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ORIGINAL ARTICLE

Prevalence and Prognostic Implication of Atrial Fibrillation in Heart Failure Subtypes: Systematic Review and Meta-Analysis

Juan Mundisugih, MBBS [a], Kyle B. Franke, MBBS [b], Phillip J. Tully, MPsych(Clin), PhD [c], Dian A. Munawar, MD, PhD [a,b,d], Saurabh Kumar, MBBS, PhD [e,f], Rajiv Mahajan, MD, PhD [a,b,*]

[a]Department of Cardiology, Lyell McEwin Hospital, Adelaide, SA, Australia
[b]Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia
[c]University of New England, Armidale, NSW, Australia
[d]Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia
[e]Department of Cardiology, Westmead Hospital, Sydney, NSW, Australia
[f]Faculty of Medicine and Health, The University of Sydney, Westmead, Sydney, NSW, Australia

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Background Atrial fibrillation (AF) and heart failure (HF) portends a poor outcome. The HF universal definition has incorporated Heart Failure with mildly reduced Ejection Fraction (HFmrEF). We sought to evaluate the relationship between AF and different HF subtypes, with emphasis on HFmrEF.

Methods PubMed and Embase databases were searched up to July 2022. Studies that classified HF with EF≥50% as Heart Failure with Preserved Ejection Fraction (HFpEF); EF 40%–49% as HFmrEF; and EF <40% as Heart Failure with Reduced Ejection Fraction (HFrEF) were included.

Results Fifty (50) eligible studies, with 126,720 acute HF and 109,683 chronic HF patients, were included. Ten percent (10%) and 12% of patients constituted HFmrEF subtype in patients with acute and chronic HF, respectively. The AF prevalence was 38% (95%CI [33, 44], I^2=96.9%) in HFmrEF, as compared to 43% (95% CI [39, 47], I^2=97.9%) in HFpEF, and 32% (95%CI [29, 35], I^2=98.6%) in HFrEF in acute HF patients. Meta-regression showed HFmrEF shared age as a determinant for AF prevalence with HFrEF and HFpEF. Similar AF prevalence also was observed in chronic HF. Compared to sinus rhythm, AF was associated with an increased risk of all-cause mortality in all HF subtypes: HFmrEF (n=6; HR 1.28, 95%CI [1.08, 1.51], I^2=71%), HFpEF (n=10; HR 1.14, 95%CI [1.06, 1.23], I^2=55%) and HFrEF (n=9; HR 1.11, 95%CI [1.02, 1.21], I^2=78%).

Conclusion The prevalence of AF was intermediate for HFmrEF in between HFpEF and HFrEF, with determinants shared with either HF subtype. The co-existence of AF and HF predicts an increased all-cause mortality across all categories of HF. (PROSPERO registry: CRD42021189411)

Keywords Atrial fibrillation • Heart failure • HFpEF • HFmrEF • HFrEF

*Corresponding author at: A/Prof Rajiv Mahajan, Department of Cardiology, Lyell McEwin Hospital, Haydown Road, Elizabeth Vale, SA 5112, Australia; Email: rajiv.mahajan@adelaide.edu.au; Twitter: @Rajiv_EP

Introduction

Atrial fibrillation (AF) and heart failure (HF) are worldwide epidemics [1]. AF has been shown to be both the cause and consequence of HF [2]. AF may lead to impairment of cardiac function [3]. Conversely, the mechanical and neurohormonal remodelling in HF predispose to the development and progression of AF [4]. The presence of AF and HF has been associated with increased adverse outcomes in comparison to either condition alone [5]. In the contemporary AF population with the improvement of anticoagulation therapy, the majority of morbidity and mortality is secondary to HF rather than stroke [6].

