impairment within 7 and 30 days in the TLV group (Table 3).

Discussion

In this retrospective cohort study, 716 elderly patients with AHF, including 361 patients with oliguria. The incidence rate of oliguria was 51.9% in all patients with AHF. This study consisted of very elderly patients with a median age of 91 years (88, 95) and a total of 43.2% (133/308) of patients with a history of CKD. The overall mortality at 7 and 90-day of AHF patients with oliguria was 21.8% (67/308) and 60.7% (187/308), respectively. 2021 ESC guidelines for the diagnosis and treatment of HF indicated that ACEIs/ARNIs, β-blockers, mineralocorticoid receptor antagonists (MRAs), sodium-glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin/empagliflozin) and loop diuretics are the cornerstone treatment for HF (23). Loop diuretics are a first-line standard treatment for AHF and are widely used clinically, and they are usually used at higher doses, especially in patients with oliguria (24). However, diuretic resistance frequently occurs in patients with renal insufficiency, RAAS activation, hypoproteinemia and hyponatremia, especially in elderly patients. Diuretics are usually not sufficient to achieve volume reduction. AHF in elderly patients is usually accompanied by one or more conditions such as RASS activation, renal dysfunction, high urea nitrogen, and acidosis. Hypoalbuminemia is also common in frail and infected elderly patients. High volume loading or anorexia in AHF often causes hyponatremia. Because of these factors, elderly patients with AHF need higher doses of loop diuretics to achieve the same effect, and diuretic resistance comes (25, 26). Diuretic resistance is different from oliguria. The presence of oliguria may mean more severe diuretic resistance, and there is little strategy for treating elderly AHF patients with oliguria. So, in this study, we evaluated not only the efficacy of TLV in diuretic resistant patients with AHF, but also in non-diuretic resistant patients with oliguria with AHF. A total of 43.5% (134/308) of the patients with AHF and oliguria took more than 100 mg of an equivalent dose of furosemide per day. We found that daily use of diuretics in excess of 100 mg furosemide equivalent dose

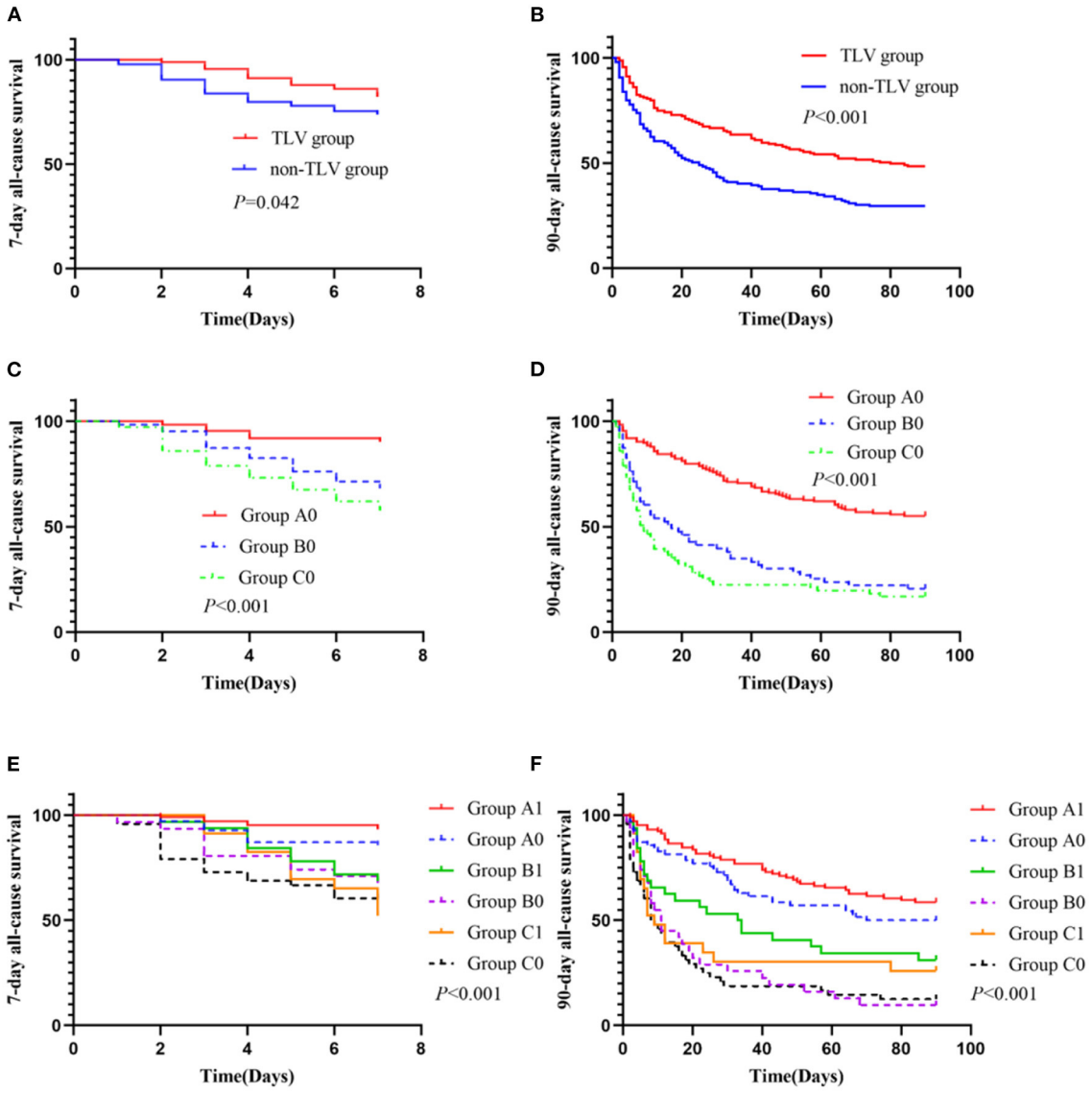

FIGURE 4
The primary outcome and subgroup analysis. Group A1 ($n = 104$): <100 mg/d equivalent doses of furosemide plus TLV; Group A0 ($n = 70$): <100 mg/d equivalent doses of furosemide only; Group B1 ($n = 32$): ≥100 and <200 mg/d equivalent doses of furosemide plus TLV; Group B0 ($n = 31$): ≥100 and <200 mg/d equivalent doses of furosemide only; Group C1 ($n = 23$): ≥200 mg/d equivalent doses of furosemide plus TLV; Group C0 ($n = 48$): ≥200 mg/d equivalent doses of furosemide only. **(C)** Subgroup comparison: Group A0 vs. Group B0, $p < 0.001$; Group A0 vs. Group C0, $p < 0.001$; Group B0 vs. Group C0, $p = 0.179$. **(D)** Subgroup comparison: Group A0 vs. Group B0, $p < 0.001$; Group A0 vs. Group C0, $p < 0.001$; Group B0 vs. Group C0, $p = 0.190$. **(E)** Subgroup comparison: Group A0 vs. Group A1, $p = 0.096$; Group B0 vs. Group B1, $p = 0.037$; Group C0 vs. Group C1, $p = 0.848$; Group A1 vs. Group B1, $p = 0.057$; Group A1 vs. Group C1, $p < 0.001$; Group B1 vs. Group C1, $p = 0.264$; **(F)** Subgroup comparison: Group A0 vs. Group A1, $p = 0.180$; Group B0 vs. Group B1, $p = 0.033$; Group C0 vs. Group C1, $p = 0.241$; Group A1 vs. Group B1, $p = 0.001$; Group A1 vs. Group C1, $p < 0.001$; Group B1 vs. Group C1, $p = 0.416$.

significantly increased the 7 and 90-day all-cause mortality in elderly patients with AHF with oliguria. There was no statistically significant difference in all-cause mortality at 7 and 90-day between the patients who received 100∼200 mg furosemide equivalent doses compared to those who received more than 200 mg furosemide equivalent doses of diuretics. In a subgroup analysis, compared with the usage of <100 mg doses of furosemide per day only, the addition of TLV on the basis of < 100 mg doses of furosemide per day had a trend in all-cause mortality reduction at 7-day in older patients with AHF and oliguria, but the difference did not reach statistical significance (Figure 4. E: Group A1 vs. Group B1, $p = 0.057$). However, compared with the usage of 100∼200 mg doses of furosemide per day only, TLV addition on the basis of 100∼200 mg doses of

TABLE 3 Safety analysis.

Characteristics	Tolvaptan	Non-tolvaptan	*p*-value
Number of patients	159	149	
AHF progression within 7 days	109 (68.6%)	114 (76.5%)	0.118
AHF progression within 30 days	91 (57.2%)	103 (69.1%)	0.031
New-onset CKD after 90 days	13 (8.2%)	5 (3.4%)	0.072
Hyponatremia* within 7 days	12 (7.5%)	5 (3.4%)	0.107
Hyponatremia within 30 days	22 (13.8%)	14 (9.4%)	0.225
Hypernatremia# within 7 days	44 (27.7%)	34 (22.8%)	0.328
Hypernatremia within 30 days	56 (35.2%)	42 (28.2%)	0.185
New-onset Liver function injury^ within 7-day	20 (12.6%)	18 (12.1%)	0.894
New-onset Liver function injury within 30-day	36 (22.6%)	27 (18.1%)	0.326

AHF, acute heart failure; CKD, chronic kidney disease. *Hyponatremia defined as serum sodium < 135 mmol/L; #Hypernatremia defined as serum sodium > 145 mmol/L; ∧New onset liver function injury defined as alanine aminotransferase (ALT) > 40 U/L or aspartate aminotransferase (AST) > 40 U/L or total bilirubin > 21 μmol/L or direct bilirubin > 8.6 μmol/L, except the history of liver function injury.

furosemide per day was associated with a reduction in 7 and 90-day all-cause mortality in elderly patients with AHF and oliguria (Figure 4. E: Group B0 vs. Group B1, $p = 0.037$ and F: Group B0 vs. Group B1, $p = 0.033$). Our study suggests that the addition of TLV on the basis of < 200 mg doses of furosemide may reduce the 7 and 90-day all-cause mortality in elderly patients with AHF and oliguria.

Tanaka et al. (6) reported that the addition of TLV for 7 days in a row but not furosemide significantly increased urine volume, decreased body weight and improved residual congestion in patients with AHF and CKD receiving furosemide treatment. Akihisa et al. (14) also reported that the administration of TLV for 7∼14 consecutive days and the decreased use of loop diuretics increased urine volume, alleviated congestion and improved renal function in patients with congestive AHF and renal dysfunction. Yusuke et al. (27) showed that continuous administration of TLV for 6 months may improve long-term adverse outcomes in AHF patients with CKD. Short-term and early administration of TLV could prevent exacerbation of AKI and improve the prognosis for AHF patients within 6 months (16). Continuous treatment with TLV for at least 180 days was also associated with better renal function and good progression because of its ability to spare the dose of loop diuretics for long-term use (13). In the present study, we found that the addition of TLV significantly increased the median urine output in 7 days in elderly patients, but had no significant effect on reducing the NT-proBNP levels and reversing the 7-day AHF status. This confirms the short-term efficacy of TLV addition at increasing urine output and improving AHF status in elderly patients with AHF and oliguria. In terms of mid-term efficacy, we found better results in that the addition of TLV significantly reduced the NT-proBNP levels, and reversed the progression of AHF within 30 days. The lack of effect on improving the AHF status within 7 days may be due to the poor cardiac and renal reserve and the slow response of these reserves to the medications in elderly patients. Within 30 days, the therapeutic effect of TLV gradually appeared.

Some prospective cohort studies showed that there was no strong evidence that proved the mortality benefit of any diuretics, including TLV, in either acute or chronic HF settings (28–30). However, a few *post hoc* analyses showed that TLV usage may be associated with improving HF-related morbidity (31, 32). Although the long-term results of the EVEREST are neutral, the EVEREST *post hoc* analysis in the low sodium subgroup (serum sodium level below 130 mmol/L) showed that the use of tolvaptan had favorable effects on decreasing the cardiovascular mortality and hospitalization rate of HF patients and had no adverse effect on renal function (28). In this retrospective cohort study, we found that the addition of TLV was associated with improving the all-cause mortality at 7 and 90-day in elderly patients with AHF combined with oliguria. This result may be related to the patients we included. In AHF patients, coexisting with oliguria means more severe diuretic resistance and volume overload, which may lead to higher mortality, especially in elderly patients. It also may be associated with the unique mechanism of TLV. When TLV is used in combination with diuretics, urine output could rapidly increase, thus achieving decongestion.

With the occurrence of oliguria, the eGFR level decreased in all AHF patients. However, the proportion of new-onset CKD after 90 days was not high (5.84%, 18/308), and the addition of TLV did not lead to an increase in new-onset CKD after 90 days when the patient's AHF and oliguria were corrected. This is consistent with previous reports (13, 33, 34). Previous studies have reported that the side effects of TLV could increase patient intake, hypernatremia, renal impairment and liver damage (35,

36). In this study, there was also no statistically significant difference between the two groups regarding new-onset CKD after 90 days. Although there was no significant difference in hypernatremia and liver injury between the TLV and non-TLV group, there was still a high incidence of these conditions in the elderly patients. The high incidence of hypernatremia and liver injury may be related to the coexistence of multiple diseases and the decline in organ function in elderly patients. Therefore, we still need to closely monitor the safety of long-term TLV use in elderly patients.

This study has several limitations. First, we could not prove the direct causal relationship between TLV therapy and all-cause mortality in this observational study. Second, this was a retrospective study that was conducted in a single center involving a moderate number of enrolled patients, which were all male and elderly. A possible selection bias could not be excluded. Third, the increase or decrease of TLV and diuretic doses (including administration mode: continuous or bolus) and the administration of other standard treatments for AHF were decided at the discretion of each doctor. Therefore, confounding effects may exist. Fourth, the observation period was relatively short, and a prospective multicenter study with an extended observation period is needed to further determine the efficacy and safety of TLV.

In conclusion, in this study we found that the addition of TLV during the use of loop diuretics was associated with an increase in urine output and may improve the all-cause mortality at 7 and 90-day in elderly patients with AHF coexisting with oliguria.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Chinese PLA General Hospital (No. S2022-342-01). Written informed consent was not required in this study as the data was collected anonymously.

Author contributions

QA and QC conceptualized the study. YL, YZ, HC, ZW, GY, and QA took responsibility for data handling and statistical analysis. YL, YZ, HC, QC, and QA drafted the manuscript. JZ, QM, XW, JH, QC, and QA contributed to the interpretation of the data, critical revision of the manuscript, and study supervision. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Rate of atrial fibrillation and flutter induced tachycardiomyopathy in a cohort of hospitalized patients with heart failure and detection of indicators for improved diagnosis

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Background: Atrial fibrillation (AF) and atrial flutter (AFL) induced tachycardiomyopathy (TCM) has been known to cause reversible heart failure (HF) for many years. However, the prevalence of the disease is unknown, and diagnosis is challenging. Therefore, the aim of the present study was (1) to assess the rate of AF/AFL induced TCM and (2) to identify indicators for diagnosis.

Methods: Consecutively, all patients with a diagnosis of HF who were hospitalized in our department within 12 months were reviewed. For the main analysis, all patients with HF with reduced ejection fraction (HFrEF) and AF or AFL were included. AF/AFL induced TCM was diagnosed when there was at least a 10% improvement in left ventricular ejection fraction under rhythm or rate control within 3 months. Patients with HFrEF with AF/AFL but without TCM served as control group.

Results: A total of 480 patients were included. AF/AFL induced TCM occurred in 26 patients (5.4%) and HFrEF with AF/AFL in 53 patients (11%). Independent indicators of AF/AFL induced TCM were age<79 years [Odds ratio 5.887, confidence interval (CI) 1.999–17.339, $p < 0.001$], NT-pro-BNP <5,419 pg/mL (Odds ratio 2.327, CI 1.141–4.746, $p = 0.004$), and a resting heart rate >112 bpm (Odds ratio 2.503, CI 1.288–4.864, $p = 0.001$).

Conclusion: Approximately 5% of all patients hospitalized for HF suffer from AF/AFL induced TCM. Improved discrimination of AF/AFL induced TCM to HFrEF with AF/AFL is possible considering age, NT-pro-BNP level, and resting heart rate >112 beats/minute. Based on these parameters, an earlier diagnosis and improved therapy might be possible.

KEYWORDS

tachycardiomyopathy, atrial fibrillation, atrial flutter, heart failure with reduced ejection fraction, diagnosis

Introduction

Heart failure (HF) is a common cardiovascular disease with considerable impact on the prognosis of patients (1). Since many years it is recognized that a sustained high heart rate can be a reason or a contributing factor for the development of HF (2, 3). This phenomenon is therefore called tachycardiomyopathy (TCM). The underlying mechanisms and the pathophysiological principles have not been fully understood. Abnormalities in myocyte calcium levels, energy balance and subclinical cardiac ischemia have been described as contributing factors (2). In addition, there is evidence for changes in the morphology of cardiomyocytes and mitochondria, accompanied by macrophage-dominated cardiac inflammation in the TCM (4, 5).

Because of the high prevalence of atrial fibrillation (AF) and atrial flutter (AFL), these two arrhythmias are the most common causes of TCM by far (2, 3). Previous studies primarily investigated patients who underwent catheter ablation. In these studies, patients with AF/AFL induced TCM were comparatively younger and more likely to have persistent AF than control groups (6, 7). Of importance, effective therapy for AF/AFL induced TCM [i.e., rhythm control or rate control (8)] results in a significant improvement in HF and normalization of ejection fraction (6, 7). Considering the good prognosis of TCM in general, it seems essential to identify appropriate patients and perform rhythm or rate control. Previous studies investigated echocardiographic parameters (9–11), serial determinations of NT-pro BNP (12), or parameters of cardiac MRI examination (13) to identify TCM. However, there are no universal recommendations on how to differentiate AF/AFL induced TCM from HF with reduced ejection fraction (HFrEF). Given these difficulties in diagnosis, the exact prevalence of AF/AFL induced TCM is not known.

The aim of the present study is to assess the rate of AF/AFL induced TCM. For this purpose, we studied a non-selected cohort of consecutively hospitalized patients with HF over a period of 12 months. Furthermore, we analyzed the characteristics of patients with AF/AFL induced TCM and how they differ from patients with HFrEF. The objective was to identify useful indicators for the identification of patients who would benefit significantly from rhythm or rate normalization.

Materials and methods

This study is a retrospective, monocentric analysis. Consecutively, all patients with the diagnosis of HF who were hospitalized in the Cardiology and Rhythmology department of the St. Josef-Hospital Bochum within 12 months from November 2020 to October 2021 were analyzed. For patients who were hospitalized for HF more than once during the specified study period, the first admission was used for the analysis. According to current European Society of Cardiology (ESC) guidelines, patients were divided into preserved, mildly reduced, and reduced ejection fraction groups based on their left ventricular ejection fraction (LVEF) (14). The study was approved by the local ethics committee of the Ruhr-University Bochum (Number 22-7531).

Inclusion criteria and data acquisition

For the main analysis, all patients with HFrEF (LVEF ≤40%) and AF or AFL were included. Patients with an age <18 years, a NT-pro-BNP <125 ng/L, continuous pacemaker stimulation or with other bradycardic or tachycardic cardiac arrhythmias were excluded. Patients' data was collected using the medical history and the medical documentation (including medication, laboratory results, ECG and echocardiography). The ECG and the laboratory results on admission were used for the analysis. The diagnosis of AF and AFL was made according to the ESC guidelines (15). The diagnosis of permanent AF was made when AF persisted for more than 12 months. This included patients in whom a failed attempt at rhythmization was attempted.

Transthoracic echocardiography was obtained according to the guidelines of the American Society of Echocardiography and European Association of Cardiovascular Imaging (16). LVEF was obtained with the Simpson biplane method. Treatment of AF and AFL was in accordance with current ESC recommendations and included rate control and rhythm control depending on individual patient characteristics and evaluation by the attending physicians (15). Methods of sinus rhythm recovery included catheter ablation and electrical cardioversion. Rhythm control after catheter ablation was verified by 24-h Holter ECG in either an inpatient or outpatient setting.

Definition of study subgroups

Current guidelines define TCM as a reversible cause of LV-dysfunction due to tachycardia. As there is a lack of standardized diagnostic criteria, the following characteristics were chosen for the definition of TCM: For the purpose of the present study, AF/AFL induced TCM was defined as the presence of (1) AF or AFL, (2) a LVEF ≤40% and (3) improvement of LVEF by at least 10% under rhythm or rate control within the first 3 months.

HF with reduced ejection fraction with AF or AFL but without AF/AFL induced TCM was defined if the following criteria were present: (1) AF or AFL, (2) a LVEF of ≤40% and either (3.1) no improvement in LVEF by at least 10% under rhythm or rate control within the first 3 months or (3.2) history of previously documented reduced LVEF (≤40%) despite rhythm or rate control. The follow-up examinations were performed in an inpatient or outpatient setting partly in our hospital outpatient clinic or also with the outpatient cardiologist.

Statistics

In the statistical analysis, we compared the characteristics of patients with AF/AFL induced TCM and HFrEF with AF/AFL. Numerical values are expressed as mean ± standard deviation. Continuous variables were compared between groups using an unpaired *t*-test (for normally distributed variables) or Mann–Whitney U test (for non-normally distributed variables). χ^2 analysis was used to compare categoric variables. All variables in **Tables 1**, **2** were evaluated for an association with AF/AFL induced TCM in a univariate regression analysis. All variables with a significant association were entered in a multivariate regression analysis to identify independent indicators of AF/AFL induced TCM. Receiver

operating characteristic curves (ROC) were generated to define cutoff values for independent indicators. Results are presented as Odds ratio. A P-value < 0.05 was considered significant. All probability values reported are 2-sided. The statistical software SPSS 26 was used for statistical analysis.

Results

A total of 480 patients diagnosed with HF were treated at St. Josef Hospital during the study period. Mean age of patients was 76.2 ± 12.9 years, 222 patients (46%) were women. The median duration of hospitalization was 8.5 ± 7.4 days (range from 1 to 55 days). Intrahospital deaths occurred in 27 patients (5.6%). The distribution of patients according to the recommendations of the ESC guidelines is given in Figure 1.

Subgroups

In total, 206 (42.9%) patients presented with HFrEF. Of these 206 patients, 100 (48.5%) were in sinus rhythm at the time of hospital admission, 22 (10.7%) had a pacemaker-stimulated rhythm, and three (1.5%) demonstrated another rhythm than AF or AFL (sustained ventricular tachycardia, $n = 1$; persistent AV block II°, $n = 1$; persistent AV block III°, $n = 1$). In the remaining 81 patients, classification was not possible in two patients (2.5%) because neither the history nor the follow-up results were conclusive. These two patients were excluded from the analysis.

Thus, 79 patients formed the final study cohort. The cardiac rhythm on admission was AFL in eight (10.1%) patients and AF in 71 (89.9%) patients (Table 2). According to their respective medical history, 28 (35.4%) patients had known permanent AF. There were 39 (49.4%) patients with persistent AF and nine (11.4%) patients with paroxysmal AF. Three (3.8%) patients had isolated AFL without history of AF.

Atrial fibrillation and flutter induced TCM was diagnosed in 26 (33%) patients and HFrEF with AF/AFL in 53 (67%) patients based on medical history and echocardiographic follow-up. The frequencies of the different patient subgroups in relation to the total number of patients with HF are presented in Figure 1.

AF/AFL induced TCM versus HFrEF with AF/AFL

In the HFrEF with AF/AFL subgroup, permanent AF was present in 26 (49%) patients, contrasting only two (8%) patients with permanent AF in the subgroup with AF/AFL induced TCM ($p = 0.001$). Patients with HFrEF with AF/AFL were significantly older, had more frequently coronary artery disease and peripheral arterial disease than patients with AF/AFL induced TCM (Table 1). In addition to a significantly higher heart rate on admission, patients with AF/AFL induced TCM displayed several significant differences in laboratory parameters compared with patients with HFrEF with AF/ALF (Table 2).

TABLE 1 Clinical characteristics of study patients ($n = 79$).

	AF/AFL induced TCM ($n = 26$)	HFrEF with AF/AFL ($n = 53$)	P-value
Age (years)	68 ± 10.1	80.8 ± 8.9	<0.001
Women, n (%)	11 (42)	24 (45)	0.802
NYHA functional class (I/II/III/IV)	4/8/11/3	1/16/24/12	0.103
Cardiovascular risk factors			
Hypertension, n (%)	22 (85)	43 (81)	0.830
Diabetes mellitus, n (%)	4 (15)	19 (36)	0.053
Dyslipidemia, n (%)	12 (46)	28 (53)	0.522
Current smoking, n (%)	6 (23)	5 (9)	0.098
Medical history			
Type of AF (paroxysmal/persistent/ permanent) (n)	2/19/2	7/20/26	0.001
Coronary artery disease, n (%)	4 (15)	29 (55)	0.001
Previous myocardial infarction, n (%)	2 (8)	12 (23)	0.088
Coronary artery bypass grafting, n (%)	1 (4)	7 (13)	0.179
Stroke/TIA, n (%)	5 (19)	7 (13)	0.509
Chronic obstructive lung disease, n (%)	2 (8)	14 (26)	0.047
Peripheral artery disease, n (%)	1 (4)	12 (23)	0.032
Pacemaker, n (%)	1 (4)	6 (11)	0.272
ICD/CRT, n (%)	0 (0)	6 (11)	0.074

TCM, tachycardiomyopathy; HFrEF, heart failure with reduced ejection fraction; AF/AFL, atrial fibrillation or atrial flutter; TIA, transient ischemic attack; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.

TABLE 2 Electrocardiographic, echocardiographic, and laboratory parameters of study patients (n = 79).

	AF/AFL induced TCM (n = 26)	HFrEF with AF/AFL (n = 53)	P-value
ECG parameter at admission			
Atrial fibrillation/atrial flutter	22/4	49/4	0.278
Heart rate at rest (bpm)	126 ± 30	99 ± 27	0.001
QRS complex (ms)	102 ± 26	113 ± 27	0.403
Left bundle branch block, n (%)	3 (12)	8 (15)	0.848
Echocardiographic parameters			
Left atrial diameter (mm)	46.5 ± 7.6	46.3 ± 6.4	0.932
Left ventricular ejection fraction (%)	28.4 ± 8.1	30.3 ± 8.4	0.330
Left ventricular end-diastolic diameter (mm)	51.2 ± 8.2	52.5 ± 7.2	0.556
Left ventricular end-systolic diameter (mm)	44.4 ± 7.6	45.4 ± 7.2	0.636
Left ventricular mass (g)	263 ± 65	287 ± 92	0.369
Pulmonary artery pressure (mmHg)	27.5 ± 9.4	37.2 ± 16.5	0.125
Aortic stenosis (none/mild/moderate/severe), n	26/0/0/0	47/1/4/1	0.364
Aortic regurgitation (none/mild/moderate/severe), n	19/7/0/0	31/17/4/1	0.363
Mitral regurgitation (none/mild/moderate/severe), n	3/17/4/2	5/31/14/3	0.739
Tricuspid regurgitation (none/mild/moderate/severe), n	6/14/5/1	12/19/16/6	0.430
Laboratory parameters			
Hemoglobin (g/dL)	14.2 ± 1.7	12.5 ± 2.2	0.001
GFR (ml/min/1.73 m^2)	70.2 ± 22.4	58 ± 24	0.034
C-reactive protein (mg/L)	10.5 ± 14	24.6 ± 40	0.087
NT-pro-BNP (pg/mL)	4,714 ± 3,871	9,610 ± 8,966	0.016
Hs Troponin T (pg/mL)	31.3 ± 28.5	67.9 ± 92.9	0.162

TCM, tachycardiomyopathy; HFrEF, heart failure with reduced ejection fraction; AF/AFL, atrial fibrillation and flutter; bpm, beats per minute; GFR, glomerular filtration rate using CKD-EPI equation; NT-pro-BNP, N terminal pro brain natriuretic peptide; Hs, high sensitive.

In the group of HFrEF with AF/AFL, five (9.4%) patients died during hospitalization [one (20%) with acute cardiac decompensation due to acute myocardial infarction, four (80%) with prolonged cardiac decompensation]. In the group of patients with AF/AFL induced TCM, no patient died during hospitalization.

Medical treatment and follow-up

In the subgroup with HFrEF with AF/AFL, primary rate-control therapy was performed in 35 (66%) patients. One patient converted spontaneously to sinus rhythm. In the remaining 17 patients, primary rhythm control was performed. This rhythm control also included several different therapies in individual patients: electrical cardioversion (n = 15), ablation of the cavotricuspid isthmus (n = 1), pulmonary vein isolation (n = 4), cardiac resynchronization therapy and AV node ablation (n = 2).

In the subgroup with AF/AFL induced TCM, rate-control therapy was primarily performed in five (19%) patients; one patient in this subgroup spontaneously converted to sinus rhythm.

In the remaining 21 patients, primary rhythm control was performed. In this subgroup, as well, several different therapies were performed in individual patients: electrical cardioversion (n = 19), ablation of the cavotricuspid isthmus (n = 5), pulmonary vein isolation (n = 12), cardiac resynchronization therapy and AV node ablation (n = 1).

A total of 14 (17.7%) patients received amiodarone therapy at discharge, and patients with AF/AFL induced TCM were significantly more likely to receive amiodarone than patients with HFrEF with AF/AFL.

There were no other notable differences between the subgroups in heart failure medication at discharge. Medications at discharge are listed in the table in the supplements (**Supplementary Table 1**).

At follow-up, surviving patients in the HFrEF with AF/AFL subgroup (n = 48) presented with sinus rhythm [n = 10 (21%)], AF [n = 36 (75%)] and pacemaker stimulated rhythm [n = 2 (4%)]. Mean heart rate at rest in the 3 month was 74.5 ± 8.9 beats per minute in AF/AFL induced TCM and 80 ± 12.8 beats per minute in HFrEF with AF/AFL (p = 0.069).

There was a significant (however, clinically minor) improvement in LVEF (31.6 ± 8.1% at baseline vs. 34.9 ± 11.8% at follow-up; p = 0.028).

In contrast, the AF/AFL induced TCM subgroup presented with sinus rhythm in 20 (77%) patients and AF in 6 (23%) patients. In AF/AFL induced TCM, a more pronounced (and clinically major) improvement in mean LVEF was observed (28.4 ± 8.1% at baseline vs. 49.4 ± 9.3% at follow-up; $p < 0.001$).

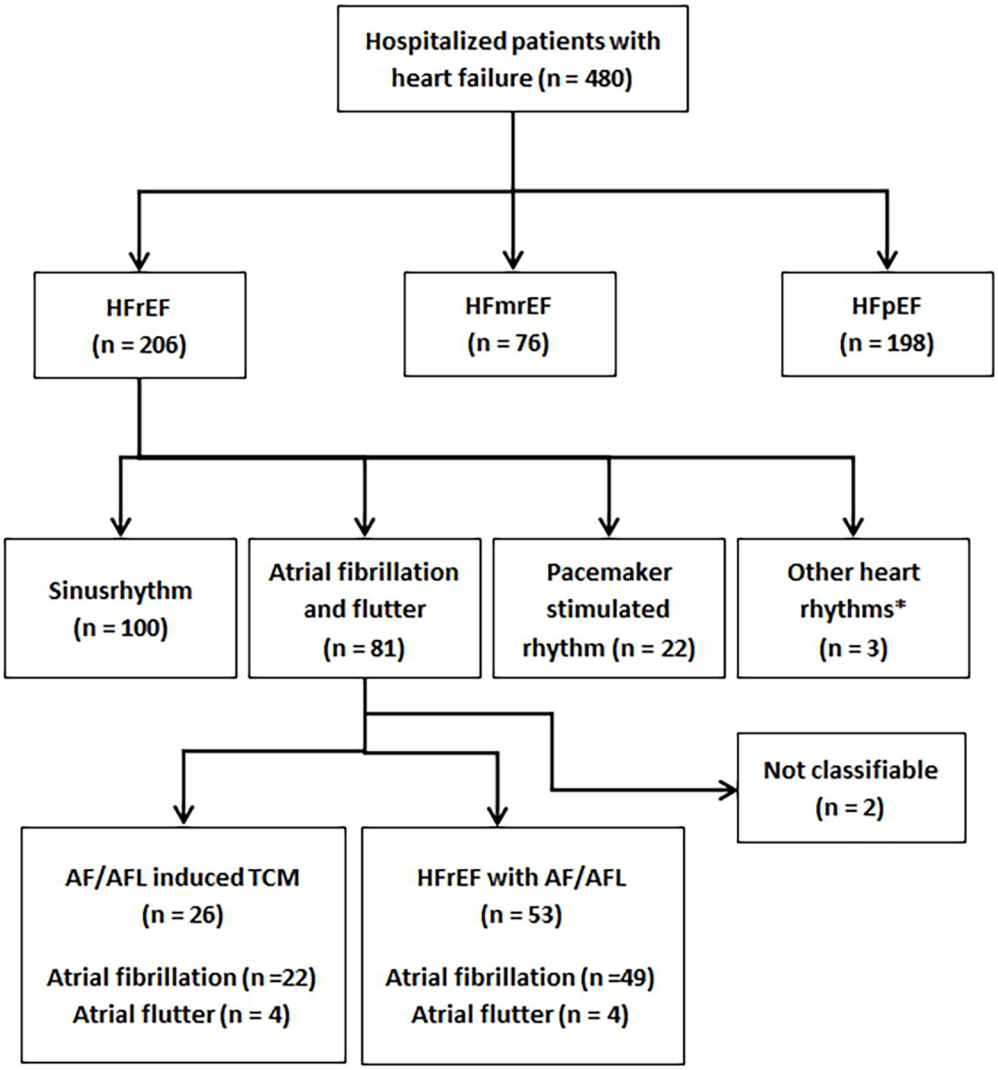

FIGURE 1
Flowchart demonstrating all patients diagnosed with heart failure during the study period and subgroups of patients. HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; TCM, tachycardiomyopathy; AF/AFL, atrial fibrillation or atrial flutter.

Indicators of AF/AFL induced TCM

On univariate analysis, age, type of AF (paroxysmal/persistent/permanent), coronary artery disease, heart rate, hemoglobin, glomerular filtration rate and NT-pro-BNP were significantly related to AF/AFL induced TCM. Stepwise multivariable analysis identified age, heart rate and NT-pro-BNP as independent indicators of AF/AFL induced TCM.

Using receiver operating characteristic (ROC) analysis cut-off values for independent indicators separating study patients were as follows: Age <79 years, Heart rate >112 beats per minute and NT-proBNP <5,419 pg/mL (**Figure 2** and **Table 3**).

Discussion

The first main finding of this study is that AF/AFL induced TCM is present in one in 20 patients in an unselected cohort of patients hospitalized for HF. In the subgroup of patients with HFrEF, AF/AFL induced TCM is found in one in 8 patients (**Figure 1**). Given the relatively high prevalence of the disease and the therapeutic options available, the identification of AF/AFL induced TCM is imperative for clinicians. The second main finding of our study is that differentiation of AF/AFL induced TCM versus HFrEF with AF/AFL is feasible using age, resting heart rate, and NT-pro-BNP (**Table 3** and **Figure 2**).

Prevalence of AF/AFL induced TCM

Although TCM can occur in several tachycardic arrhythmias, AF and AFL are the most frequent underlying diseases of TCM (17). Therefore, previous studies have been conducted primarily in patient cohorts undergoing catheter ablation. In this particular collective, the prevalence of tachymyopathy was 8–14% (7, 18–20). In the subgroup of patients with LVEF <40%, the prevalence even exceeded 50% (7, 19).

Recently, in a prospective observational study, Stronati et al. (21) studied patients admitted for acute HFrEF who had evidence of atrial

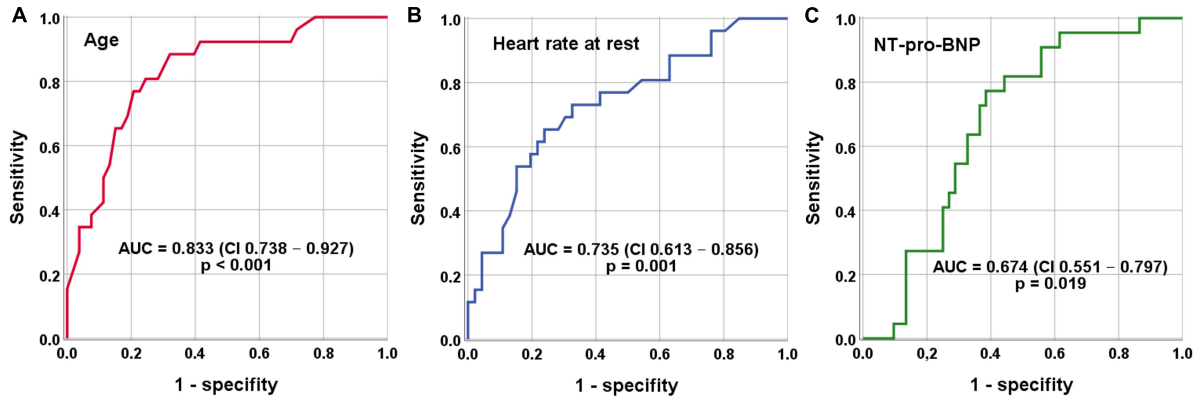

FIGURE 2
Receiver operating characteristics (ROC) analysis for indication of AF/AFL induced TCM. **(A)** Cut-off value age <79 years (sensitivity = 89% and specificity = 68%). **(B)** Cut-off value heart rate at rest >112 beats per minute (sensitivity = 73% and specificity = 67%). **(C)** Cut-off value NT-proBNP <5,419 pg/mL (sensitivity = 73% and specificity = 64%).

TABLE 3 Multivariate regression analysis for the indicators of AF/AFL induced TCM.

	Odds ratio	95% CI	*P*-value
Age < 79 years	5.887	1.999–17.339	<0.001
Heart rate at rest > 112 bpm	2.503	1.288–4.864	0.001
NT-pro-BNP < 5,419 pg/mL	2.327	1.141–4.746	0.004

TCM, tachycardiomyopathy; AF/AFL, atrial fibrillation and flutter; CI, confidence interval; NT-pro-BNP, N terminal pro brain natriuretic peptide.

or ventricular arrhythmias on admission. Among patients diagnosed with TCM, AF (77.6%) and AFL (15%) were the most common underlying arrhythmias. In patients with diagnosis of heart failure on admission, the prevalence of TCM was approximately 9% (21).

The present study examined a non-selected collective of patients hospitalized for HF over a 12-month period. Thus, the present collective substantially differs from the collectives of other studies (7, 18–20). From a clinical point of view, the present study may therefore be more suitable to estimate the prevalence of AF/AFL induced TCM in relation to all patients with HF. Overall, AF/AFL induced TCM affected approximately 5% of all patients with a diagnosis of HF.

In our study, the group of patients with HFrEF was the largest subgroup (**Figure 1**). Stratification was performed based on heart rhythm on ECG on admission, and nearly 40% of these patients had AF or AFL. AF/AFL induced TCM occurred in more than 30% of these patients. Although the rates in our study are somewhat lower than in previous studies (21), our findings underline the clinical significance of the disease.

Indicators of AF/AFL induced TCM

In contrast to many other diseases leading to heart failure, TCM is a principally reversible disease with a good prognosis when treated effectively (2, 3). Therefore, the diagnosis of a TCM is of utmost clinical importance. Despite the high relevance of the disease, clinicians may often struggle to identify TCM as there are currently no universal recommendations on how to distinguish TCM from other diseases. Several studies have approached this dilemma: Patients with TCM demonstrated a lower left ventricular end-diastolic diameter (LVEDD) than patients with dilated cardiomyopathy (9, 10). An LVEDD of ≤61 mm was able to distinguish TCM from dilated cardiomyopathy with a sensitivity of 100% and a specificity of 71% in one study (9). However, it remains unclear how this data translates to a heterogeneous study population without defined dilated cardiomyopathy. Contrasting previous study results, in the present cohort of unselected patients, echocardiographic parameters were not able to adequately distinguish patients with AF/AFL induced TCM from patients with HFrEF with AF/AFL (**Table 2**).

However, our study demonstrated that patients with AF/AFL induced TCM had lower NT-pro-BNP levels than patients with HFrEF and AF/AFL (**Table 2**). Moreover, NT-pro-BNP was an independent indicator of AF/AFL induced TCM (**Table 3**). These results suggest that the extent of myocardial injury in patients with AF/AFL induced TCM is less than that in patients with HFrEF with AF/AFL. This might also explain the better prognosis of AF/AFL induced TCM observed in other studies (4).

Previous studies demonstrated that TCM patients were comparatively younger than control groups (6, 7). The higher percentage of older patients with HFrEF with AF/AFL might be due to the greater proportion of comorbidities (coronary artery disease, peripheral arterial disease, renal failure, etc.) (**Table 1**). Age was associated with AF/AFL induced TCM in the present study as well (**Table 1** and **Figure 2**). Moreover, we were able to identify a cutoff age of <79 years to discriminate patients with AF/AFL induced TCM and HFrEF with AF/AFL with good sensitivity and moderate specificity. The present results therefore extent the results of previous studies, giving clinicians a more detailed indication on when to suspect AF/AFL induced TCM. It should also be mentioned that older patients suffered from permanent AF to a higher extent, which also indicates more advanced and longer-lasting disease.

Interestingly, a definite cutoff for a heart rate that can induce TCM has not been defined, yet. For many years, a ventricular heart rate of >100 beats/minute has been suspected to be harmful (22). In contrast, the RACE (Race Control Efficacy in Permanent Atrial Fibrillation) II randomized controlled trial in patients with

permanent AF found no difference in clinical events of rate-controlled therapy with a heart rate of <110 beats/minute compared with a heart rate of <80 beats/minute (23). This finding was also corroborated by an analysis of data from AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) (24). Therefore, current ESC guidelines recommend lenient rate control except for TCM (15). In our study, a higher resting heart rate on admission was associated with AF/AFL induced TCM (**Figure 2**). The optimal cut-off value for differentiating AF/AFL induced TCM from HFrEF with AF/AFL was >112 beats/minute (**Figure 2**). Our study thus suggests that this resting heart rate of 112 beats/minute should not be exceeded in the treatment of patients with AF and AFL.

Limitations

Previous studies have defined TCM differently as there are no universally recognized diagnostic criteria or cut-off values. In some cases, patients with arrhythmias other than AF or AFL were included. In some cases, the study periods were longer and the improvement in LVEF had to be more marked. In the present study, a 10% improvement in LVEF within 3 months was used to define TCM. Therefore, a comparison of our results with those of other studies is only possible to a limited extent. Due to the retrospective design of the present study and since there were no universally accepted parameters to differentiate AF/AFL induced TCM from HFrEF with AF/AFL, an investigator bias cannot fully be excluded. While the present study was conducted over a period of 12 months, the number of patients with the diagnosis of AF/AFL induced TCM and the comparative collective remained relatively small. Strengths of the present study include the unselected cohort of patients, the clinical approach to the phenomenon of AF/AFL induced TCM and the clear identification of parameters to facilitate the discrimination of AF/AFL induced TCM and HFrEF with AF/AFL.

Conclusion

Approximately 5% of all patients hospitalized for HF suffer from AF/AFL induced TCM, which in principle is a reversible condition. Improved discrimination of AF/AFL induced TCM to HFrEF with AF/AFL is possible considering age, NT-pro-BNP level, and resting heart rate >112 beats/minute. Based on these parameters, an earlier diagnosis might be possible, and a more effective therapy could be initiated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ruhr-University Bochum (Number 22-7531). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MG, LE, and FK contributed to conception and design of the study. LE organized the database. MG performed the statistical analysis. MG and LE wrote the first draft of the manuscript. DQ, AM, and AP wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.940060/full#supplementary-material

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Value of baseline characteristics in the risk prediction of atrial fibrillation

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Introduction: Atrial fibrillation (AF) is prone to heart failure and stroke. Early management can effectively reduce the stroke rate and mortality. Current clinical guidelines screen high-risk individuals based solely on age, while this study aims to explore the possibility of other AF risk predictors.