Atrial fibrillation was similarly linked to unfavourable outcomes in the HF population. However, the prevalence and prognostic implication of AF in HF patients can vary depending on the HF subtypes defined by left ventricular ejection fraction (EF) [4,7–9]. HF patients have been historically classified as HF with preserved EF (HFpEF) and reduced EF (HFrEF). The recent consensus statement recommends a universal definition and classification. It has incorporated the term 'HF with mildly reduced EF (HFmrEF)', recognising that patients with EF range from 40% to 49% have different underlying characteristics and clinical trajectory [10,11]. Previous studies have tried to address this area of interest, but the results have been inconsistent. The Korean Acute Heart Failure (KorAHF) registry showed the AF prevalence in HFpEF, HFmrEF, and HFrEF to be 45.2%, 39.8% and 28.9%, respectively [7]. The KorAHF registry also showed that AF had a variable effect on mortality depending on HF subtypes and was associated with an increased risk for all-cause mortality only in the HFpEF group [7]. The Swedish Heart Failure registry showed a much higher AF prevalence (HFpEF: 65%; HFmrEF: 60%; and HFrEF: 53%) and reported that AF was associated with increased risk of all-cause mortality in all HF subtypes [8]. In contrast, the European Society of Cardiology (ESC)-HF long-term registry showed a lack of association between AF and all-cause mortality in all HF subtypes after multivariate adjustment [9].

We, therefore, conducted these meta-analyses to evaluate the relationship between AF and each HF subgroup defined by the universal HF classification [10]. Our objectives were to systematically assess the prevalence and prognostic implication of AF in these HF subtypes, highlighting differences in clinical trajectories.

Methods

Search Strategy

This meta-analysis complies with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [12] and Meta-analysis of Observational Studies in the Epidemiology (MOOSE) statements [13]. This study was prospectively registered in the PROSPERO registry (CRD42021189411). PubMed and Embase were searched up to 1 July 2022 in the English literature using the keywords described in the Supplementary Material (Supplemental Methods S1). The references were exported to Endnote (Clarivate, Philadelphia, PA, USA), and duplicate citations were removed.

Study Selection

The abstracts of searched articles were screened to exclude studies that were unsuitable and the full-text manuscripts of the selected articles were then reviewed and evaluated. For inclusion criteria, studies must have: (i) HF patients who were categorised based on the EF cut-off of the latest guidelines (i.e., HFpEF as EF≥50%, HFmrEF: EF 40%–49%, and HFrEF: EF<40%) [10] irrespective the term of HF subtype the study used; and (ii) the AF prevalence in either of the HF subtypes cohorts. The exclusion criteria were: (i) case reports, editorials, reviews, and conference abstracts; (ii) cross-section study; (iii) primary case series reporting on less than 50 HF patients. Data from multiple published reports from the same registry were included only once to ensure the independence of effect sizes.

Data Extraction and Quality Assessment

The searches and data extraction were conducted and completed independently by two investigators (J.M. and K.B.F.) in accordance with the inclusion and exclusion criteria. Review articles, though excluded, were reference checked for potentially relevant publications. Any discrepancies between the two investigators were resolved by consensus with the help of a third investigator (R.M.). Included studies had the following data extracted: study characteristics, population characteristics, AF prevalence, and study outcomes, especially hazard ratios of mortality. Only data consistent with the EF cut-off of the 2021 HF consensus statement were included in the analyses from the included studies. For example, if the included study divided their HF population into 'HFpEF' and 'HFrEF', defined by EF≥50% and EF<50%, respectively, data from the 'HFrEF' group was not included in the analyses because it had a different EF category than the latest HF classification. The outcome of this meta-analysis includes the weighted prevalence of AF in patients presenting with: 1) acute HF; 2) chronic HF; and 3) AF hazard ratio of all-cause mortality in each HF subtype. The quality of included studies was assessed by the modified Newcastle-Ottawa quality assessment Scale (NOS). The modified NOS assigned a score of 0 to 3 for each section on population selection, performance bias, detection bias and information bias, with 0 representing high risk and 3 representing low risk of bias [14].