Methods: A total of 18,738 elderly people (aged over 60 years old) in Chinese communities were enrolled in this study. The baseline characteristics were mainly based on the diagnosis results of electrocardiogram (ECG) machine during follow up, accompanied by some auxiliary physical examination basic data. After the analysis of both independent and combined baseline characteristics, AF risk predictors were obtained and prioritized according to the results. Independent characteristics were studied from three aspects: Chi-square test, Mann–Whitney U test and Cox univariate regression analysis. Combined characteristics were studied from two aspects: machine learning models and Cox multivariate regression analysis, and the former was combined with recursive feature elimination method and voting decision.

Results: The resulted optimal combination of risk predictors included age, atrial premature beats, atrial flutter, left ventricular hypertrophy, hypertension and heart disease.

Conclusion: Patients diagnosed by short-time ECG machines with the occurrence of the above events had a higher probability of AF episodes, who are suggested to be included in the focus of long-term ECG monitoring or increased screening density. The incidence of risk predictors in different age ranges of AF patients suggests differences in age-specific patient management. This can help improve the detection rate of AF, standardize the management of patients, and slow down the progression of AF.

KEYWORDS

atrial fibrillation, statistical test, baseline characteristics, risk prediction, electrocardiogram machine

1. Introduction

Atrial fibrillation (AF) is the most common type of supraventricular arrhythmia in clinical practice. Its hazards include: stroke and thromboembolism (1), heart failure (2), myocardial infarction (3), cognitive decline (4), renal function injury (5), and decreased quality of life (6). The incidence of AF in the general population is about 0.4–1% (7), and increases gradually with age for individuals. This is consistent with the content in the 2020 ESC guidelines (8): "Common AF screening strategies include opportunistic or systematic screening of individuals over a

certain age (usually > 65 years) or with other characteristics suggestive of increased stroke risk". Besides, some studies (9–12) have shown that the prevalence and incidence of AF are relevant to other factors such as gender and regions, which may contribute to the assessment of AF risk.

The risk prediction of AF is conducive to early detection, diagnosis, intervention, and standardized treatment of AF, which can avoid complications and further deterioration of the condition; otherwise, paroxysmal AF at the initial stage will progress to permanent AF (13). To reduce AF related mortality through risk prediction, AF risk factors, not just age, must be identified in order to develop effective and targeted interventions. Since ECG machines with analytical and diagnostic capability are an indispensable monitoring means in the medical field (14), multi-year follow-up studies that combine their diagnosis with some physical examination baseline characteristics will help identify AF predictors in addition to age.

The remainder of the paper is organized as follows. Section 2 describes study organization, inclusion criteria of participants, data collection and AF risk prediction methods. Specifically, a total of 18,738 elderly people (aged over 60 years) were enrolled and followed up for 1–4 years. The assessment of baseline characteristics related to AF risk prediction corresponding to each follow-up was recorded as a single task that included independent and combined risk predictors. The obtained results are summarized in Section 3 and next discussed in Section 4. Finally, Section 5 concludes the paper.

2. Materials and methods

2.1. Organization and participants

Since July 2015, we have provided annual physical examinations for residents aged 60 years and older at four community health centers (Shihudang, Maogang, Xinbang and Dongjing) in Songjiang District, Shanghai, China. The data inclusion criteria of this study were as follows: (1) aged over 60 years old, (2) registered residents in the four above-mentioned towns, and (3) diagnosed without AF by the resting12-lead ECG obtained during the physical examination in 2015. Those who did not agree to undergo the medical examination funded by the local government were excluded. A total of 18,738 participants were examined from July 2015 to December 2020. This is a prospective cohort study approved by the Ethical Review Board of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (No. 201508).

2.2. Data collection

The data used in this study includes physical examination basic data (age, sex, blood pressure, body mass index (BMI), hypertension, diabetes mellitus and cardiovascular disease history) and diagnosis data of ECG machine (sinus arrhythmia, atrial premature beats (APBs), atrial flutter, ventricular premature beat, left ventricular hypertrophy (LVH), ST segment change, etc.). Specific data list is shown in **Supplementary material 1**. Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg, diastolic blood pressure (DBP) $\geq$ 90 mmHg, or current antihypertensive therapy. Diabetes mellitus was defined as a previous diagnosis of diabetes mellitus, treatment with oral hypoglycemic agents or insulin, or having a fasting plasma glucose $\geq$ 126 mg/dL (7.0 mmol/L) or hemoglobin A1c level $\geq$ 6.5% (15). Heart disease is defined as a previous diagnosis of heart failure or coronary heart disease.

Before the physical examination and ECG monitoring, the subjects should avoid strenuous exercise, radiation examination and other matters. They are expected to keep the whole body relaxed and keep the supine state during the data measurement. The 12-lead ECG recordings were obtained using a MAC 2000 resting ECG machine (GE Healthcare, Milwaukee, Wisconsin, USA) and analyzed by the Marquette 12SL ECG analysis program. The program can label arrhythmia, measure standard intervals, and perform waveform analysis. The diagnosis of the ECG machine was checked by an experienced clinical physiologist. All ECG abnormalities were confirmed and coded according to the Minnesota ECG Coding Classification System by two cardiologists who were unaware of the clinical data. In addition, the three factors including hypertension, diabetes mellitus and cardiovascular disease history were coded 0-1, with 1 indicating a related history. All subjects were expected to undergo an annual follow-up after enrollment, but some participants failed to continue their appointments.

There were more subjects without AF within a fixed time frame, which was denoted as pre_NAF group. In contrast, the subjects with AF episodes detected were denoted as the pre_AF group, and the data distribution is shown in **Table 1**. The pre_NAF group made up a large proportion, which was also consistent with the fact that non-AF population accounted for a higher proportion in the overall distribution. The 1^{st} year in **Table 1** meant that the subjects were followed up for just one year, and similarly, the 4^{th} year indicated that the subjects were followed up for four years. Subjects in pre_NAF group were different from healthy population because they may have other types of heart disease besides AF.

2.3. Preprocessing

NAN values (966 in total) and outliers need to be removed from the data due to biases introduced during manual data registration and measurement. The interquartile ranges of the boxplot were used to detect outliers in the remaining 17772 cases, and the formulae are as follows:

$$LW = Q_1 - 1.5 \times (Q_3 - Q_1) \tag{1}$$

$$UW = Q_3 + 1.5 \times (Q_3 - Q_1) \tag{2}$$

where Q_1 and Q_3 represent the lower and upper quartiles, respectively, and LW and UW represent the lower and upper edges of the boxplot, respectively.

Sample points outside this range were judged as outliers. The height of the box reflects the degree of data fluctuation to some extent, and the upper and lower edges represent the maximum and minimum values of the data group. Removal of outliers was operated on only three factors (SBP, DBP and BMI) because all indicators except Age, SBP, DBP and BMI were discrete variables coded 0-1 and it is believed that there was no measurement error in age. Then the total data is standardized with max-min normalization method to eliminate the influence of dimension. The formula is as follows:

$$x'_{i,j} = \frac{x_{i,j} - min(x_j)}{max(x_j) - min(x_j)} \tag{3}$$

TABLE 1 Distribution of subjects' number and age during follow-up.

	pre_AF group		pre_NAF group	
	Sample number	Age (years old)	Sample number	Age (years old)
The 1st year	97	72.47 ± 6.37	808	74.72 ± 7.80
The 2nd year	98	74.79 ± 6.94	1,044	72.53 ± 8.32
The 3rd year	75	72.08 ± 6.68	2,174	69.08 ± 7.69
The 4th year	81	70.96 ± 6.64	14,361	67.95 ± 5.94

where $x_{i,j}$ and $x'_{i,j}$ are data in row i and column j before and after normalization, respectively. $max\left(x_j\right)$ and $min\left(x_j\right)$ are the maximum and minimum data in column j, respectively.

2.4. Assessment tasks of AF risk predictors

Four assessment tasks corresponding to the follow-up were constructed for the AF risk predictors from the data of the pre_NAF group and the pre_AF group. Repeated random sampling (20 times) was adopted to minimize the bias caused by unbalanced samples.

2.4.1. Machine learning models

Logistic regression (LR) assigns estimation coefficients to the linear model such that the sum of squared residuals between the observed target and the predicted target of the linear approximation in the dataset is minimized.

Support vector machine (SVM) is often used for bivariate classification of data, and its decision boundary is the maximum margin hyperplane solved for the learning samples, which can be transformed into a convex quadratic programming problem. In this study, radial basis functions (RBF) are used as kernel functions.

Random forest (RF) is composed of a set of tree classifiers $\left\{h\left(x,\ \Theta_k\right), k = 1, \ldots\right\}$, where $\{\Theta_k\}$ is an independent identically distributed random vector generated in conformity with the kth tree. Each tree votes on the most popular class corresponding to the input vector x, which is essentially an integration of multiple decision trees. In this paper, Gini impurity is chosen as the selection criterion of decision trees, which indicates the probability of a randomly selected sample being misclassified in a subset. Supposing the probability that a node is estimated as a different class at position t is $p\left(k|t\right), k = 1, 2, \ldots, Q$, and Q is the number of sample types, then the Gini index $G\left(t\right)$ is defined as:

$$G\left(t\right) = 1 - \sum_{k=1}^{Q} p^2\left(k|\mathrm{t}\right) \tag{4}$$

After preprocessing, the data sampled from the pre_NAF group and the fixed pre_AF group were subjected to 10-fold cross-validation each time, and there was no data overlap between the training set and the test set in the same run. Finally, the results of multiple machine learning models were averaged after feature selection optimization.

2.4.2. Feature selection (FS)

Recursive feature elimination (RFE) uses the backward selection method to compute the feature subset recursively. The steps of the algorithm are as follows:(1) the initial set is trained and the importance of each feature is obtained by an external estimator; (2) the least important features are removed and the remainder are put into machine learning models again for filtering; (3) the above elimination steps are repeated recursively to receive the optimal feature combination. The importance of features is calculated by different supervised learning estimators. In LR and SVM, it is measured by the absolute value of the feature coefficients, that is, the weight w corresponding to the independent variable x, while RF uses Gini index to estimate the feature importance.

2.4.3. Statistical test

For numerical variables, the normality test was conducted. If each group met the normality, the t-test was performed for inter-group comparison. Otherwise, the median, minimum and maximum were used for statistical description, and the non-parametric test was used for inter-group comparison. Categorical data were compared between two groups with Chi-Square test. And Mann–Whitney U test was used to determine whether there are statistically significant differences between medians of independent sample groups (pattern of AF and NAF).

Cox proportional-hazards model is a semi-parametric regression model, which can simultaneously study the relationship between multiple risk factors and the occurrence time of events. Cox regression has low requirement to data distribution, while multiple linear regression and logistic regression require data distribution to be approximately normal and binomial, respectively. The arguments of Cox regression model can be continuous numerical variables or discrete categorical variables, and stepwise regression method is used to screen effective characteristics from multiple influencing factors. We calculated the hazard ratio (HR) values, confidence intervals (CI) and p-values using both Cox univariate and multivariate regression models to investigate the effect of baseline characteristics on the prediction of AF and to check disruptive factors. $p < 0.05$ was considered of statistical significance.

2.5. Evaluation

The evaluation criterions of the classification results are accuracy (ACC), sensitivity (SEN), specificity (SPEC), F1 score and positive predictive value (PPV). The F1 score is defined as the harmonic mean of precision and sensitivity. Their formulas are as follows:

$$ACC = \frac{TP+TN}{TP+TN+FP+FN} \tag{5}$$

$$SEN = \frac{TP}{TP+FN} \tag{6}$$

$$SPEC = \frac{TN}{TN+FP} \tag{7}$$

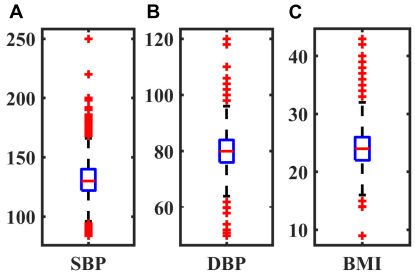

FIGURE 1
Boxplot of three factors. **(A)** SBP; **(B)** DBP; **(C)** BMI.

TABLE 2 The number of outliers and number of remaining samples in pre_AF group and pre_NAF group.

	pre_AF group				pre_NAF group			
	Task1	Task2	Task3	Task4	Task1	Task2	Task3	Task4
SBP outliers	2	0	1	2	15	11	32	200
DBP outliers	1	4	4	1	26	36	65	410
BMI outliers	4	1	2	0	10	8	26	132
NAN	3	7	3	4	61	71	126	691
Remainder	88	86	65	74	699	921	1935	12997

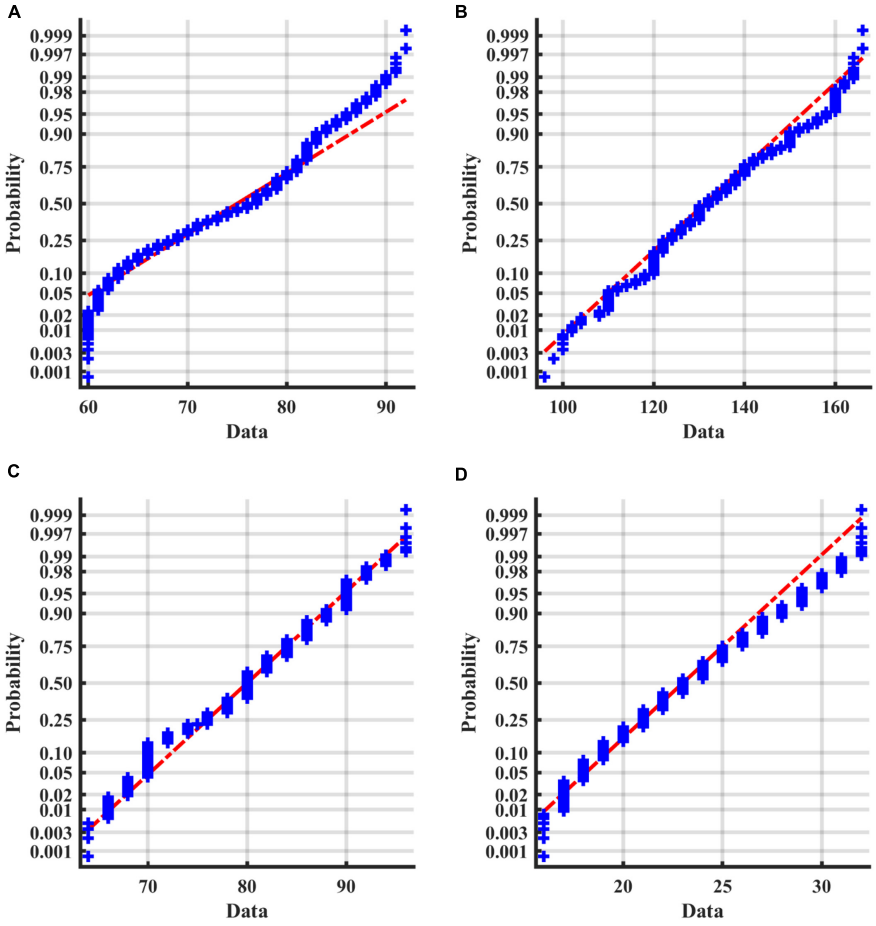

FIGURE 2
Normal probability diagrams of 4 factors in the pre_NAF group in task1. The probabilities for different values of the factors are shown in blue. If all the sample points are close to the red line, it is reasonable to assume that the samples follow a normal distribution. **(A)** Age; **(B)** SBP; **(C)** DBP; **(D)** BMI.

$$F1\ score = \frac{2\times TP}{N+TP-FN} \quad (8)$$

where TP, TN, FP, FN and N stand for true positive, true negative, false positive, false negative and the total number of samples respectively.

3. Results

3.1. Removal of outliers

The outliers of SBP, DBP and BMI were eliminated respectively. The boxplot in Figure 1 reflects the central location and distribution range of three groups of discrete quantitative data. The number of outliers and the number of remaining samples in the 4 tasks are shown in Table 2.

3.2. Independent AF risk factors

For numerical variables (age, SBP, DBP, and BMI), the normality tests were conducted by normal probability diagrams and Figure 2 shows the examples of the pre_NAF group in task1. The non-parametric Mann–Whitney U tests were performed for inter-group comparison on all samples, since two groups of numerical variables in the four tasks cannot meet the normal distribution at the same

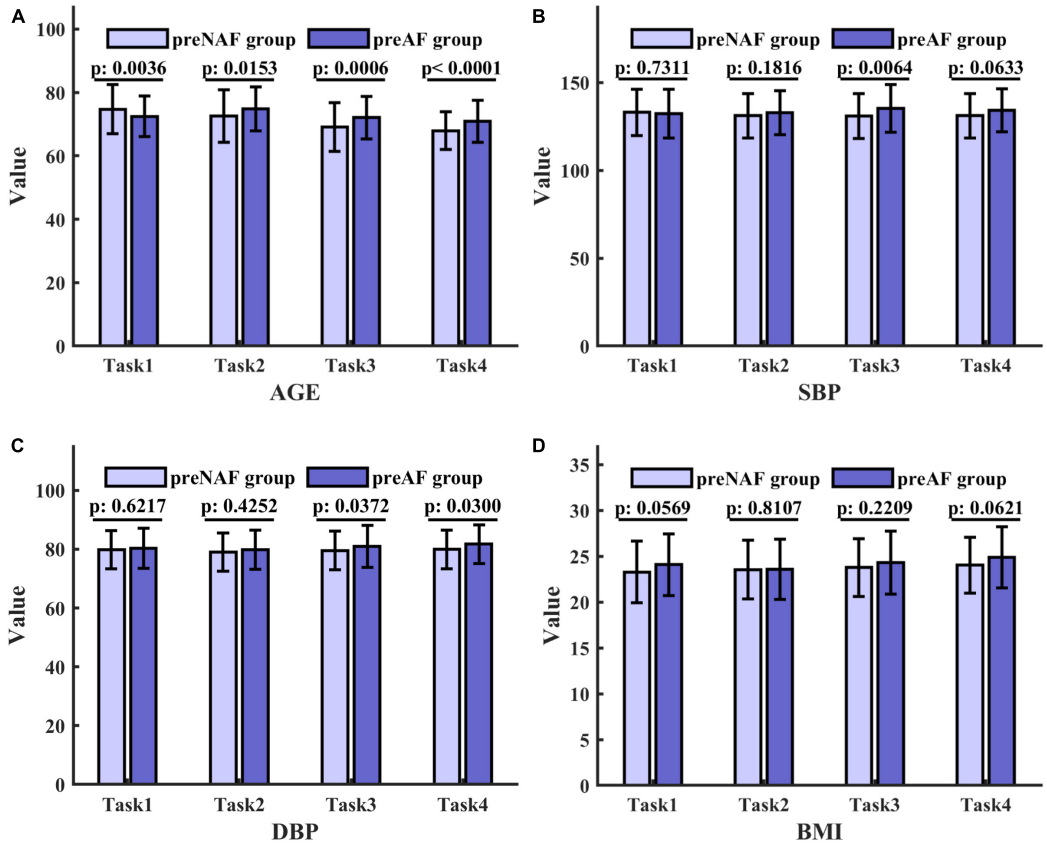

FIGURE 3
Mean, error bars and *p*-values of 4 numerical variables in the pre_NAF group and pre_AF group in 4 tasks. The height of the columns represents the mean, and the error bar reflects the standard deviation. p values are obtained by the Mann–Whitney U test and indicate the existence of significant differences. **(A)** Age; **(B)** SBP; **(C)** DBP; **(D)** BMI.

time. Mean, error bars and p-values of 4 numerical variables shown in Figure 3 indicated that only age was of significant difference in 4 separate tasks between patients who were detected positive for AF and subjects without AF symptoms during the follow-up.

The baseline characteristics of specific subjects for tasks 1 to 4 were shown in Tables 3, 4. Among various categorical variables, only APBs and heart disease were significant under the Chi-square test during the follow-up in at least 3 separate tasks. Due to the small number of subjects recruited in the pre_AF group, the statistical number of indicators coded as 1 tended to be smaller than that in the general elderly population (more than 60 years old).

To investigate whether these baseline variables were appropriate independent AF risk predictors with comprehensive significance over a four-year period, we performed Chi-square test and Mann-Whitney U test for categorical and numerical variables respectively, and Cox regression models were applicable for both variables. Cox regression models required random sampling to avoid unbalanced data distribution. It should be noted that for the inclusion of negative samples, only subjects who successfully completed 4 years of follow-up (12997 negative samples) were considered due to the unstable contact status of the pre_NAF group in the previous 3 years, while all 313 positive samples were included. Considering that some variables appeared more frequently in pre_NAF patients, we excluded them to keep consistent with the objective of this study to find positive AF risk predictors. Table 5 shows baseline characteristics with p-values less than 0.05 under the Chi-square test and Mann-Whitney U test in this case. APBs, LVH and hypertension had an incidence of more than 20% in AF patients. Based on results in Table 5, there were 8 baseline characteristics with HR $>$ 1 and p-value $<$ 0.05 obtained by univariate Cox regression analysis (Table 6), including age, APBs, atrial flutter, junctional premature beat, LVH, ST and T change, hypertension and heart disease. They were identified as independent AF risk predictors finally and supposed to have higher priority in search for independent AF risk predictors.

3.3. Combined AF risk factors

The combined AF risk related baseline characteristics were investigated from two aspects: machine learning models and multivariate Cox regression analysis.

3.3.1. Results of machine learning models

Three typical machine learning models are used to measure predictive ability of all baseline characteristics in tasks 1 to 4 (Table 7). LR models had comparable high predictive performance after parameter optimization in the overall data distribution. Their results were positively correlated with time evolution and the gap between SEN and SPEC narrowed in the last two tasks.

By reducing feature dimension and redundancy, RFE method combined with LR models contributed to the establishment of AF risk prediction models (Table 8). The final variable subset was

TABLE 3 Subjects' characteristics at baseline in tasks 1 and 2.

	Task1			Task2		
Characteristics	pre_NAF (n = 699)	pre_AF (n = 88)	p-value	pre_NAF (n = 921)	pre_AF (n = 86)	p-value
Female gender, n (%)	346 (49.5)	42 (47.7)	0.607	517 (56.1)	43 (50.0)	0.199
Age, years old, median	77 (60–92)	72.5 (60–86)	***0.004***	73 (60–93)	74 (60–92)	***0.015***
SBP, mmHg	132 (96–166)	131 (100–166)	0.731	130 (98–166)	132 (106–164)	0.182
DBP, mmHg	80 (64–96)	80 (66–96)	0.622	80 (64–96)	80 (70–96)	0.425
BMI, kg/m^2	23 (16–32)	24 (16–32)	0.057	23 (16–32)	23 (16–31)	0.811
Sinus bradycardia, n (%)	55 (7.9)	8 (9.1)	0.690	61 (6.6)	8 (9.3)	0.347
Sinus arrhythmia, n (%)	11 (1.6)	6 (6.8)	***0.001***	19 (2.1)	2 (2.3)	0.870
Sinus tachycardia, n (%)	24 (3.4)	2 (2.3)	0.566	30 (3.3)	1 (1.2)	0.282
Atrial premature beats, n (%)	92 (13.2)	18 (20.5)	0.063	77 (8.4)	20 (23.3)	***<0.001***
Atrial rhythm, n (%)	0 (0)	1 (1.1)	***0.004***	0 (0)	0 (0)	–
Atrial tachycardia, n (%)	2 (0.3)	3 (3.4)	***<0.001***	5 (0.5)	2 (2.3)	0.057
Atrial flutter, n (%)	2 (0.3)	4 (4.5)	***<0.001***	0 (0)	0 (0)	–
Junctional premature beat, n (%)	6 (0.9)	3 (3.4)	***0.034***	5 (0.5)	1 (1.2)	0.475
Junctional rhythm, n (%)	0 (0)	1 (1.1)	***0.005***	0 (0)	1 (1.2)	***0.001***
Ventricular premature beat, n (%)	26 (3.7)	4 (4.5)	0.703	35 (3.8)	5 (5.8)	0.361
Short PR interval, n (%)	0 (0)	0 (0)	–	0 (0)	1 (1.2)	***0.001***
First degree atrioventricular block, n (%)	20 (2.9)	0 (0)	0.108	15 (1.6)	2 (2.3)	0.631
Left anterior fascicular block, n (%)	14 (2.0)	0 (0)	0.180	9 (1.0)	1 (1.2)	0.869
Incomplete right bundle branch block, n (%)	14 (2.0)	3 (3.4)	0.392	18 (2.0)	2 (2.3)	0.814
Complete right bundle branch block, n (%)	49 (7.0)	3 (3.4)	0.200	46 (5.0)	3 (3.5)	0.535
Low voltage, n (%)	7 (1.0)	3 (3.4)	0.057	5 (0.5)	1 (1.2)	0.475
Left ventricular hypertrophy, n (%)	124 (17.7)	22 (25.0)	0.098	167 (18.1)	17 (19.8)	0.708
Dilated right atrium, n (%)	1 (0.1)	2 (2.3)	***0.002***	0 (0)	0 (0)	–
ST segment change, n (%)	29 (4.1)	2 (2.3)	0.394	30 (3.3)	4 (4.7)	0.494
T wave abnormality, n (%)	97 (13.9)	8 (9.1)	0.213	100 (10.9)	10 (11.6)	0.827
ST and T change, n (%)	24 (3.4)	5 (5.7)	0.291	35 (3.8)	4 (4.7)	0.696
Hypertension, n (%)	349 (49.9)	46 (52.3)	0.679	431 (46.8)	46 (53.5)	0.235
Diabetes mellitus, n (%)	72 (10.3)	7 (8.0)	0.490	115 (12.5)	2 (2.3)	***0.005***
Heart disease, n (%)	30 (4.3)	16 (18.2)	***<0.001***	28 (3.0)	8 (9.3)	***0.003***

Bold values represent the $p < 0.05$. Italic values indicate significant differences.

decided by more than half of the votes, named as unified feature selection (unified FS). A slightly lower predictive performance of unified optimal feature collection is acceptable, provided that it had some generalization ability for various optimal sets obtained under different data distributions.

Table 9 shows important variables selected from the combination of RFE method and unified FS in 4 tasks based on LR models. Variables that appeared more frequently in pre_NAF patients were excluded, even though they were valid for machine learning models. In this case, factors that played a role in all tasks included age, APBs, hypertension and heart disease. Variables valid in three tasks included SBP, DBP, BMI, sinus bradycardia, atrial flutter, junctional premature beat, ventricular premature beat, LVH and ST and T change. There were no variables valid only for tasks 1 or 2. Variables valid only for tasks 3 or 4 included ST segment change. Unstable factors other than the above were ignored due to their seemingly weak association with AF risk prediction.

3.3.2. Results of multivariate Cox regression analysis

We conducted multivariate Cox regression analysis (Table 10) to measure whether the important independent predictors in Table 6 (univariate Cox regression analysis) were simultaneously positively associated with AF risk prediction and had future practicability. All HR values were more than 1, indicating that they were risk factors and can promote positive outcomes. P-values of variables including age, APBs, atrial flutter, LVH, hypertension and heart disease were less than 0.05, indicating that these independent variables were significant for the interpretation of the whole model. Compared with the four risk predictors obtained by the machine learning models

TABLE 4 Subjects characteristics at baseline in tasks 3 and 4.

Characteristics	Task3			Task4		
	pre_NAF (n = 1935)	pre_AF (n = 65)	*p*-value	pre_NAF (n = 12997)	pre_AF (n = 74)	*p*-value
Female gender, n (%)	788 (40.7)	36 (55.4)	***0.018***	7,127 (54.8)	34 (45.9)	0.125
Age, years old, median	68 (60–92)	73 (60–84)	***<0.001***	67 (60–95)	71.5 (60–87)	***<0.001***
SBP, mmHg	130 (96–166)	136 (102–160)	***0.006***	130 (96–166)	134 (110–160)	0.063
DBP, mmHg	80 (64–96)	82 (66–94)	***0.037***	80 (64–96)	80 (66–96)	***0.030***
BMI, kg/m2	24 (16–32)	24 (16–32)	0.221	24 (16–32)	24.5 (18–32)	0.062
Sinus bradycardia, n (%)	158 (8.2)	10 (15.4)	***0.039***	1,469 (11.3)	13 (17.6)	0.090
Sinus arrhythmia, n (%)	48 (2.5)	1 (1.5)	0.629	349 (2.7)	2 (2.7)	0.993
Sinus tachycardia, n (%)	39 (2.0)	3 (4.6)	0.151	237 (1.8)	0 (0)	0.241
Atrial premature beats, n (%)	145 (7.5)	13 (20.0)	***<0.001***	835(6.4)	18 (24.3)	***<0.001***
Atrial rhythm, n (%)	4 (0.2)	0 (0)	0.714	9 (0.1)	0 (0)	0.821
Atrial tachycardia, n (%)	6 (0.3)	0 (0)	0.653	32 (0.2)	0 (0)	0.669
Atrial flutter, n (%)	3 (0.2)	1 (1.5)	***0.014***	3 (0.0)	0 (0)	0.896
Junctional premature beat, n (%)	9 (0.5)	0 (0)	0.582	52 (0.4)	1 (1.4)	0.199
Junctional rhythm, n (%)	2 (0.1)	0 (0)	0.795	8 (0.1)	0 (0)	0.831
Ventricular premature beat, n (%)	54 (2.8)	5 (7.7)	***0.022***	309 (2.4)	4 (5.4)	0.089
Short PR interval, n (%)	6 (0.3)	0 (0)	0.653	12 (0.1)	0 (0)	0.794
First degree atrioventricular block, n (%)	41 (2.1)	5 (7.7)	***0.003***	235 (1.8)	2 (2.7)	0.565
Left anterior fascicular block, n (%)	19 (1.0)	0 (0)	0.422	129 (1.0)	0 (0)	0.389
Incomplete right bundle branch block, n (%)	16 (0.8)	1 (1.5)	0.539	134 (1.0)	1 (1.4)	0.786
Complete right bundle branch block, n (%)	66 (3.4)	1 (1.5)	0.409	382 (2.9)	0 (0)	0.134
Low voltage, n (%)	14 (0.7)	0 (0)	0.491	68 (0.5)	0 (0)	0.533
Left ventricular hypertrophy, n (%)	316 (16.3)	17 (26.2)	***0.036***	2,237 (17.2)	16 (21.6)	0.317
Dilated right atrium, n (%)	4 (0.2)	0 (0)	0.714	10 (0.1)	0 (0)	0.811
ST segment change, n (%)	67 (3.5)	5 (7.7)	0.072	340 (2.6)	4 (5.4)	0.135
T wave abnormality, n (%)	188 (9.7)	6 (9.2)	0.896	1,260 (9.7)	11 (14.9)	0.134
ST and T change, n (%)	54 (2.8)	1 (1.5)	0.544	251 (1.9)	3 (4.1)	0.187
Hypertension, n (%)	846 (43.7)	45 (69.2)	***<0.001***	5,680 (43.7)	50 (67.6)	***<0.001***
Diabetes mellitus, n (%)	175 (9.0)	10 (15.4)	0.083	1,152 (8.9)	6 (8.1)	0.819
Heart disease, n (%)	61 (3.2)	10 (15.4)	***<0.001***	398(3.1)	4 (5.4)	0.244

Bold values represent the $p < 0.05$. Italic values indicate significant differences.

for all tasks, Cox multivariate analysis suggested that LVH and atrial flutter were also important variables. These baseline characteristics are supposed to have higher priority in this cohort study. Besides, we calculated the p-values for the 4 tasks (0.0310, 0.0191, 0.0016, and 0.0015, respectively) by comparing single age factor and combined characteristics using the Mann–Whitney U test. The results indicated a gap between AF risk predictors combination and the single age element suggested by traditional guidelines (8, 16).

3.4. Baseline characteristics of subjects at different age ranges

Subjects in the following 7 age ranges were studied separately (**Table 11**) and it is clear that the incidence of APBs increased substantially with age. The incidence of AF events and heart disease increased in the first six and five intervals, respectively. The probability of LVH increased in the first three ranges, then stabilized at about 21% in people aged 75–89 and only 10.7% in people aged 90 and older. The trend in hypertension was relatively erratic and peaked among participants aged 85–89 years. Similarly, we calculated the incidence of baseline characteristics across age ranges in AF patients alone (**Table 12**).

4. Discussion

AF is the most common supraventricular arrhythmia in clinic. Previous works have reported that approximately 15% to 31% of paroxysmal AF patients at the early-stage progress to persistent or permanent AF during a time period between 4 and 8 years (17). Although AF itself poses little threat to life, ischemic stroke caused by AF is one of the main causes of death (17%) in Chinese community patients with AF (15). To optimize the early management of AF patients and slow down the progression of AF, Chinese guideline (16) provides suggestions for AF risk prediction by age and this has been demonstrated by many studies that there is a positive association between the incidence of AF and advancing age (18–22).

TABLE 5 Baseline characteristics of 12997 negative samples and 313 positive samples with p-values less than 0.05 under the Chi-square test and Mann-Whitney U test.

Characteristics	pre_NAF (n = 12997)	pre_AF (n = 313)	*p*-value
Age, years old, median	67 (60–95)	73 (60–92)	<0.001
SBP, mmHg	130 (96–166)	134 (100–166)	0.002
DBP, mmHg	80 (64–96)	80 (66–96)	0.036
Atrial premature beats, n (%)	835 (6.4)	69 (22.0)	<0.001
Atrial flutter, n (%)	3 (0.0)	5 (1.6)	<0.001
Junctional premature beat, n (%)	52 (0.4)	5 (1.6)	0.001
Ventricular premature beat, n (%)	309 (2.4)	18 (5.8)	<0.001
Left ventricular hypertrophy, n (%)	2237 (17.2)	72 (23.0)	0.008
ST segment change, n (%)	340 (2.6)	15 (4.8)	0.018
ST and T change, n (%)	251 (1.9)	13 (4.2)	0.005
Hypertension, n (%)	5680 (43.7)	187 (59.7)	<0.001
Heart disease, n (%)	398 (3.1)	38 (12.1)	<0.001

However, AF risk prediction only based on age can fail to screen positive cases and conduct clinical evaluation in a timely and effective manner due to the high proportion of asymptomatic AF patients (23). This study aims to help the progress of AF risk prediction through the diagnosis results of ECG machine that can reflect the changes of cardiac electrophysiology. The principal contributions of this study were as follows: (1) Diagnosis data of ECG machine and some physical examination basic data were explored to create more possibilities for AF risk prediction; (2) Both independent and combined risk predictors of positive correlation with AF were obtained and analyzed in detail, and combined risk predictors are more valuable in clinical applications; (3) This study functions as a preliminary step to reduce the target population for long-term ECG monitoring, which is beneficial to optimize the management of high AF risk population and improve the detection rate of AF.

4.1. Advantage of ECG machine for AF risk prediction

As a widely used automated algorithm for computer-based interpretation, GE Healthcare 12SL ECG Analysis Programs used in this study refines itself through regular clinical input and clinically relevant gold standard databases. Although there are small systematic differences between the measurements obtained with automated electrocardiographs from different manufacturers (24, 25), their diagnostic results are similar in differentiating between specific individuals and populations. Nowadays, most of the efficacy tests are skewed to pathologic rhythms with much emphasis on AF (26), which accords with its increasing prevalence and the topic of this study. In the absence of absolute medical definition of waveform fiducial points, the stability of the "gold standard" of human judgment is subject to uncertainty (25). This makes the absolute acceptance of any "gold standard" controversial, even if it is quantifiable. Therefore, the integrated stable analysis algorithms of ECG machines are suitable for clinical applications due to its simplicity, reliability and repeatability. As an extension of analysis algorithms of ECG machines, this study aims to explore effective AF risk predictors in the existing clinical experiment circumstances, and in turn serve the clinical diagnosis. Since the ECG monitoring systems used in this community-based cohort study aims to provide service applied to medical fields instead of non-medical applications (such as sports and elderly activities),

TABLE 6 Independent predictors for subjects with and without AF (cox proportional hazard model, univariate analysis).

Risk factors list	HR	95% CI	*p*-value
Age	1.038	1.022–1.054	<0.001
Atrial premature beats	1.782	1.364–2.329	<0.001
Atrial flutter	5.093	2.091–12.404	<0.001
Junctional premature beat	2.536	1.047–6.140	0.039
Left ventricular hypertrophy	1.397	1.074–1.818	0.013
ST and T change	1.782	1.023–3.106	0.042
Hypertension	1.260	1.005–1.580	0.045
Heart disease	2.115	1.505–2.972	<0.001

HR, hazard ratio; CI, confidence interval.

TABLE 7 The results of three machine learning models used for all baseline characteristics in 4 tasks.

		ACC (%)	SEN (%)	SPEC (%)	F1 score	PPV (%)
Task1	LR	***60.41***	***55.71***	***64.80***	***0.568***	60.66
	SVM	55.94	46.53	65.21	0.503	57.34
	RF	59.62	50.42	68.59	0.540	***61.23***
Task2	LR	***59.10***	***54.93***	63.21	***0.565***	***60.11***
	SVM	56.76	53.80	59.81	0.547	58.04
	RF	55.78	46.78	***65.03***	0.502	57.54
Task3	LR	66.08	63.69	***68.24***	0.640	***67.38***
	SVM	***66.15***	***71.67***	60.40	***0.675***	66.29
	RF	61.08	55.60	66.10	0.573	62.67
Task4	LR	***65.00***	62.16	***67.87***	***0.635***	***67.78***
	SVM	62.71	***62.64***	62.54	0.622	64.20
	RF	60.20	52.57	68.02	0.563	63.66

Bold and italic values represent the highest value of evaluation criterions in the three classifiers.

TABLE 8 The predictive performance of LR models combined with different FS methods.

	FS	ACC (%)	SEN (%)	SPEC (%)	F1 score	PPV (%)
Task1	Without FS	60.41	55.71	64.80	0.568	60.66
	RFE	65.41	59.93	70.53	0.617	66.35
	RFE and unified FS	64.12	58.50	69.42	0.599	64.61
Task2	Without FS	59.10	54.93	63.21	0.565	60.11
	RFE	61.78	57.79	65.71	0.595	63.22
	RFE and unified FS	61.48	57.22	65.88	0.589	63.45
Task3	Without FS	66.08	63.69	68.24	0.640	67.38
	RFE	67.85	66.43	69.02	0.663	69.13
	RFE and unified FS	66.85	65.36	68.21	0.656	69.28
Task4	Without FS	65.00	62.16	67.87	0.635	67.78
	RFE	67.06	64.25	70.09	0.657	70.35
	RFE and unified FS	65.52	62.40	69.07	0.637	68.64

TABLE 9 Important variables in different tasks based on LR models and FS.

Risk factors list	Task1	Task2	Task3	Task4
Gender		✓		✓
Age	✓	✓	✓	✓
SBP		✓	✓	✓
DBP		✓	✓	✓
BMI	✓		✓	✓
Sinus bradycardia		✓	✓	✓
Atrial premature beats	✓	✓	✓	✓
Atrial flutter	✓	✓	✓	
Junctional premature beat	✓	✓		✓
Ventricular premature beat		✓	✓	✓
Incomplete right bundle branch block	✓		✓	
Left ventricular hypertrophy	✓		✓	✓
ST segment change			✓	✓
ST and T change		✓	✓	✓
Hypertension	✓	✓	✓	✓
Heart disease	✓	✓	✓	✓

TABLE 10 Combined predictors for subjects with and without AF (cox proportional hazard model, multivariate analysis).

Risk factors list	HR	95% CI	*p*-value
Age	1.058	1.040–1.075	***<0.001***
Atrial premature beats	1.494	1.230–1.976	***0.005***
Atrial flutter	3.473	1.355–8.882	***0.009***
Junctional premature beat	1.603	0.660–3.891	0.297
Left ventricular hypertrophy	1.406	1.074–1.841	***0.013***
ST and T change	1.600	0.906–2.823	0.105
Hypertension	1.322	1.051–1.664	***0.017***
Heart disease	1.519	1.051–2.194	***0.026***

HR: hazard ratio; CI: confidence interval. Bold values represent the $p < 0.05$. Italic values indicate significant differences.

performance improvements such as cost, energy efficiency, and battery life are not considered.

It should be pointed out that our focus is on the value of the diagnosis results of ECG machines in the AF risk prediction and there were some limitations in the experimental environment of data acquisition. Therefore, not all AF related factors such as hyperthyroidism were taken into account, but they can be included in the future work.

4.2. Evaluation of results

Tables 7, 8 show the average predictive performance of the machine learning models in four tasks. These evaluation indexes basically did not reach 70% but mostly exceed 60%, and there are two possible reasons. On the one hand, this study performed dichotomy tasks between AF and non-AF rather than AF and healthy subjects, and many subjects in the non-AF group actually had other cardiovascular diseases and related complications. The similarity of symptoms may bias the results. On the other hand, the data provided by the ECG machines were the simplified 0-1 code instead of specific values, so some valuable information can be lost in the process. Besides, ACC, SEN and SPEC in task 3 and task 4 were higher than those in task 1 and task 2, indicating that individuals can more possibly have AF attack caused by risk accumulation. Furthermore, some variables may show temporal change, with different distributions in various tasks (e.g., age increases with the task).

4.3. AF risk predictors

The independent AF predictors were analyzed by Chi-square test, Mann–Whitney U test and Cox proportional-hazards models. The chi-square test dealt with categorical variables and Mann-Whitney U test dealt with numerical variables, while Cox proportional-hazards models accepted both types of variables. There were 8 baseline characteristics in the intersection of their significance variables sets, including age, APBs, atrial flutter, junctional premature beat, LVH, ST and T change, hypertension and heart disease.

The combined AF risk predictors were determined by Cox regression analysis and LR models with RFE method. The Cox regression models simultaneously assessed the effect of several variables on events, allowing us to examine how specific factors affected the incidence of AF occurring at a given time point. The resulting covariates with HR values greater than 1 and p values less than 0.05 were considered to be significantly positively associated with increased AF risk. The combined baseline characteristics included age, APBs, atrial flutter, LVH, hypertension and heart disease. The p-values (less than 0.05) obtained with the Mann-Whitney U test indicated a gap between combined AF risk predictors and the single age element. Although age is associated with higher AF sensitivity, the consequent sacrifice of specificity may cause anxiety and overdiagnosis. In clinical practice, independent variables cannot fully reflect the outcome variables (positive or negative), and are susceptible to the interference of other variables when they are not completely independent. In particular, AF risk prediction using dozens of variables or a single variable is difficult to implement. Therefore, we focus on the combined AF risk predictors that evolved from univariate analysis.

APBs and AF are arrhythmias of atrial origin. If the large number of APBs indicates atrial fibrosis or electrical activity disorder, it can easily develop into AF in the future. In the community-based Chinese cohort study, we found that the presence of ECG machine-diagnosed APBs was a strong independent and combined predictor of AF risk in the elderly population ($\geq$ 60 years). During the follow-up of 1 to 4 years, the APBs detection rate in this cohort was 22% in patients with AF versus 6.9% in patients without AF. Many studies (27–35) used 24-hour Holters to analyze the relationship between APBs and AF, which can count baseline APBs and use different thresholds to define its frequency of occurrence in the 24-hour recordings. However, the relationship between the count of APBs and the probability of developing AF highly depends on baseline information (such as relevant medical history, medication history, etc.) of the AF-risk population, indicating the limitations of thresholds setting. While in this study, only the occurrence events of APBs reflected by ECG machine with short-term data collection were required to perform AF risk prediction, which could be an effective pre-step before long-term ECG monitoring for high-risk groups. In

TABLE 11 The number and proportion of baseline characteristics for all subjects of different age ranges.