Statistical Analysis

Categorical variables are presented as n (%) and continuous variables as mean. The statistical analyses were performed using the Review Manager version 5.0 (Nordic Cochrane Center, Copenhagen, Denmark), StatsDirect version 3.2.7 (StatsDirect Ltd, Merseyside, United Kingdom), and the R Statistical Software version 4.1.1 (R Foundation for Statistical

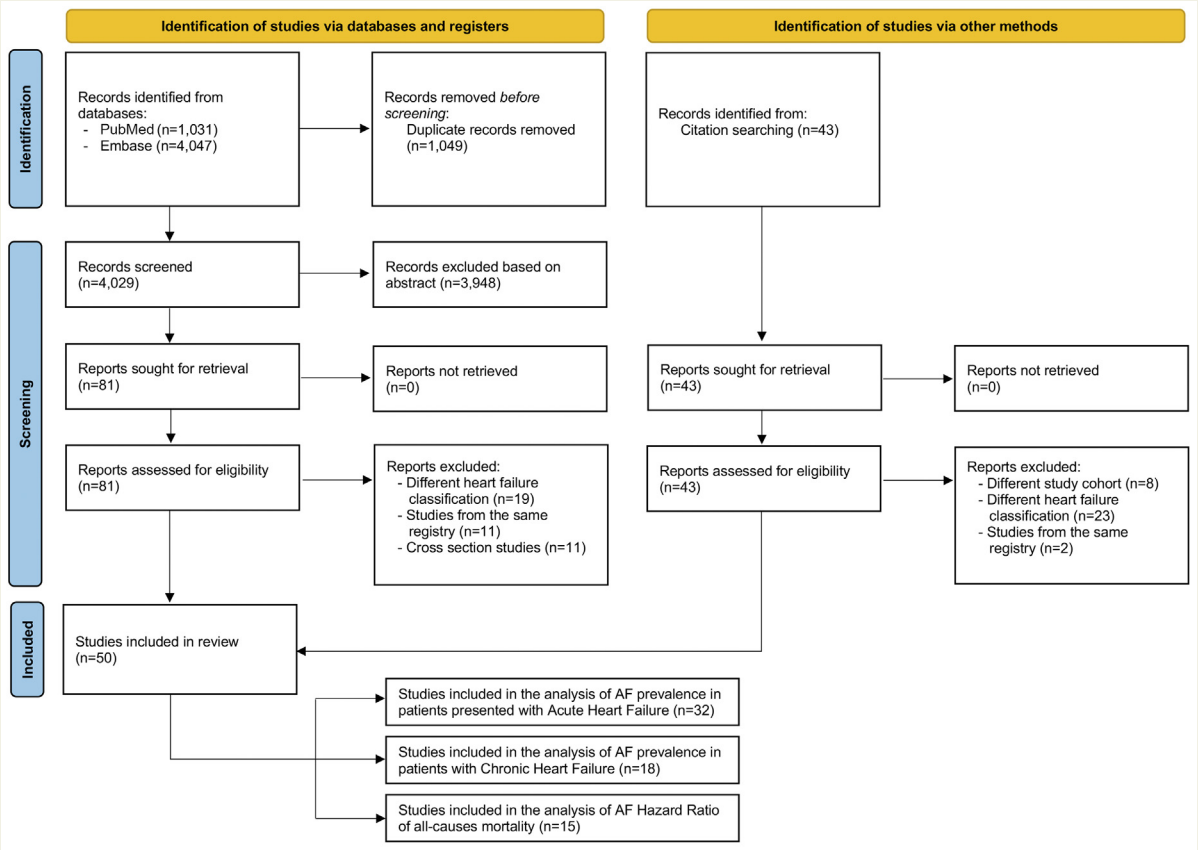

Figure 1 CONSORT diagram showing search strategy.
Abbreviation: AF, atrial fibrillation.

Computing, Vienna, Austria) utilising the R package meta (v5.2-0; Schwarzer, 2007; Balduzzi et al., 2019) [15,16]. Statistical significance was set at $p < 0.05$ for all analyses. The weighted proportions, incidence risk ratio, pooled hazard ratio (HR) and 95% CIs were calculated employing random effects estimates. Heterogeneity was tested using I^2 statistics, and considerable heterogeneity was considered if $I^2 > 50\%$. A predefined sub-analysis was performed based on the study design. Also, methodological heterogeneity was explored for analyses with 10 or more effect sizes using the meta-regression function in Comprehensive Meta-Analysis software [17]. Utilising the unrestricted maximum likelihood assumption, the univariate meta-regression shows the unit change in effect size per unit change in predictor variables (i.e., age per 5-years, proportion of females per 5%, follow-up per 12-months), with associated 95%CI and p value. Forest plots were also constructed for graphical illustrations, and publication bias was assessed with Egger's test.