Age range (years old)	Sample number	AF (n,%)	APBs (n,%)	LVH (n,%)	Hypertension (n,%)	Heart disease (n,%)
60–64	5465	42, 0.8%	241, 4.4%	812, 14.9%	1958, 35.9%	114, 2.1%
65–69	4719	62, 1.3%	276, 5.8%	765, 16.2%	2084, 44.2%	151, 3.2%
70–74	3279	91, 2.8%	258, 7.9%	610, 18.6%	1719, 52.4%	121, 3.7%
75–79	1985	62, 3.1%	207, 10.4%	427, 21.5%	1007, 50.7%	95, 4.8%
80–84	1204	46, 3.8%	191, 15.9%	262, 21.8%	609, 50.6%	67, 5.6%
85–89	184	9, 4.9%	38, 20.7%	37, 20.1%	103, 56.0%	6, 3.3%
≥90	28	1, 3.6%	7, 25.0%	3, 10.7%	13, 46.4%	1, 3.6%

The proportion was obtained by calculating the ratio of the number of subjects with baseline characteristics to the sample number in the corresponding age range.

TABLE 12 The number and proportion of baseline characteristics for subjects with AF of different age ranges.

Age range (years old)	AF patients number	APBs (n,%)	LVH (n,%)	Hypertension (n,%)	Heart disease (n,%)
60–64	42	7, 16.7%	4, 9.5%	20, 47.6%	3, 7.1%
65–69	62	11, 17.7%	14, 22.6%	37, 59.7%	8, 12.9%
70–74	91	16, 17.6%	23, 25.3%	57, 62.6%	13, 14.3%
75–79	62	16, 25.8%	15, 24.2%	38, 61.3%	8, 12.9%
80–84	46	14, 30.4%	11, 23.9%	29, 63.0%	5, 10.9%
85–89	9	5, 55.6%	4, 21.7%	5, 55.6%	0, 0.0%
≥ 90	1	0, 0.0%	1, 100.0%	1, 100.0%	1, 100.0%

The proportion was calculated by considering the probability among AF patients.

addition, many strokes occurred without a temporal association with the AF episodes (36, 37), suggesting that frequent APBs may be a stroke risk marker independent of the causal mechanism of AF.

Atrial flutter and AF are proposed to be related entities and may transform into one another (38). Since they usually co-exist before and after medication or ablation, most studies (39–42) have explored the incidence of new AF in patients undergoing ablation. In this study, 16552 patients without AF and 313 patients with AF who had no previous history of successful ablation of atrial flutter were tested by ECG machines. However, the incidence of atrial flutter was only 1.6% in positive samples and only 0.05% in negative samples during the follow-up. This may be affected by the short monitoring period and insufficient follow-up time, and more data is expected to be included.

Left ventricular hypertrophy is usually a compensatory hypertrophy of the heart caused by hypertension. Studies (43–48) investigating the AF predictive role of ECG-based LVH were mainly based the population including both hypertension and normotension. The follow-up period ranged from 3.2 to 11.9 years and the mean age of subjects was 55.4 ± 11 years (49). On this basis, LVH was observed in 258 of 3,235 AF events (8%), compared to 72 of 313 AF events (23%) in the elderly population during the follow-up of 1-4 years in this study. Differences in LVH criteria may limit the confidence of the results and more large randomized controlled studies are necessary. But the differences of results may indicate a higher incidence of LVH in the elderly over 60 years. In addition, there was an apparent correlation between hypertension and LVH in this study, especially for subjects suffering from AF. Among 313 patients with AF, 43 out of 187 (23%) hypertensive patients had LVH and 43 of the 72 patients (60%) with LVH had hypertension. Although LVH was determined to be an independent AF risk predictor, its high occurrence rate in people without AF (2844 cases out of 16552, 17%) may result in inevitable high misdiagnosis rate as does hypertension (7306 cases out of 16552, 44%). We suggest that LVH and hypertension should be diagnosed in conjunction with other AF risk predictors, rather than independently, in the elderly population.

Heart disease in this study refers to a previous diagnosis of heart failure or coronary heart disease. Recording of histories of heart disease is essential before AF risk prediction in the elderly population, but it is supposed to be combined with other risk predictors for diagnosis to avoid low specificity.

In this study, the positive association between the baseline characteristics above and AF was confirmed in residents aged 60 years and older at four community health centers in China. Their combination is beneficial to reduce the misdiagnosis rate caused by single factor diagnosis for AF risk prediction. Besides, the prioritization of risk predictors can help physicians to specify relevant strategies and help the hierarchical management of AF in specific applications. For patients with a large number of abnormal primary risk factors, the density of AF screening should be strengthened, and long-term monitoring should be performed if necessary. It reflects the nature of this study's use of short-time ECG recordings as a pre-step to reduce the target population for long-term ECG monitoring. For patients with abnormal range of only secondary risk factors, follow-up, regular physical examination and health education should be carried out to guide patients' self-health management. For AF patients with relatively stable diagnosis and treatment, routine treatment, rehabilitation and long-term follow-up are expected.

4.4. Association of AF risk predictors with age ranges

Given the small sample size of participants over 90, we focused on the first six age ranges. Traditional guidelines consider individuals

over 65 years of age to be at high AF risk, and this was confirmed according to the increasing incidence of AF in **Table 11**. The incidence of APBs was positively correlated with the age range, both for all samples and for AF participants. The incidence of LVH, hypertension and heart disease in all samples increased in the first few age ranges and then stabilized or fluctuated slightly. But in patients with AF, there was a small decline in their incidence in subjects older than 74. Compared with the probability of occurrence in the total sample, the incidence of APBs increased in AF patients (85–89 years old) by up to 34.9% and by an average of 16.5%. The average risk of hypertension in AF patients increased by 9.8%, followed by heart disease (5.9%) and LVH (2.35%). Considering that these baseline characteristics were independent and combined risk predictors, we ranked their importance in terms of their increased probability of AF episodes: APBs, hypertension, heart disease, and LVH. This can provide suggestions for the increase of weights when constructing prediction models with other characteristics that were not covered in this study, or managing AF-related age-specific populations. In addition, APBs was only 1 and 1.4% less common in AF patients and total samples aged 60–64 than in those aged 65–69, respectively (**Tables 11**, **12**). This suggests that the age range for screening high-risk groups can be appropriately extended to over 60 years of age.

5. Conclusion

In this community-based cohort study, independent and combined AF risk predictors based on the diagnosis results of ECG machine and some basic physical examination data were explored and analyzed. On the basis of univariate analysis, the recommended combined characteristics included age, APBs, atrial flutter, LVH, hypertension and heart disease, and they were verified superior to the single age factor. The combined AF risk predictors are beneficial to reduce the misdiagnosis rate caused by independent factor diagnosis for AF risk prediction. As a pre-step to reduce the target population for long-term ECG monitoring, the positive association between the baseline characteristics above and AF can provide suggestions for people to be included in the focus of AF screening. In this case, the enhancement of screening density and the arrangement of long-term monitoring for these high-risk population can improve the detection rate of AF, standardize the management of patients, and slow down the progression of AF. Besides, AF risk predictors had different incidence rates in different age ranges, which can provide suggestions for the setting of model weights for the management of AF in specific age groups. Additional data especially in the AF group will be collected in the future, and the study will be expanded to include people aged 30 to 60 years. Furthermore, other influencing factors like Hyperthyroidism will be taken into account.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Board of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China and Songjiang Central Hospital, Shanghai, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JH designed research, performed research, analyzed data, and wrote and edited the manuscript. SL and CY designed research and edited the manuscript. YW designed research, edited the manuscript, and had full access to all of the data in the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1068562/full#supplementary-material

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Association of serum N-terminal pro-brain natriuretic peptide levels with survival and renal outcomes among elderly patients with acute kidney injury in chronic heart failure

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Background: Elderly patients exhibit a higher incidence of chronic heart failure (CHF). Patients with CHF can develop acute kidney injury (AKI) during follow-up, which can result in poor prognosis. This relationship between kidney dysfunction and levels of N-terminal pro-brain natriuretic peptides (NT-proBNP), with regard to prognosis, is complicated and has rarely been analyzed in elderly patients with CHF.

Method: We conducted a retrospective cohort study involving patients with a CHF history aged ≥ 65 years, who experienced an episode of AKI. Kaplan–Meier curves and Cox or logistic proportional hazards regression models were used to evaluate the association between serum NT-proBNP concentrations and mortality or renal recovery by day 90.

Results: A total of 1,160 eligible patients with AKI were available for the study. Of this sample, 41.5% of patients died within 90 days of the onset of AKI. Patients with a decreased change in NT-proBNP accompanying the episode of AKI had a lower risk (adjusted OR = 0.56, 95% CI = 0.34–0.91) of more severe AKI (stage 2 and 3 vs. stage 1). The more severe AKI were associated with higher mortality and non-recovery of renal function in elderly patients with CHF, independent of NT-proBNP levels. Elevated levels of baseline lnNT-proBNP (adjusted HR = 1.27, 95% CI = 1.17–1.38) predicted mortality in elderly patients with CHF within 90 days of AKI onset. Patients with a decrease in NT-proBNP accompanying AKI had a lower risk of mortality (adjusted HR = 0.62, 95% CI = 0.48–0.79). However, a decrease in NT-proBNP is a risk factor (adjusted OR = 1.59, 95% CI = 1.02–2.48) for the non-recovery of renal function following AKI–especially in elderly survivors with low baseline NT-proBNP levels.

Conclusion: A decreased change in NT-proBNP maybe protective for elderly patients with CHF by improving survival outcomes and preventing severe AKI. However, an excessive decrease in NT-proBNP is a risk factor for the non-recovery of renal function following AKI. Avoiding excessive changes in NT-proBNP may be protective for survival and renal injury prognosis.

KEYWORDS

chronic heart failure, natriuretic peptides, acute kidney injury, elderly, prognosis

1. Introduction

The prevalence of chronic heart failure (CHF) is high and increasing in aging populations worldwide. The higher incidence of CHF in elderly persons can be attributed to aging and the high frequency of comorbidities, particularly coronary heart disease and hypertension. CHF with preserved ejection fraction is particularly prevalent in geriatric patients. The aging-related changes in the diastolic properties of the myocardium predispose older adults to develop CHF with preserved ejection fraction and atrial fibrillation (1). Elderly patients with heart failure (HF) experience high mortality rates. Compared to younger patients, elderly patients with HF are characterized by more severe clinical conditions, an increased proportion of non-cardiovascular death, and poorer prognoses (2). Considering the high incidence of CHF and poor CHF prognoses in the elderly, more CHF-related studies focusing on this vulnerable patient group are necessary.

B-type natriuretic peptide (BNP) and the precursor of BNP, N-terminal pro-brain natriuretic peptide (NT-proBNP), are produced mainly by cardiomyocytes in response to stretch from volume overload and myocardial ischemia. Circulating natriuretic peptides are widely used biomarkers that are indicative of HF and volume overload. In elderly patients with heart disease, elevated NT-proBNP levels are associated with a greater risk of cardiovascular mortality (3). In elderly patients with CHF, diuretics are frequently utilized as decongestion treatment, which accompanies a decrease in BNP level (4).

Patients with CHF are often characterized by impaired renal function, also referred to as cardiorenal syndrome (CRS). Cardiorenal syndrome is prevalent in the elderly, and a dynamic interplay between the heart and kidneys exists (5). Patients with CHF can develop chronic renal dysfunction or acute kidney injury (AKI) during follow-up. In elderly patients with CHF, pre-renal AKI is frequent due to decreased renal perfusion caused by HF or depletion of effective circulating volume. Elderly patients are more prone to the development of volume depletion because of their restricted ability to access fluids and the frequent use of diuretics (6). AKI is associated with an increased mortality risk that is proportional to the severity of the AKI (7). Furthermore, many patients cannot recover from AKI and thus, progress to more severe stages of chronic kidney disease (CKD) (8). Renal injury is associated with a higher risk of adverse outcomes and is also a predictor of all-cause mortality and rehospitalization in HF (9). However, recent findings indicate that improving renal function is paradoxically associated with worse outcomes in acute HF, but outcomes may differ based on the response to decongestion (decreased change in NT-proBNP) (4).

Since most of the randomized clinical trials for CHF and AKI were designed to exclude elderly patients, only limited data on elderly patients with cardiorenal syndrome are available. In the current analysis, we conducted a retrospective observational study to investigate the relationships between change in NT-proBNP, renal function and adverse outcomes in elderly patients with AKI in CHF.

2. Materials and methods

2.1. Study design and cohort formation

We conducted a retrospective cohort study at the Second Medical Center (Geriatric Department) of the Chinese PLA General Hospital to assess AKI outcomes in older patients with CHF. Patients 65 years of age or older, with a history of CHF with preserved and mildly reduced ejection fraction [left ventricular ejection fraction (LVEF) > 40%], were enrolled if they experienced an episode of AKI between 1 January 2008 and 31 December 2018. Patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m^2) or incomplete medical histories were excluded from the study. Patients were also excluded if they lacked serum creatinine (SCr) or NT-proBNP data, either at baseline or at AKI onset. We followed all patients for 90 days after the initial AKI episode, to determine clinical outcomes relating to mortality and renal function.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Chinese People's Liberation Army General Hospital (S2022-342-01), and the requirement for informed consent was waived.

2.2. Clinical definitions and outcomes

The ICD10 codes I50.22 and I50.32 were used to retrieve data on patients with CHF history. The diagnosis of CHF was based on clinical findings, symptoms, abnormal electrocardiogram, elevation of brain natriuretic peptide level (NT-proBNP > 125 pg/mL), and structural cardiac abnormalities identified on echocardiography according to 2021 ESC guidelines (10). To select patients who experienced an episode of AKI, AKI was defined and classified based on the KDIGO (Kidney Disease Improving Global Outcomes) criteria, using SCr and urine output criteria (11). AKI is defined as any of the following: increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h; or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 h. AKI was classified into three

stages for severity. Baseline SCr values were obtained in a stable state within 3 months of AKI onset. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation. AKI at stage 2 or 3 was defined as more severe AKI. All patients were followed up for 90 days after the initial AKI diagnosis, to assess primary outcomes and all-cause 90-day mortality.

The secondary outcome of the study was non-recovery from AKI, defined as the last available SCr measurement (during the follow-up of 90 days) where SCr remained at more than 150% of the baseline value (thus still meeting the criteria for AKI).

2.3. Data collection

All data were obtained from hospital electronic health records. Demographic characteristics (age and sex), medical history [including LVEF value, the use of medication (ACEI or ARB, beta-blockers, aldosterone antagonist, loop diuretics), hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, prior myocardial infarction, atrial fibrillation, chronic obstructive pulmonary disease (COPD), and malignant tumors], accompanying conditions (proteinuria, extremity edema, infection, and blood pressure), and laboratory test results [including plasma SCr, NT-proBNP, hemoglobin, cardiac troponin I (cTnI), glucose, potassium, calcium, and phosphorus] were recorded. SCr levels were routinely measured in our clinical laboratory, using the Cobas c 501 analyzer (Roche Diagnostics). The serum NT-proBNP concentration was measured using Dimension EXL with an LM Integrated Chemistry System (Siemens). Within 3 months before AKI onset, the NT-proBNP level at baseline (NT-proBNP at baseline) was measured together with the baseline SCr value in a stable state. The NT-proBNP at AKI diagnosis (NT-proBNP at AKI) was measured together with the increased SCr value, which contributed to the diagnosis of AKI. The change in NT-proBNP (continuous) accompanying the episode of AKI was expressed as the ratio of NT-proBNP $_{atAKI}$ to NT-proBNP $_{atbaseline}$. The change in NT-proBNP was also analyzed as a binary variable. A decreased change in NT-proBNP was defined by the ratio of NT-proBNP $_{atAKI}$ to NT-proBNP $_{atbaseline} < 1$.

2.4. Statistical analysis

Continuous variables were presented as mean ± standard deviation for normally distributed data or median [25−75% interquartile ranges (IQR)] for non-normal distributions. Discrete variables were presented as percentages. Patient characteristics were compared by the Student's t-test, the Mann–Whitney *U* test (continuous variables), or Pearson's χ^2 test (categorical variables). NT-proBNP concentrations were log-transformed to reduce skew, modeled as continuous variables, and divided into quartiles. Kaplan–Meier, log rank, and univariate and multivariate Cox regression analyses were used for the outcomes of 90-day mortality. Univariate and multivariate logistic regression models were used to evaluate the associations between NT-proBNP concentrations and the severity of AKI and the 90-day renal recovery. Multivariable models were constructed including NT-proBNP levels, severe AKI and confounding factors that were significantly associated with outcomes in the univariate analyses ($P < 0.05$). Interaction testing was performed between the direction of change in NT-proBNP, before and after AKI, and the quartiles of baseline NT-proBNP levels, with renal outcomes. The association between the change in NT-proBNP levels and non-recovery from AKI was further examined within different quartiles of baseline NT-proBNP levels. *P*-values of < 0.05 were considered statistically significant for all analyses, including interaction terms.

3. Results

3.1. Clinical characteristics and survival outcomes of patients

A total of 1,160 eligible patients with CHF and AKI were enrolled and assessed in this study. Clinical characteristics and survival outcomes of the enrolled geriatric patients are shown in **Table 1**. A total of 482 patients (41.5%) died within 90 days of the onset of AKI. The age of non-survivors was higher than that of the survivors. Substantially elevated NT-proBNP levels (at baseline and at AKI diagnosis) and greater changes in NT-proBNP levels (ratio of NT-proBNP $_{atAKI}$/NT-proBNP $_{atbaseline}$) were found in the non-survivors. Stage 1 AKI occurred in 746 patients (64.3%), stage 2 in 245 patients (21.1%), and stage 3 in 169 patients (14.6%). In the non-surviving group, the percentage of patients with more severe AKI was higher than that in the surviving group (stage 3, 28.4 vs. 4.7% and stage 2, 25.7 vs. 17.8%, respectively). Moreover, non-survivors experienced a higher incidence of comorbidities including prior myocardial infarction, atrial fibrillation, COPD, and malignant tumors, as well as abnormal conditions including lower LVEF, proteinuria, extremity edema, infection, higher blood glucose, electrolyte disturbance, lower blood pressure, lower hemoglobin and higher cTnI. Additionally, survivors were more often treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and non-survivors were more often treated with loop diuretics.

3.2. AKI stages and NT-proBNP

As shown in **Supplementary Table 1**, a higher baseline NT-proBNP level is a protective factor [adjusted odds ratio (OR) = 0.78 95% CI = 0.68−0.89] against more severe stage AKI. Patients with the highest quartile of baseline NT-proBNP (Q4: NT-proBNP > 3,729 vs. Q1: NT-proBNP ≤ 480) had a lower incidence of more severe AKI. However, patients with greater changes in NT-proBNP represented as the ratio of NT-proBNP at AKI/NT-proBNP at baseline, had a significantly higher incidence of more severe AKI. Patients with a decreased change in NT-proBNP accompanying the episode of AKI had a lower risk (adjusted OR = 0.56, 95% CI = 0.34−0.91) of severe AKI.

Severe AKI may result from several associated risk factors. **Supplementary Table 2** shows that infection, higher fasting blood glucose, elevated phosphorus, lower hemoglobin, use of loop diuretics and non-use of ACEI/ARB were risk factors for more severe AKI. A lower level of baseline NT-proBNP and an increased change in NT-proBNP at AKI were associated with a severe AKI episode.

3.3. Survival analysis and hazard ratio for 90-day mortality based on NT-proBNP or AKI stages

Kaplan–Meier curves for 90-day mortality showed that patients with higher NT-proBNP levels at baseline (log rank, $P < 0.001$; **Figure 1A**) had higher mortality concerning the four quartiles of NT-proBNP levels. Patients with a decreased change in NT-proBNP had significantly higher survival rates (**Figure 1B**). With regard to AKI stages, the 90-day survival rate ranged from 70.4% in those with stage 1 to 49.4% and 18.9% in those with stage 2 and 3 AKI, respectively. Kaplan–Meier curves (**Figure 1C**) showed significantly increased mortality in stage 2 (log rank $P < 0.001$) and stage 3 (log rank $P < 0.001$) compared to stage 1.

TABLE 1 Patient characteristics between elderly survivors and non-survivors.

	Non-survivors (*n* = 482)	Survivors (*n* = 678)	*P*-value
Age (years), median (IQR)	91 (87,95)	90 (87,94)	0.044
Male, *n* (%)	432 (89.6)	595 (87.8)	0.350
Baseline eGFR, (mL/min/1.73 m^2), median (IQR)	67.2 (44.5,82.6)	70.1 (48.3,83.0)	0.196
NT-proBNP $_{atbaseline}$ (pg/mL), median (IQR)	2122 (790,5830)	907 (361,2512)	<0.001
NT-proBNP $_{atAKI}$ (pg/mL), median (IQR)	4460 (1731,12173)	1570 (526,4488)	<0.001
Ratio of NT-proBNP $_{atAKI}$/ NT-proBNP $_{atbaseline}$, median (IQR)	1.80 (1.02,3.75)	1.23 (0.88,2.56)	<0.001
AKI stages			<0.001
Stage 1 AKI, *n* (%)	221 (45.9)	525 (77.4)	-
Stage 2 AKI, *n* (%)	124 (25.7)	121 (17.8)	-
Stage 3 AKI, *n* (%)	137 (28.4)	32 (4.7)	-
LVEF, *n* (%)			<0.001
40% < LVEF < 50%	163 (33.8%)	90 (13.3%)	-
EF ≥ 50%	319 (66.2%)	588 (86.7%)	-
Medications, *n* (%)			
ACEI or ARB	67 (13.9%)	231 (34.1%)	<0.001
Beta-blockers	72 (14.9%)	122 (18.0%)	0.169
Aldosterone antagonist	125 (25.9%)	195 (28.8%)	0.288
Loop diuretics	195 (40.5%)	161 (23.7%)	<0.001
Comorbidities, *n* (%)			
Hypertension	350 (72.6)	544 (80.2)	0.003
Diabetes mellitus	244 (50.6)	379 (55.9)	0.083
Hyperlipidemia	190 (39.4)	325 (47.9)	0.004
Coronary heart disease	388 (80.5)	581 (85.7)	0.020
Prior myocardial infarction	165 (34.2)	165 (24.3)	<0.001
Atrial fibrillation	159 (33.0)	179 (26.4)	0.015
COPD	192 (39.8)	231 (34.1)	0.044
Malignant tumor	229 (52.4)	208 (47.6)	<0.001
Information at AKI			
Proteinuria, *n* (%)	288 (59.8)	357 (52.7)	0.017
Extremity edema, *n* (%)	214 (44.4)	204 (30.1)	<0.001
Infection[a]	275 (57.1)	235 (34.7)	<0.001
Fasting glucose (mmol/L), median (IQR)	8.54 (6.37,11.61)	6.9 (5.56,9.40)	<0.001
Potassium (mmol/L), median (IQR)	4.40 (3.91,4.90)	4.27 (3.90,4.70)	0.002
Calcium (mmol/L), median (IQR)	2.20 (2.04,2.37)	2.24 (2.13,2.37)	<0.001
Phosphorus (mmol/L), median (IQR)	1.20 (0.90,1.51)	1.10 (0.90,1.30)	<0.001
Systolic blood pressure (mmHg), median (IQR)	111 (100,124)	123 (109,136)	<0.001
Diastolic blood pressure (mmHg), median (IQR)	57 (50,66)	62 (55,70)	<0.001
Hemoglobin (g/dL), median (IQR)	95 (82,110)	109 (95,122)	<0.001
cTnI (μg/L), median (IQR)	0.108 (0.04,0.44)	0.04 (0.01,0.11)	<0.001

[a]Infection including: respiratory tract infection, gastrointestinal infection, urinary tract infection, skin and soft tissue infection, and fever of unknown origin.

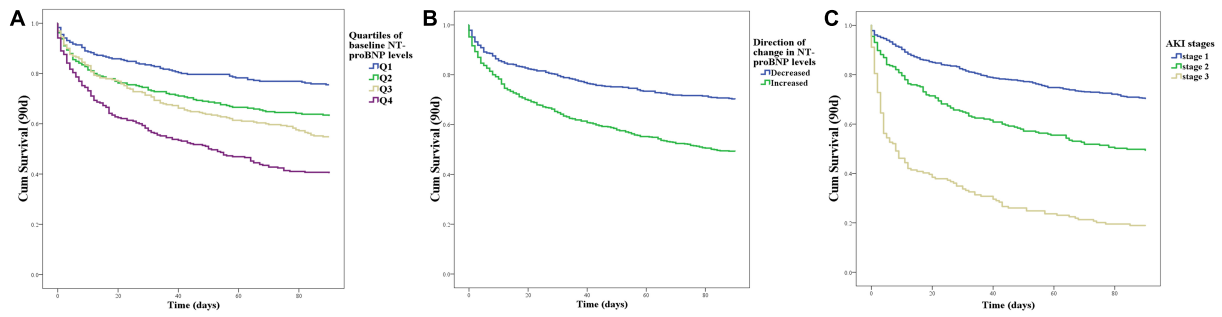

FIGURE 1
Patient survival on day 90 with respect to the NT-proBNP levels or AKI stages. **(A)** Kaplan–Meier curves for 90-day mortality with respect to the four quartiles of baseline NT-proBNP levels at baseline. **(B)** Kaplan–Meier curves for 90-day mortality with respect to the direction of change in NT-proBNP levels accompanied by an episode of AKI. **(C)** Kaplan–Meier curves for 90-day mortality with respect to the AKI stages.

TABLE 2 Univariable and multivariable Cox regression analysis for 90-day mortality by AKI stages and NT-proBNP levels.

	Unadjusted HR (95% CI)	Unadjusted *P* value	Adjusted HR (95% CI) in model 1[a]	Adjusted *P* value[a]	HR (95% CI) in model 2[b]	Adjusted *P* value[b]
More severe AKI	2.02 (1.62, 2.52)	<0.001	2.12 (1.70, 2.66)	<0.001	1.52 (1.20−1.93)	0.001
ln NT-proBNP $_{\text{at baseline}}$	1.37 (1.28, 1.46)	<0.001	1.46 (1.36, 1.56)	<0.001	1.27 (1.17, 1.38)	<0.001
Change in NT-proBNP						
Ratio of NT-proBNP $_{\text{at AKI}}$ to NT-proBNP $_{\text{at baseline}}$	1.008 (1.00,1.02)	0.075	1.01 (1.01,1.02)	0.001	1.01 (1.00,1.02)	0.007
Decreased change in NT-proBNP[c]	0.55 (0.44,0.70)	<0.001	0.49 (0.38,0.61)	<0.001	0.62 (0.48−0.79)	<0.001

[a]Mortality model 1: ln NT-proBNP at baseline, change in NT-proBNP, severe AKI.
[b]Mortality model 2: ln NT-proBNP at baseline, change in NT-proBNP, severe AKI, LVEF, Loop diuretics, ACEI/ARB, hypertension, hyperlipidemia, coronary heart disease, prior myocardial infarction, atrial fibrillation, COPD, malignant tumor, edema, infection, glucose, potassium, calcium, phosphorus, hemoglobin, cTnI, systolic blood pressure and diastolic blood pressure.
[c]Ratio of NT-proBNP $_{\text{atAKI}}$/NT-proBNP $_{\text{at baseline}}$ < 1 compared to ratio of NT-proBNP $_{\text{atAKI}}$/NT-proBNP $_{\text{at baseline}}$ ≥ 1.

TABLE 3 Univariable and multivariable logistic regression analysis for 90-day renal non-recovery by AKI stages and NT-proBNP levels.

	Unadjusted OR (95% CI)	Unadjusted *P* value	Adjusted[a] OR (95% CI) in model 1[a]	Adjusted[a] *P* value	Adjusted[b] OR (95% CI) in model 2[b]	Adjusted[b] *P* value
More severe AKI	1.88 (1.04, 3.43)	0.038	2.12 (1.15, 3.90)	0.016	2.11 (1.09, 4.10)	0.026
ln NT-proBNP $_{\text{at baseline}}$	1.04 (0.89, 1.21)	0.610	1.03 (0.88, 1.20)	0.714	1.01 (0.84, 1.21)	0.921
Change in NT-proBNP						
Ratio of NT-proBNP $_{\text{atAKI}}$ to NT-proBNP $_{\text{at baseline}}$	0.90 (0.83, 0.98)	0.010	0.89 (0.81, 0.97)	0.006	0.90 (0.83, 0.98)	0.014
Decreased change in NT-proBNP[c]	1.55 (1.03, 2.33)	0.034	1.63 (1.07, 2.48)	0.022	1.59 (1.02, 2.48)	0.041

[a]Mortality model 1: lnNT-proBNP at baseline, change in NT-proBNP, severe AKI.
[b]Mortality model 2: lnNT-proBNP at baseline, change in NT-proBNP, severe AKI, baseline eGFR, loop diuretics, atrial fibrillation, malignant tumor, proteinuria, glucose, calcium and hemoglobin.
[c]Ratio of NT-proBNP $_{\text{atAKI}}$/NT-proBNP $_{\text{at baseline}}$ < 1 compared to ratio of NT-proBNP $_{\text{atAKI}}$/NT-proBNP $_{\text{at baseline}}$ ≥ 1.

The Cox proportional hazard analyses (Table 2) showed that baseline lnNT-proBNP was associated with mortality in the unadjusted and adjusted models [adjusted hazard ratio (HR) = 1.27, 95% CI = 1.27−1.38]. A significant association between the direction of change in NT-proBNP levels and mortality was found. Patients with a decrease in NT-proBNP at the time of AKI diagnosis had a lower risk of mortality (adjusted HR = 0.62, 95% CI = 0.48−0.79). However, the continuous change in NT-proBNP, expressed by the ratio of NT-proBNP at AKI to NT-proBNP at baseline, was not significantly associated with mortality. Compared with those with stage 1 AKI, patients with more severe AKI had higher unadjusted and adjusted HR (1.52, 95% CI = 1.20–1.93) for 90-day mortality. Factors considered for the adjustments in Cox proportional hazard analyses for mortality are listed in Supplementary Table 3. In multivariable model, Lower LVEF, non-use of ACEI/ARB, malignant tumors, infection, higher blood glucose, higher phosphorus lower hemoglobin level, higher cTnI and lower systolic pressure were significantly associated with 90-day mortality.

TABLE 4 Odds ratios for 90-day renal non-recovery associated with decreased change in NT-proBNP within quartiles of baseline NT-proBNP levels.

	Unadjusted			Adjusted[a]		
	OR (95% CI)	*P* value	*P* value for interaction	OR (95% CI)	*P* value	*P* value for interaction
$NT\text{-}proBNP_{atbaseline}$						
Overall	1.55 (1.03−2.33)	0.034	0.002	1.66 (1.08, 2.56)	0.022	0.026
Q1 ≤ 480	4.72 (2.23, 9.99)	<0.001		3.94 (1.67, 9.28)	<0.002	
Q2 (480−1,295)	1.06 (0.46, 2.44)	0.889		1.07 (0.44, 2.58)	0.887	
Q3 (1,295−3,729)	1.21 (0.55, 2.67)	0.634		1.21 (0.53, 2.78)	0.657	
Q4 > 3729	0.64 (0.24, 1.74)	0.383		0.83 (0.29, 2.40)	0.725	

[a]With adjustment for more severe AKI, baseline eGFR, loop diuretics, proteinuria, and fasting glucose.

3.4. Renal recovery and NT-proBNP

Renal outcomes were evaluated in 678 survivors on day 90 after the episode of AKI. The renal function of 122 (18%) survivors did not recover from AKI. Significant variables (baseline eGFR, loop diuretics, atrial fibrillation, malignant tumor, proteinuria, glucose, calcium, and hemoglobin) from univariate logistic regression analyses and retained adjustors (NT-proBNP levels and AKI stages) were analyzed in multivariate models (**Supplementary Table 4**) as covariates. As shown in **Table 3**, the baseline NT-proBNP level was not associated with non-recovery in the unadjusted and adjusted logistic regression models. However, the decreased change in NT-proBNP level was shown to be a risk factor (adjusted OR = 1.59, 95% CI = 1.02−2.48) in the non-recovery of renal function. Patients with more severe AKI were associated with the non-recovery of renal function.

Interaction testing between the baseline NT-proBNP and the ratio of $NT\text{-}proBNP_{atAKI}$ to $NT\text{-}proBNP_{atbaseline}$ for non-recovery of renal function was not statistically significant. However, interaction testing was significant (adjusted $P = 0.026$) for the interaction between the direction of change in NT-proBNP and the quartiles of baseline NT-proBNP levels. In the lowest quartile of baseline NT-proBNP (Q1, NT-proBNP ≤ 480), patients with decongestion accompanied by an episode of AKI had significantly worse renal outcomes (**Table 4**). Meanwhile, among patients with higher NT-proBNP levels at baseline (from Q2 to Q4), a decreased change in NT-proBNP levels did not significantly affect renal outcomes.

4. Discussion

Chronic heart failure is a common disease in the elderly, with the prognosis worsening with age (12). Chronic and acute renal insufficiency are highly prevalent in patients with CHF and associated with poor outcomes (13). According to previous studies (14, 15), the prevalence of heart failure with preserved ejection fraction (HFpEF) or mildly reduced ejection fraction (HFmrEF) increases sharply with age. Therefore, elderly patients with a history of HFmrEF or HFpEF (LVEF > 40) were included in this study.

Elderly patients are often frail and have multiple comorbidities (such as hypertension and coronary heart disease), which could contribute to the decline in heart and renal function, leading to the deterioration of systemic functions and worse outcomes (16). Elderly patients with HFmrEF or HFpEF had more comorbidities and died more often from non-cardiovascular causes, compared to those with heart failure with reduced ejection fraction (HFrEF) (15, 17). Infection, malignant tumors and lower systolic pressure were significantly associated with 90-day mortality in patients with AKI in CHF according to this study.

Elderly patients have the highest prevalence of HF, and a positive correlation between natriuretic peptides and age has been found (18). Natriuretic peptides are released from the heart, in response to wall stretch induced by volume or pressure overload. BNP and NT-proBNP correlate with markers of cardiac dysfunction and volume overload and are clinically used as valuable diagnostic and prognostic markers of HF (19). Due to the longer half-life of NT-proBNP compared to that of BNP (120 vs. 22 min), NT-proBNP is more stable in reflecting changes in hemodynamics. Natriuretic peptides are predictors of all-cause mortality in patients with HF, as previously reported (20). NT-proBNP-guided decongestive treatment has been suggested in patients with CHF (21). According to our study, both high levels of baseline NT-proBNP and an increased change in NT-proBNP at follow-up were associated with a higher risk of all-cause mortality. A decreased change in NT-proBNP, accompanying the episode of AKI was considered protective for survival in elderly patients with CHF.

Cardiorenal syndrome is a common clinical condition in the elderly. Cardiorenal syndrome occurs when dysfunction of either the heart or kidneys progresses to the other organ, leading to both cardiac and renal failure. Patients with CHF can develop AKI during follow-up (13). Pre-renal AKI is prevalent in patients with HF due to decreased renal perfusion from any cause, such as HF or depletion of effective circulating volume (6). Natriuretic peptides are important biomarkers of cardiorenal syndrome and play essential roles in its progression (22). Elevated NT-proBNP/BNP ratios were found to predict worsening renal function in patients with acute HF (23). Many mechanisms have been proposed to explain the decline in renal function in patients with HF, including low cardiac output and renal congestion due to volume overload (24). Elevated NT-proBNP was a significant independent predictor for the accelerated progression of renal dysfunction to end-stage kidney disease, after adjustment for other variables was made (25). In our study, an increased change in NT-proBNP, rather than a high baseline level of NT-proBNP, was found to be associated with more severe AKI. Thus, continuous monitoring of NT-proBNP is recommended in patients with CHF.

The role of kidney dysfunction in mortality has been frequently observed in patients with HF, especially acute decompensated HF. Improving renal function was previously reported to be paradoxically associated with worse outcomes in acute HF, but outcomes may

differ based on the response to decongestion (decrease in NT-proBNP) (4). The relationship of kidney dysfunction with mortality in acute HF was not independent on the congestion status and differed by BNP trajectory. Worsening renal function accompanied by decongestion is not associated with worse outcomes, whereas patients with worsening renal function and residual congestion have a particularly poor prognosis (26, 27). However, few studies have examined the interesting relationship between changes in NT-proBNP and kidney dysfunction in patients with CHF. In this study, 41.5% of elderly patients died within 90 days of AKI onset. The more severe stages of AKI were shown to predict mortality and renal outcomes in elderly patients with CHF–independent of NT-proBNP levels. The decline of renal function should be avoided in patients with CHF.

In this study, 18% of survivors did not fully recover from AKI. Compared with non-elderly patients, impaired recovery of kidney function after AKI is more common in elderly patients (28). Non-recovery from AKI in elderly patients leaves this population at a higher risk of long-term morbidity and mortality (29). Therefore, avoiding AKI episodes and facilitating prompt prophylactic strategies in the elderly is vital to improve prognosis. A decreased change in NT-proBNP during AKI was shown to be a risk factor for the non-recovery of renal function–an effect that was most obvious in patients with low baseline NT-proBNP levels. In addition to HF, volume depletion (as indicated by decreased serum NT-proBNP levels) is another important cause of pre-renal AKI in the elderly. Fluid removal has been observed to increase the risk of worsening renal function in patients with acute HF (30). Elderly patients are more prone to dehydration, owing to impaired renal concentrating ability, diuretic use, and restricted ability to access fluids (6). According to our study, a decrease in NT-proBNP was found to prevent severe AKI in patients with CHF. However, a decrease in NT-proBNP and the use of loop diuretics predicted a higher risk of non-recovery of renal function in patients with AKI in CHF–especially in patients with low baseline NT-proBNP levels. Thus, excessive fluid removal may result in the non-recovery of the kidneys. Continuous monitoring of NT-proBNP is recommended in elderly patients with CHF. Avoiding excessive changes in NT-proBNP may be protective for the survival and renal injury prognosis.

There were several limitations of our study. This was a retrospective study in a single center that was restricted to a former member of the armed forces. Identified or unidentified confounders may have influenced the result. We lacked adequate data on the history of CHF (detailed echocardiogram indicators and vascular calcification) and the etiology of HF was difficult to precisely determine. We also lacked detailed data at AKI onset. In addition to BNP and extremity edema, lung congestion, liver congestion, and other indicators of volume and congestion status were unavailable and not included in our analyses. The causes of AKI and mortality in elderly patients with CHF are diverse and may have influenced the result. Subgroup analysis based on different causes is further required.

In conclusion, a decreased change in NT-proBNP was associated with a lower risk of more severe AKI in elderly patients with CHF. Elevated levels of baseline NT-proBNP and increased change in NT-proBNP accompanying the episode of AKI predicted a higher 90-day mortality in elderly patients with a CHF history. However, an excessive decrease in NT-proBNP is a risk factor for the non-recovery of renal function following AKI–especially in elderly CHF patients with low baseline NT-proBNP levels. Continuous monitoring of NT-proBNP is recommended in elderly patients with CHF and avoiding excessive changes in NT-proBNP may be protective for survival and renal injury prognosis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Chinese People's Liberation Army General Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JH and XZ contributed to the data analysis and drafting the manuscript. ZW contributed to the data collection and data analysis. YL, YZ, JZ, XW, HC, GY, and QM contributed to the data collection of the study. QC and QA contributed to the design of the study and data analysis. All authors reviewed the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1104787/full#supplementary-material

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MicroRNA-21 mediated cross-talk between cardiomyocytes and fibroblasts in patients with atrial fibrillation

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Background: Atrial fibrosis represents a major hallmark in disease progression of atrial fibrillation (AF). We have previously shown that circulating microRNA-21 (miR-21) correlates with the extent of left atrial fibrosis in patients undergoing catheter ablation for AF and can serve as a biomarker to predict ablation success. In this study, we aimed to validate the role of miR-21-5p as a biomarker in a large cohort of AF patients and to investigate its pathophysiological role in atrial remodeling.

Methods: For the validation cohort, we included 175 patients undergoing catheter ablation for AF. Bipolar voltage maps were obtained, circulating miR-21-5p was measured, and patients were followed-up for 12 months including ECG holter monitoring. AF was simulated by tachyarrhythmic pacing of cultured cardiomyocytes, the culture medium was transferred to fibroblast, and fibrosis pathways were analysed.

Results: 73.3% of patients with no/minor LVAs, 51.4% of patients with moderate LVAs and only 18.2% of patients with extensive LVAs were in stable sinus rhythm (SR) 12 months after ablation ($p<0.01$). Circulating miR-21-5p levels significantly correlated with the extent of LVAs and event-free survival. *In-vitro* tachyarrhythmic pacing of HL-1 cardiomyocytes resulted in an increased miR-21-5p expression. Transfer of the culture medium to fibroblasts induced fibrosis pathways and collagen production. The HDAC1 inhibitor mocetinostat was found to inhibit atrial fibrosis development.

Conclusion: We validated miR-21-5p as a biomarker that reflects the extent of left atrial fibrosis in AF patients. Furthermore, we found that miR-21-5p is released *in-vitro* from cardiomyocytes under tachyarrhythmic conditions and stimulates fibroblasts in a paracrine mode to induce collagen production.

KEYWORDS

miR-21, atrial fibrillation, fibrosis, low-voltage area, mocetinostat

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a life-time risk of 1 in 3 individuals in Europe (1). AF accounts for 20–30% of all strokes and can also lead to congestive heart failure, cognitive dysfunction, cardiovascular morbidity and mortality. Its prevalence is more than 9% for those above 80 years compared to 0.1% for those under 55 years (2, 3). A common theory states that ectopic foci located in the pulmonary veins trigger the arrhythmia, whereas its perpetuation is mediated by atrial fibrosis in the atria themselves, serving as the substrate that creates multiple functional and structural re-entry mechanisms (4, 5). Importantly, frequent AF episodes fuel the development of adverse atrial remodeling with substrate creation ("AF begets AF"). It is well established that the extent of left atrial fibrosis is a key negative predictor for AF recurrence after catheter ablation (6, 7).

MicroRNAs, non-coding, small (18–22 nucleotides long), and conserved RNAs have been known to play crucial roles in the pathogenesis of cardiac fibrosis. Among numerous microRNAs, microRNA-21 (miR-21) plays an exceptional role in the pathogenesis of tissue fibrosis. miR-21 signaling is critical in atrial fibrotic remodeling of an AF rat model (8), in lung fibrosis (9) and after myocardial ischemia in mice (10).

We have previously shown that circulating miR-21 is upregulated in patients with AF and that its serum concentration measured in blood samples obtained from the left atrium (LA) correlates with the extent of left atrial low voltage areas (LVAs) (11), which give an estimation of fibrosis (12). MiR-21 strongly correlate to treatment outcome after catheter ablation of AF, thereby serving as a biomarker to predict potential treatment success.

In this study, we aimed to validate the role of miR-21-5p (here onwards referred as miR-21) as a biomarker for AF in a large cohort of patients by assessing miR-21 concentrations and correlating them to left atrial fibrosis. In addition, we analyzed the pathophysiological role of miR-21 *in-vitro* using disease-modeling with cultured cardiomyocytes and fibroblasts.

2. Materials and methods

2.1. Patients

A total of 175 consecutive patients >18 years old who presented for catheter ablation due to AF (paroxysmal and persistent) at the university hospital RWTH Aachen were included in this study. 165 patients had their first ablation for atrial fibrillation, 10 had a re-do ablation. All patients gave their informed consent. The study was approved by the local ethics committee (EK054/21). All clinical characteristics of patients are listed in Table 1.

TABLE 1 Demographic and clinical characteristics of AF patients included in the study.

Age, year	66.9 ± 8.9
Male	109 (62.2%)
BMI, kg/m^2	28.8 ± 7.3
Fibrosis stage (left atrial LVA)	
0–10%	65 (37.14%)
10–30%	39 (22.29%)
>30%	71 (40.57%)
EHRA-Score	2.3 ± 0.65
CHA_2DS_2-VASc score	2.7 ± 1.5
Left atrial diameter, mm	42 ± 2.1
Systolic blood pressure, mmHg	127 ± 12.4
LV ejection fraction, %	51.3 ± 8.2
Mitral valve disease (>first degree)	15 (8.5%)
Previous stroke	16 (9.1%)
Previous PCI	31 (17.7%)
Previous myocardial infarction	17 (9.7%)
Previous CABG	5 (2.9%)
LV hypertrophy	49 (28%)
Chronic kidney disease	44 (25.1%)
Type 2 diabetes mellitus	32 (18.2%)
OSAS	16 (9.1%)
Hyperlipidemia	100 (57.1%)
Ablation strategy	
PVI RF	175 (100%)
Left atrial roof line	41 (23.4%)
Mitral line	60 (34.2%)
CFAE ablation	1 (0.57%)
RA isthmus line	93 (53.1%)

[a]AF, Atrial fibrillation; BMI, Body mass index; LVA, Low-voltage area; EHRA, European heart rhythm association; CHA2DS2-VASc, Congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, stroke (double point), vascular disease, age 65–74 years (double point) and sex category (female); LV, Left ventricle; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; OSAS, Obstructive sleep apnoea syndrome; PVI, Pulmonary vein isolation; RF, Radiofrequency; CFAE, Complex fractionated electrogram; RA, Right atrium.

2.2. Mapping

After transseptal puncture, an electrical cardioversion was performed to achieve sinus rhythm (SR). A high-density 3D-anatomical voltage map in SR was obtained, using the Carto3 System (Johnson & Johnson) with a Pentaray high density mapping catheter. A minimum of 6,000 voltage points were obtained per patient. A local electrogram of <0.5 mV during SR was attributed as LVA. The Carto-3 built-in software was used to remove the pulmonary veins and the mitral anulus. The percentage of LVAs was then calculated from the surface of the left atrial corpus. In case of a re-do ablation, lesions generated from the first PVI were excluded for calculation of LVAs. Maps shown in Figure 1A are color-coded in red (<0.5 mV, substantial LVAs) or purple (>0.5 mV, normal voltage). Patients were divided into three groups according to the extents of LVAs: group A (<10% LVAs), group B (10–30% LVAs), and group C (>30% LVAs). Prior to ablation, 20 ml blood was drawn from a peripheral artery (radial artery) and a peripheral vein (femoral vein) and processed for microRNA isolation. The miR-21 concentration was determined as described previously (11).

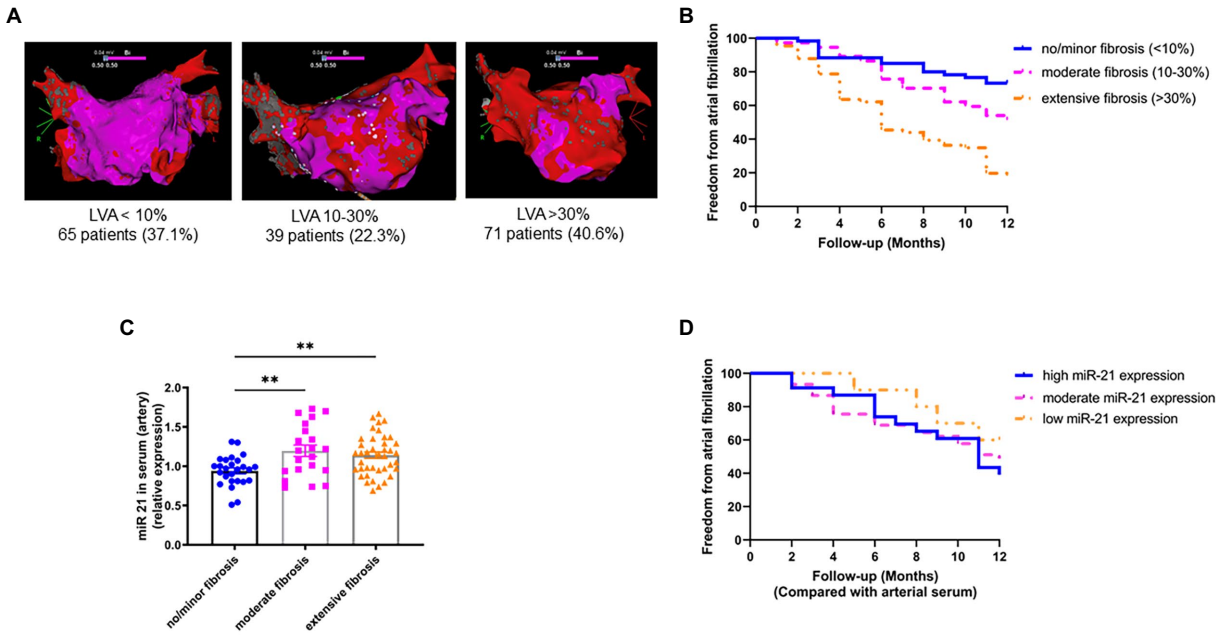

FIGURE 1
Circulating miR-21 correlates with left atrial LVAs and treatment outcome. **(A)** Representative high-density bipolar voltage maps from patients undergoing AF catheter ablation. No/minor LVAs: 37.1%, moderate LVAs: 22.3%, Extensive LVAs: 40.6% (semi-quantitative illustration, no scale bar available). **(B)** Left atrial LVAs strongly correlate with treatment outcome after ablation. Patients in SR after 12 months: 73.3% having no/minor LVAs, 51.4% having moderate LVAs and 18.2% having extensive LVAs. *n*=37–66. **(C)** Circulating miR-21 positively correlates with left atrial LVAs. Patients with low miR-21 serum concentration had low LVAs and patients with high miR-21 had significantly more LVAs. *n*=21–40. **(D)** Circulating miR-21 in arterial serum correlates with treatment outcome after catheter ablation. 39.1% of patients with high miR-21 serum levels were in stable SR 12 months after ablation, whereas 48.9% with moderate miR-21 concentration and 60% with low miR-21 concentration were free from AF 12months after ablation. *n*=10–45. Data are expressed as mean±SEM. ***p*<0.01. LVAs=low voltage area.

2.3. Ablation

All patients considered for ablation underwent pulmonary vein isolation with a force-controlled irrigated radiofrequency ablation catheter (Thermocool Smarttouch SF, Johnson & Johnson). Additional ablation strategies targeting the substrate were allowed if indicated by the operator. Detailed follow up procedures is available in the Supplementary material.

2.4. *In-vitro* AF model

The medium of confluent cultured murine atrial cardiomyocytes (HL-1 cells) was substituted with supplemented Claycomb medium with reduced (2%) FBS and paced with 1 Hz (simulating SR) or 5 Hz, 25 V, 6 ms with an 80% variability (simulating AF) for 4.5 h in a 6 well C-dish culture dish using the c-Pace EP cell culture stimulator (Ionoptix). The voltage was confirmed by Rohde and Schwarz RTO 1024 Oscilloscope/2Ghz 10 GS a/s. A control group was maintained under unstimulated conditions. After 4.5 h, the medium was centrifuged at 1,200 rpm for 5 min and the supernatant was transferred to NIH/3T3 fibroblasts. Pathway analysis was performed using a profiler PCR array (RT2 profiler PCR Array mouse fibrosis 96 well format, Qiagen), western blot and immunofluorescence. A luciferase reporter assay under the control of a miR-21 promoter was used for drug screening with selected FDA-approved drugs. Expanded methods section is available in the Supplementary material.

2.5. Statistical analysis

For patient sample analysis, univariable cox regression analysis was performed to correlate recurrence of arrhythmia to individual clinical covariates. Multivariable linear regression analyses were performed to correlate miR-21 expression and left atrial LVA for recurrence of arrhythmia after adjusting for the covariates: sex, age, congestive heart failure, diabetes mellitus, mitral valve disease and hypertension. All risks were estimated using the Kaplan–Meier estimator with 95% confidence intervals. All other values for *in-vitro* experiments are expressed as mean ± SEM. Student's *t*-test or one-way ANOVA were performed. Data were analysed using GraphPad Prism.

3. Results

3.1. LVAs and miR-21 expression correlates with ablation success in AF patients

High density 3D-anatomical voltage mapping of patients undergoing catheter ablation for AF (all-comer collective at the university hospital RWTH Aachen, Germany) showed that 37.1% had no or only minor LVAs (group A, <10% of the LA surface), 22.3% had moderate LVAs (group B, 10–30% of the LA surface) and 40.6% had extensive LVAs (group 3, >30% of the LA surface; Figure 1A). Successful pulmonary vein isolation was achieved in all patients. An additional left atrial roof line ablation was performed in 23.4%, a

mitral line in 34.2%, and a right atrial isthmus line in 53.1% of patients. Ablation of complex fractionated electrograms was performed in 0.6% of cases. All baseline characteristics and the procedure details are listed in Table 1.

We found a strong correlation between LVAs and outcome after catheter ablation. 73.3% of patient with no/minor LVAs, 51.4% of patients with moderate LVAs and only 18.2% of patient with extensive LVAs were in stable SR 12 months after ablation (Figure 1B). After adjustment for multiple confounders, a 1% increase in LVA resulted in a 1.021 (1.013–1.029. $p < 0.01$) hazard ratio of AF recurrence (Table 2).

Patients were assigned in 3 groups according to their miR-21 serum concentration: group I with very high relative miR-21 expression (>1.20 AU), group II with intermediate relative miR-21 expression (0.80–1.20 AU), and group III with very low miR-21 serum concentration (<0.80 AU). We found a significant positive correlation between LVAs and circulating miR-21 (in arterial serum; Figure 1C). After adjusting multiple confounders, an increase of 1 AU miR-21 (arterial serum) concentration resulted in a 1.104 (0.398–3.063, $p < 0.850$) hazard ratio of AF recurrence (Table 2).

Since presence of left atrial LVAs is strongly correlated with treatment outcome and LVAs are correlated with miR-21 serum concentrations, we also found a correlation between miR-21 and treatment outcome. Figure 1D shows the Kaplan–Meier curve on event-free survival after ablation of AF. 39.1% of patients in group I were in stable SR during the observation period, whereas 48.9% of patients in group II and 60.0% patients in group III had SR 12 months after ablation.

TABLE 2 Clinical characteristics and risk factor associated with AF patients.

	Hazard ratio	95% confidence interval	*p*-value
AF recurrence per 1 AU increase in miR-21 (artery)	1.104	0.398–3.063	0.850
AF recurrence per 1 AU increase in miR-21 (vein)	0.191	0.083–0.440	<0.01*
AF recurrence per 1% increase in LVAs	1.021	1.013–1.029	<0.01*
Male sex	0.94	0.573–1.543	0.807
Age (per year)	1.005	0.979–1.031	0.718
BMI (per unit)	1.016	0.970–1.064	0.502
Previous PCI/ CABG	1.118	0.610–2.050	0.717
Previous myocardial infarction	1.052	0.455–2.434	0.905
LV hypertrophy	1.106	0.655–1.866	0.707
Chronic kidney disease	1.607	0.970–2.663	0.066
Hypertension	1.474	0.878–2.475	0.142
CHA2DS2-VASc score (per point)	1.032	0.877–1.216	0.702
LVEF, %	0.969	0.941–0.997	0.028*
LA size, mm	1.075	1.021–1.133	<0.01*
OSAS	0.817	0.328–2.034	0.664
Mitral valve disease	1.997	0.985–4.051	0.055
Diabetes mellitus	0.973	0.510–1.858	0.934

[b]AF, Atrial fibrillation; AU, Arbitrary unit; miR-21, microRNA-21; LVA, Low-voltage area; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; LV, Left ventricle; EHRA, European heart rhythm association; LVEF, Left ventricular ejection fraction; LA, Left atrium; OSAS, Obstructive sleep apnoea syndrome. *$p < 0.05$.

3.2. Irregular tachyarrhythmic pacing of HL1 cardiomyocytes leads to increased miR-21 expression

To study the underlying mechanisms of miR-21 mediated fibrosis, murine atrial cardiomyocytes (HL1 cells) were either paced regularly (simulating SR; Figure 2A) or with irregular elevated frequency simulating AF (Figure 2B). After 4.5 h of pacing, miR-21 was found to be overexpressed only in the cardiomyocytes of AF paced group (Figure 2C) and released to the medium (Figure 2D). A 21-fold increment of miR-21 expression was observed in AF paced cells medium compared to SR ($p < 0.0001$). The medium from paced (AF and SR) or control HL1 cardiomyocytes was transferred to NIH/3T3 fibroblast and incubated. Relative expression of miR-21 in the fibroblasts, 24 or 72 h after the medium transfer, was relatively constant (Figure 2E).

3.3. miR-21 stimulates fibroblasts while anti-miR-21 prevents the activation of fibroblasts for collagen production

To evaluate whether cardiomyocyte specific overexpression of miR-21 induces fibrosis, the medium of paced (AF and SR) and control HL1 cardiomyocytes was transferred to NIH/3T3 fibroblast and incubated. A fibrosis profiling array obtained from the fibroblasts showed strong induction of 24 transcripts associated with fibrosis pathways and collagen expression (Figure 3A). Most of the upregulated candidates were related to the TGF-β pathway (TGF-β 1 and its receptors, Ccl11/eotaxin-1- a promoter of TGF-β receptor, Integrin-av- an activator of TGF-β, Endoglin- a glycoprotein of the TGF-β receptor, inhibin- a member of the TGF-β superfamily of proteins and smad2 and 3- downstream actors of the TGF-β signaling). Moreover, two TGF-β pathway inhibitors, SMAD family member 7 (smad7) and decorin, were not detectable. Likewise, the fibrotic markers collagen1a, matrix-metalloproteinase-2 and 9 (MMP2 and 9), tissue inhibitor of metalloproteinases-3 (Timp3), connective tissue growth factor and marker for epithelial mesenchymal transition in fibroblast (Snail1) were upregulated.

TGF-β is key mediator of tissue fibrosis and a central regulator of fibrosis response (13). However, TGF-β has a pleiotropic effect and targeting it as therapeutic marker is complex (14). As fibrosis is the result of activated fibroblast that has been transformed to

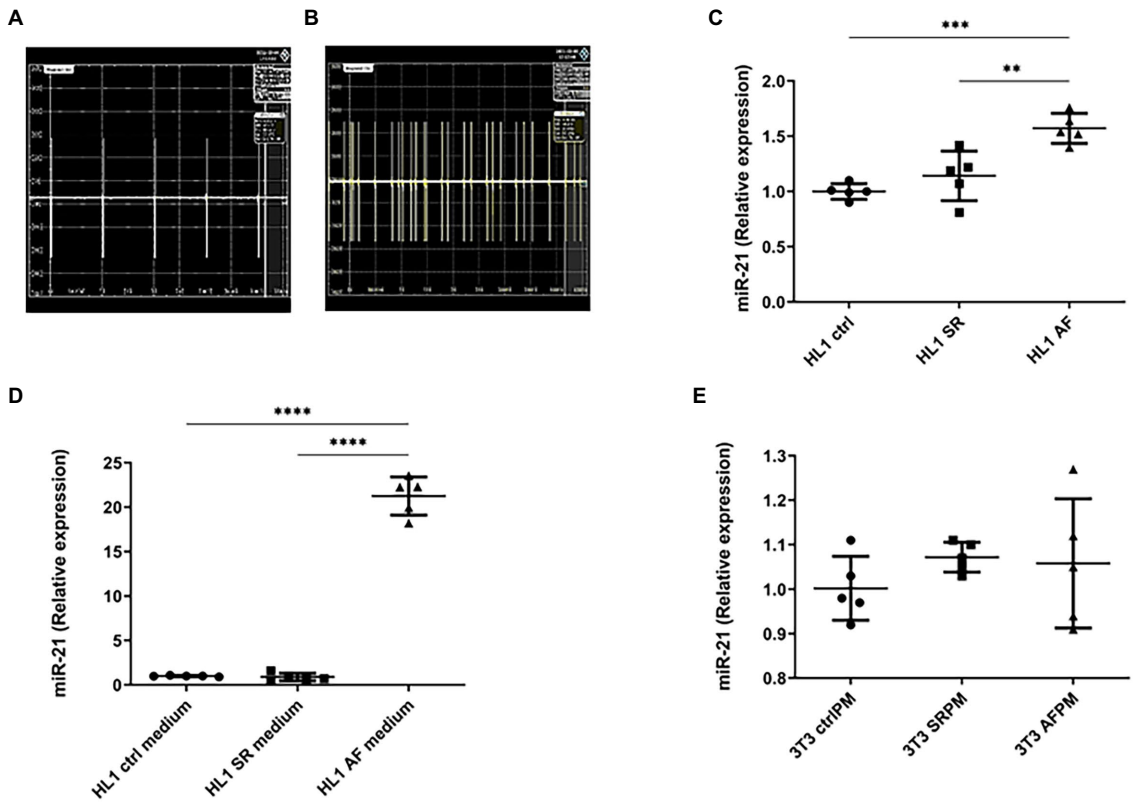

FIGURE 2
AF model with cultured murine cardiomyocytes (HL-1 cells) and fibroblast (NIH/3T3 cells). **(A)** Sinus rhythm was simulated using a regular wave form at 25V 6ms 1Hz. **(B)** For the simulation of AF, a faster, irregular pacing protocol was used (25V 6ms 5Hz, 80% variability). **(C)** After 4.5h of pacing, increased miR-21 expression under tachyarrhythmic conditions could be observed in the HL-1 cardiomyocytes. **(D)** miR-21 concentration in the medium of cardiomyocytes that were held under tachyarrhythmic conditions was strongly increased, whereas no release of miR-21 to the medium under SR conditions could be observed. **(E)** No increase in miR-21 expression in NIH/3T3 fibroblast was observed, when treated with control, SR and AF paced medium from HL1 cardiomyocyte cells. **(C–E)** Representative data out of 3 similar experiments. Data are expressed as mean±SEM. ****p<0.0001, ***p<0.001, **p<0.01. CtrlPM, control pacing medium; SRPM, sinus rhythm pacing medium; AFPM, atrial fibrillation pacing medium.

myofibroblast, we decided to analyse the marker of activated fibroblasts. For this, we examined alpha-smooth muscle actin (α-SMA) and connective tissue growth factor (Ctgf). α-SMA is a biomarker for myofibroblast (15) and Ctgf is a central mediator of fibrosis produced by fibroblast that stimulates myofibroblast function and cardiac fibrosis (16).

Fibrosis profiler array data was confirmed by RT-PCR, western blot and immunofluorescence. mRNA expression of α-SMA and Ctgf was significantly increased in fibroblasts that received the AF paced medium compared to cells that received SR medium (4.5 fold for α-SMA, $p < 0.0001$ and 1.5 fold for Ctgf, $p < 0.05$; Figures 3B,C). The corresponding proteins were also upregulated, as shown by western blot and immunofluorescence (Figures 4E–I).

3.4. The HDAC1 inhibitor mocetinostat and anti-miR-21 attenuates miR-21 release in AF and fibrosis development

An *in-vitro* screen was performed with selected FDA-approved drugs using a miR-21 luciferase promoter assay (Supplementary Figure 2). Among the screened drugs, the HDAC1 inhibitor mocetinostat was found to significantly inhibit miR-21 expression (Figure 4A) in a dose dependent manner. Therefore, we decided to further evaluate the potential of mocetinostat to intervene the miR-21 pathway and curb the fibrotic pathway. Mocetinostat at a concentration of 1 μM reduced miR-21 activity by 1.82 fold, whereas a 2.5 μM concentration led to 7.64 fold and 5 μM concentration to a 6.4 fold reduction in miR-21 activity. PCR profiling array of fibroblasts incubated with AF, SR or control medium and later treated with either mocetinostat or anti-miR-21 showed that inhibition of miR-21 reversed the activation of the pro-fibrotic transcripts with the exception of Smad3 and restored the expression of the TGF-β pathway inhibitors smad7 and decorin (Figure 4B). Mocetinostat led to a reduction of Ctgf expression (2.8 fold, $p < 0.001$) and α-SMA expression (around 20 fold, $p < 0.0001$) in fibroblasts incubated with AF-paced medium (Figures 4C,D). The anti-fibrotic effects of mocetinostat and anti-miR-21 could also be confirmed by western blot and immunofluorescence (Figures 4E–I, Supplementary Figure 3). Mocetinostat reduced Ctgf by 20% ($p < 0.05$) and α-SMA expression by 43% ($p < 0.01$) in fibroblasts incubated with AF-paced medium (Figures 4F,G).

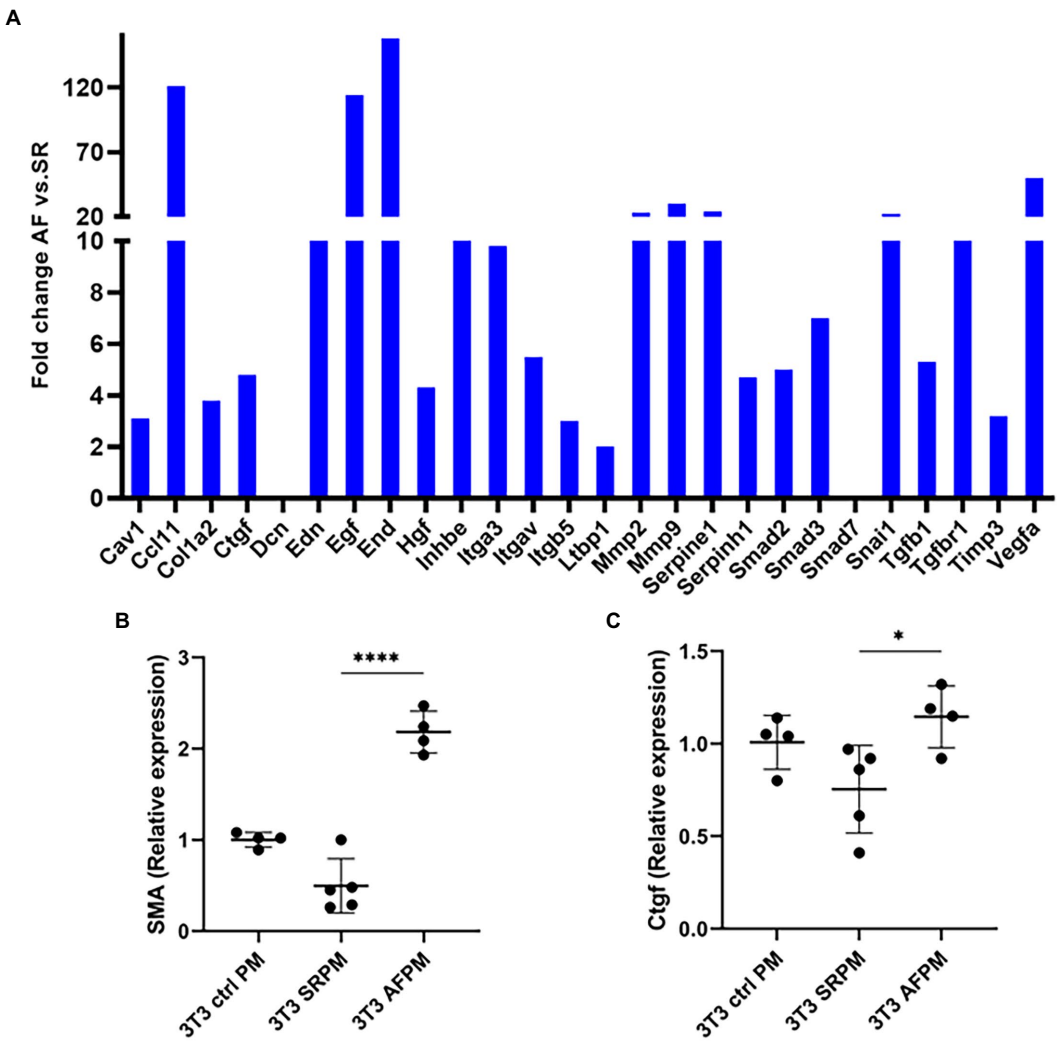

FIGURE 3
miR-21 released from cardiomyocytes induces pro-fibrotic pathways in NIH/3T3 fibroblasts. **(A)** The medium of tachyarrhythmic paced cardiomyocytes was transferred to fibroblasts and incubation was done for 72h, then the pathway analysis was performed. A fibrosis profiler array showed a strong induction of pro-fibrotic pathways and collagen expression in the NIH/3T3 cells incubated with AF medium. Each sample type represents a pool of one 6 well plate. The induction is especially true for the fibrosis markers α-SMA **(B)** and Ctgf **(C)**. **(B,C)** Representative data out of 3 similar experiments. Data are expressed as mean±SEM. ****$p<0.0001$, *$p<0.05$. Cav1: caveolin-1, Ccl11: c-c motif chemokine 11, Col1a2: collagen type I alpha 2, Ctgf: connective tissue growth factor, Dcn: decorin, Edn: endothelin, Egf: epidermal growth factor, End: endoglin, Hgf: hepatocyte growth factor, Inhbe: inhibin subunit beta E, Itga3: integrin subunit alpha3, Itgav: integrin alpha V, Itgb5: integrin beta 5, Ltbp1: latent transforming growth factor-β-binding protein-1, Mmp2: matrix metalloproteinase-2, Mmp9: matrix metalloproteinase-9, Serpine1: serpin family E member 1, Serpinh1: serpin family H member 1, Smad2: SMAD family member 2, Smad3: SMAD family member 3, Smad7: SMAD family member 7, Snai1: snail family transcriptional repressor 1, Tgfb1: transforming growth factor beta 1, Tgfbr1: transforming growth factor beta receptor 1, Timp3: tissue inhibitor of metalloproteinases-3, Vegfa: vascular endothelial growth factor a, α-SMA: alpha smooth muscle actin, Ctrl PM: control pacing medium, SRPM: sinus rhythm pacing medium, AFPM: atrial fibrillation pacing medium.

4. Discussion

Atrial fibrillation is a complex disease with multiple pathomechanisms. A generally recognized model of AF states that ectopic foci located in the pulmonary veins initiate the arrhythmia. AF then leads to adverse atrial remodeling with collagen production, creating micro-re-entries in the left atrium that sustain the disease. The theory that "AF begets AF" is a well-established clinical observation, however, exact mechanisms of LA fibrosis development in AF are poorly understood.

Our study shows that:

1. Circulating miR-21 correlates with left atrial fibrosis in a large cohort of AF patients undergoing catheter ablation
2. miR-21 also correlates with event-free survival after ablation and is a reliable predictor for treatment outcome
3. miR-21 is released *in-vitro* from cultured cardiomyocytes under tachyarrhythmic conditions
4. miR-21 stimulates fibroblasts in collagen expression and contributes to adverse atrial remodeling
5. Atrial remodeling can be mitigated *in-vitro* by the HDAC1-inhibitor mocetinostat, which might serve as a novel therapeutic option for AF patients

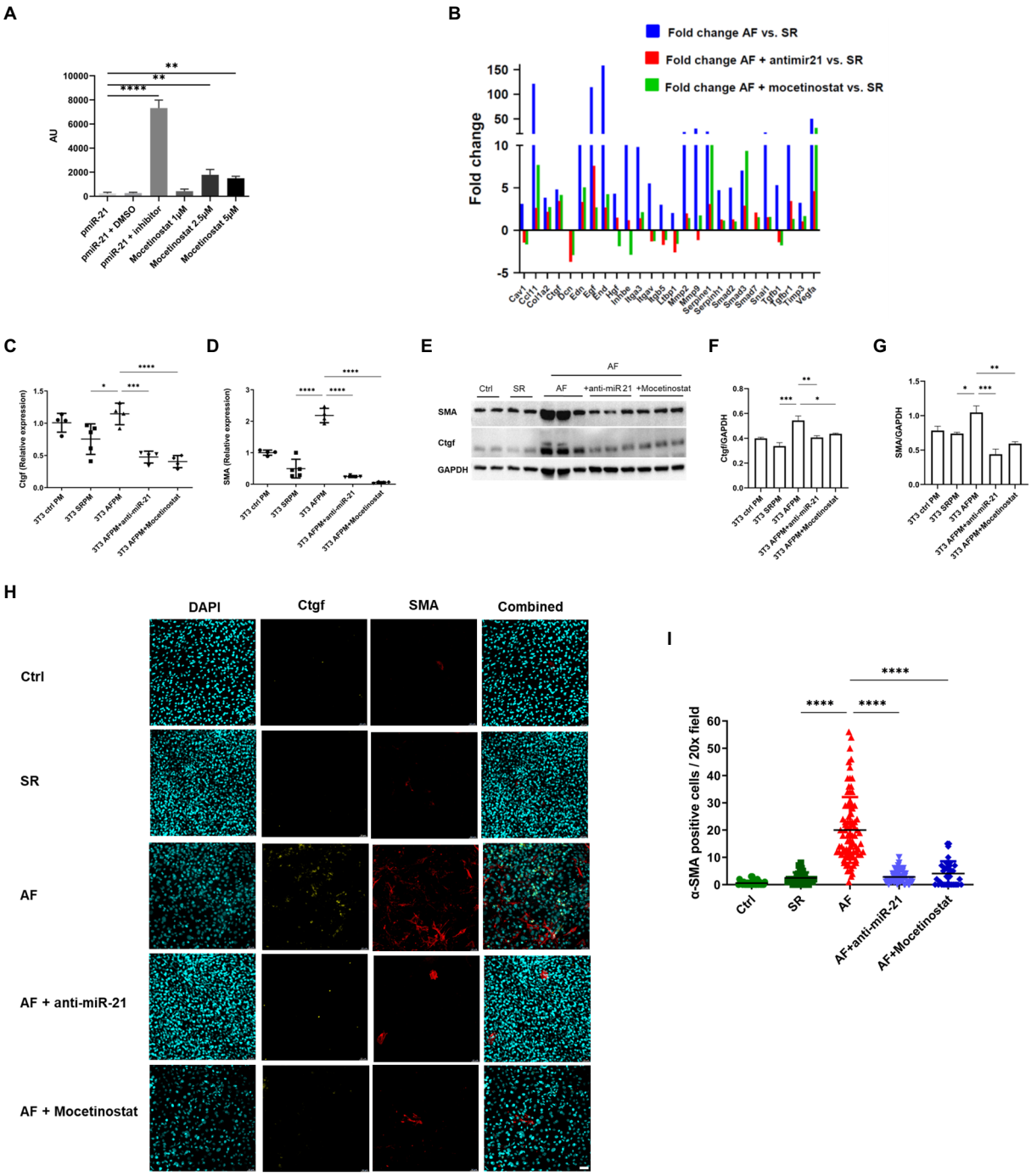

FIGURE 4
The HDAC1 inhibitor mocetinostat attenuates miR-21 expression and collagen production in AF. **(A)** A luciferase assay was performed with miR-21, miR-21 with DMSO, miR-21 and miR-21 inhibitor, different concentration of mocetinostat. **(B)** Mocetinostat attenuated activation of pro-fibrotic pathways and collagen expression in NIH/3T3 fibroblasts incubated with medium from AF- paced cells. Anti-mir-21, that specifically antagonizes miR-21 in the medium, showed similar effects. Each sample type represents a pool of one 6 well plate. Real time PCR **(C,D)**, Western blot analysis **(E–G)** and immunofluorescence staining **(H,I)** antibody against Ctgf and α-SMA and counterstaining with DAPI, representative pictures shown in **(H)** of the fibrosis markers Ctgf and SMA in fibroblasts incubated with SR and AF medium, could confirm the results of the profiler array. Scale bars=50μm. **(A,C–G)** Representative data out of three similar experiments. Data are expressed as mean±SEM. ****$p<0.0001$, ***$p<0.001$, **$p<0.01$, *$p<0.05$. Abbreviations same as Figure 3.

To investigate the mechanisms involved in miR-21 mediated atrial fibrosis, we utilized an established *in-vitro* AF model (17). We found increased expression and release of miR-21 to the culture medium after tachyarrhythmic pacing. This positively correlates with the increased expression of miR-21 in the patient arterial serum. Interestingly, transferring the medium of the paced

cardiomyocytes to cultured fibroblasts resulted in activation of profibrotic pathways and collagen expression. Several studies confirm miR-21 mediated transformation of cardiac fibroblast to myofibroblast leading to cardiac fibrosis by targeting many pathways: Jagged1, cell adhesion molecule 1 (CADM1)/signal transducer and activator of transcription 3 (STAT3), transforming growth factor β (TGF-β1)/Smad7 and phosphatase and tensin homologue (PTEN) pathway (10, 18–20). miR-21 is also known to target TGF-β1 thereby increasing collagen I, smooth muscle actin and connective tissue growth factor in both mRNA and protein levels (10, 20).

MiR-21 as a biomarker in AF is well established (21–23). For example, a study by McManus et al. as well as a study by Dawson et al. found lower miR-21 concentrations in patients with AF compared to healthy controls (21, 23). Interestingly, our previous study with blood taken directly from the left atrium (11) and our current study with blood from a peripheral artery (radial artery) showed a positive correlation between miR-21 concentration and left atrial fibrosis. However, in clinical routine, atrial or arterial blood collection seems barely feasible. Therefore, in addition to arterial blood, we also analysed miR-21 expression in peripheral venous blood in our patients. Interestingly, circulating miR-21 concentration in venous blood was different from arterial blood (Supplementary Figures 1A,B). Although we do not have a conclusive explanation for this discrepancy, we hypothesize that different miR-21 expression levels depend upon tissue typecasts or specific area from where the blood samples were collected. This supports the notion that arterial and venous blood have different miRNA characteristics (24, 25). Further, miR-21 is a hypoxia regulated element (26) and there could be differential expression of miRNA in response to oxygen concentration. For example, Xu et al. (24) have shown that miRNA expression profiles are not identical in arterial and venous plasma and arterial plasma miRNA had a higher correlation with the tissue miRNA expression profile. It is also important to mention that the study population was older, had more LA fibrosis, larger left atrias, higher CHA2DS2-VASc scores and a lower LV-EF compared to the AF population in our previous study (11), which might have influenced miR-21 expression. It would therefore be of interest to further explore the mechanism how miR-21 or other micro-RNAs are regulated in the body (Figure 5).

Pulmonary vein isolation, an interventional approach to eliminate triggers that induce AF, is the cornerstone in AF treatment with considerable success of long-term freedom from the arrhythmia (27, 28). However, with progression of the disease and increasing adverse atrial remodeling, durable restoration of SR gets increasingly difficult and long-term treatment outcomes decrease dramatically (7). Although there seems to be a linkage between increased atrial fibrosis and more advanced stages of AF, targeting areas with atrial fibrosis for substrate ablation have failed to show a clinical benefit with current ablation strategy (29, 30). It would therefore be of immense importance to establish a method to stop or reverse adverse atrial remodeling and substrate generation. However, such a treatment option does not exist so far.

In our study, we raise the hypothesis that mocetinostat could act as a potential modulator of atrial cardiomyopathy. The role of HDAC and its inhibition affecting the AF has been already shown (31–33). However, the mechanism through which mocetinostat acts in fibrosis has not been explored yet. Epigenetic modulation plays an important role in activated fibroblasts. Histone deacetylation which is associated with gene repression, is increased and treatment with HDAC inhibitors suppresses the proliferation and epithelial mesenchymal transition of the fibroblasts. Consequently, HDAC inhibitors can reduce extracellular matrix production and influence the inflammatory response (TGF-β pathway) (34, 35). Yoon et al. (36) showed that in murine cardiac fibroblasts, HDAC inhibitors attenuated myofibroblast differentiation thereby impeding the development of hypertrophy and cardiac fibrosis. In our study, we could confirm the anti-fibrotic effects of HDAC1 inhibitor mocetinostat in activated fibroblasts by inhibiting miR-21 expression. Consistent with our data, mocetinostat decreased the expression of α-SMA, collagen III and matrix-metalloproteinase-2 and was able to reverse cardiac fibrosis (37). Mocetinostat, which is currently under clinical investigation for the treatment of various cancers including follicular lymphoma, Hodgkin's lymphoma and Leiomyosarcoma (38–40), might therefore also be a therapeutic option to stop or reverse disease progression in AF.

We acknowledge following limitations in our study: Different strategies have been used for AF ablation (PVI alone, +/− roof line, mitral isthmus line, CFAE ablation, CTI line), which might have influenced treatment outcome. The ablation strategy was determined by the operator (without randomisation) and mainly depended on the presence of LVAs and inducibility of regular tachycardias. Our study was therefore not designed to compare different ablation strategies and treatment outcome has not been differentiated between the ablation techniques.

We have not assessed other markers of atrial cardiomyopathy that are currently under investigation (e.g., fibroblast growth factor 23 and N-terminal-pro hormone B-type natriuretic peptide). Likewise, delayed enhancement magnetic resonance imaging (DE-MRI) of the left atrium to visualize left atrial fibrosis was not performed. For our *in-vitro* studies, cardiomyocytes and fibroblasts were cultured separately which may not represent an exact *in-vivo* scenario. Direct co-culturing would have been preferable, but was not feasible, since fibroblasts have a higher proliferation rate and outgrew the HL1 cardiomyocytes, which made it complicated to execute our protocol of pacing and incubating the cells for 72 h. Furthermore, production of miR-21 *in-vivo* might have a different source than cardiomyocytes and its effects might also be beyond fibroblasts. Finally, we focused on the effect of mocetinostat on fibrosis induced by HL-1 derived miR-21. We have not included a miRNA mimic to determine the post-transcriptional regulatory relationship between miR-21 and fibrosis.

In conclusion, our results confirm that miR-21 plays an important role as a biomarker for atrial fibrosis and for prediction of treatment outcome after AF catheter ablation. We also found that miR-21 is involved in the pathogenesis of disease progression and substrate creation by mediating a cross-talk between cardiomyocytes and fibroblasts. We suggest mocetinostat as a potential treatment option that might attenuate atrial fibrosis development, interfering with the vicious circle between arrhythmia and adverse atrial remodeling.

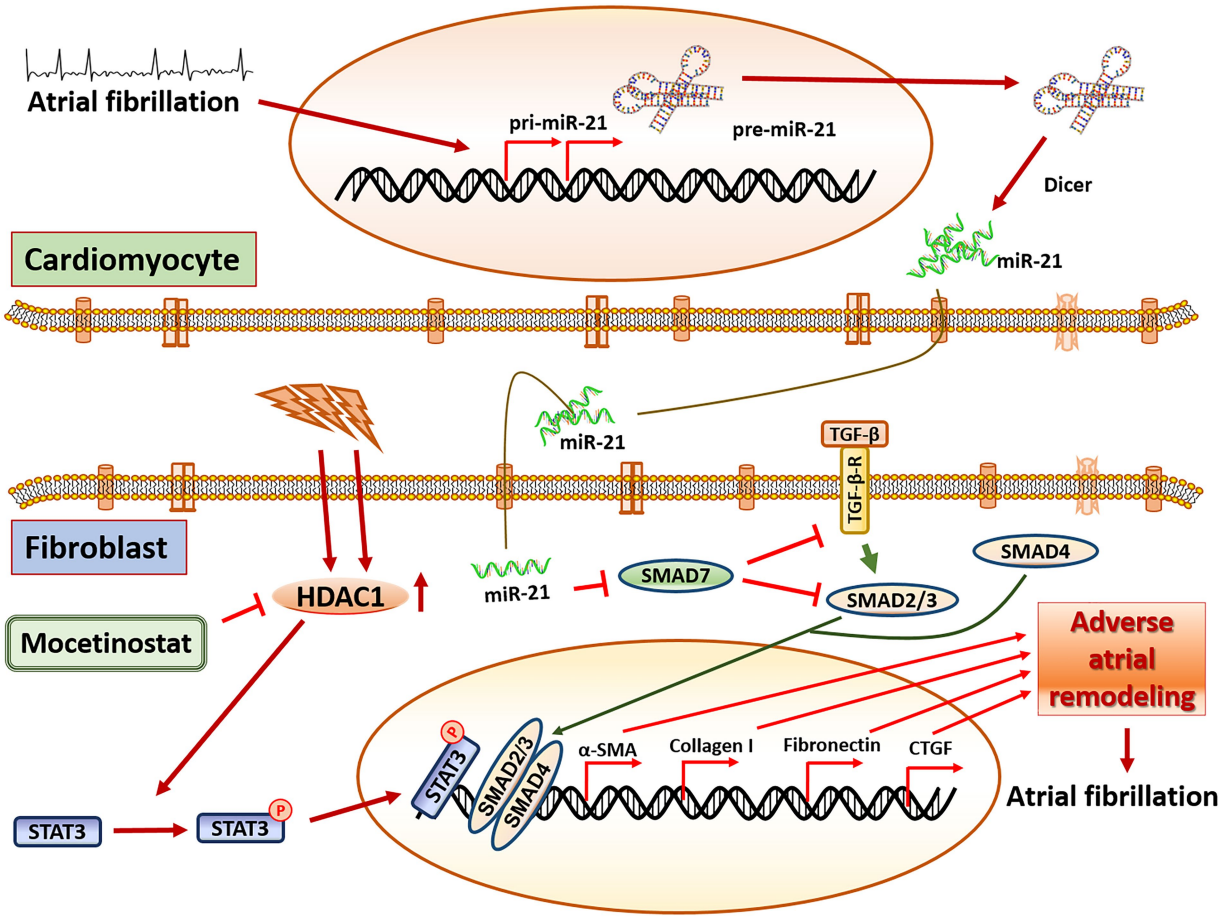

FIGURE 5
Central illustration. The proposed pathway in miR-21 mediated adverse atrial remodeling. miR-21 is released from cardiomyocytes under tachyarrhythmic conditions and triggers pro-fibrotic pathways in fibroblasts, mainly through the SMAD7/TGF-b pathway. Mocetinostat, an HDAC1 inhibitor, attenuates miR-21 dependent adverse atrial remodeling and collagen creation by antagonizing the STAT3-pathway. Tgf-β: transforming growth factor beta 1, Tgf-β-R: transforming growth factor beta receptor, HDAC1: Histone deacetylase 1, Smad7: SMAD family member 7, Smad2/3: SMAD family member 2/3, Smad4: SMAD family member 4, STAT3: signal transducer and activator of transcription 3, α-SMA: alpha smooth muscle actin, CTGF: connective tissue growth factor.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of the medical faculty of RWTH Aachen. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KP and MG contributed to the study design, data analysis and interpretation and manuscript preparation. KP, PN, BN, and CM contributed to the experimental works, data analysis, and interpretation. AS-Y, ME, MZ, AN, and NM contributed with significant intellectual work and manuscript preparation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1056134/full#supplementary-material

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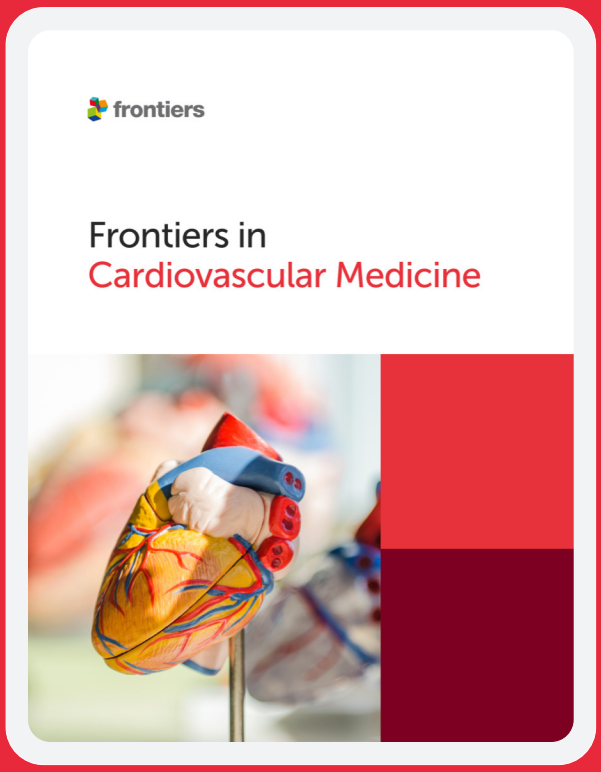

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