Results

Search and Synthesis of Literature

A total of 4,029 articles were identified through the database searches. Of these, 3,948 were excluded based on title and abstracts because they were not relevant to the present meta-analysis. After a manual reference check, an additional 43 studies were identified. A total of 124 full-text articles were reviewed and evaluated. Fifty (50) studies were included, of which 29 were prospective studies, four were RCT sub-studies, and 17 were retrospective studies. The oldest study that fulfilled inclusion criteria was published in 1996. Thirty-two (32), 18, and 15 studies were included in the analyses of the weighted prevalence of AF in patients presenting with acute HF [7,18–48], chronic HF [8,9,49–64], and AF hazard ratio of all-cause mortality [7–9,20,24,29,32,35,37,38,43,48,50,59,62], respectively. Figure 1 shows the study selection for the meta-analysis.

A summary of the study characteristics is provided in Supplemental Table 1. A total of 126,720 and 109,683 patients with acute HF and chronic HF, respectively, were included. Of these patients presenting with acute HF, 35,722 patients had HFpEF (28%), 12,966 patients had HFmrEF (10%), and 78,032 patients had HFrEF (62%). Similarly, there were 32,818 patients with HFpEF (30%), 13,375 patients with HFmrEF (12%) and 63,490 patients with HFrEF (58%) in chronic HF population. The mean age ranged from 51.3–81 years, and the female representation ranged from 21%–70% in different studies. Follow-up duration ranged from 6 days to 120 months. The baseline characteristics of AF patients in

Table 1 Characteristics of patients with atrial fibrillation in each heart failure subtypes.

Author Publication Year	Patients (n)	Age	Gender (Male%)	BMI (kg/m^2)	HTN (%)	DM (%)	CKD (%)	CAD (%)	NT-pro BNP (pg/mL)	LA Diameter (cm)
HFpEF—AF										
Shamagian et al. 2005 [36]	192	71.6	89 (46.3)	-	103 (53.6)	39 (20.3)	-	44 (22.9)	-	-
Fung et al. 2007 [19]	42	73.8	9 (21)	28.2	33 (79)	9 (21)	-	4 (10)	-	5.02
Rusinaru et al. 2008 [20]	132	77.9	60 (45.5)	-	99 (75)	30 (22.7)	-	21 (15.9)	-	-
Zakeri et al. 2013 [50]	489	78.4	189 (38.7)	29.2	337 (68.9)	101 (20.7)	-	66 (13.5)	-	-
Sartipy et al. 2017 [8]	6,250	79.1	2,861 (46)	27.3	4,405 (70)	1,666 (27)	-	2,998 (48)	2,547	-
Zafrir et al. 2018 [9]	1,519	74.3	667 (43.9)	28.6	1,099 (72.4)	478 (31.5)	386 (25.4)	362 (24)	2,500	-
Xu et al. 2019 [29]	74	77	45 (60.8)	24.1	42 (56.8)	24 (32.4)	-	26 (35.1)	-	4.90
Son et al. 2020 [7]	614	73.2	228 (37.1)	23.5	407 (66.3)	190 (30.9)	110 (17.9)	125 (20.4)	-	-
Schonbauer et al. 2020 [53]	153	72	55 (35.9)	30.2	147 (96)	48 (31.4)	-	-	1,419	6.51
Tan et al. 2020 [51]	365	73	173 (47.4)	26.3	277 (76)	159 (44)	168 (53)	101 (31)	2,808	-
Temma et al. 2020 [30]	275	80.2	139 (50.5)	23.1	207 (75.3)	102 (37.1)	127 (46.2)	68 (24.7)	-	4.52
HFmrEF—AF										
Sartipy et al. 2017 [8]	5,312	76.8	3,198 (60)	27.1	3,446 (65)	1,385 (26)	-	2,814 (53)	2,710	-
Zafrir et al. 2018 [9]	900	70.4	555 (61.7)	28.7	606 (67.6)	295 (32.8)	217 (24.2)	358 (40.1)	2,615	-
Xu et al. 2019 [29]	62	71	30 (48.4)	22.7	28 (45.2)	16 (25.8)	-	22 (35.5)	-	4.60
Son et al. 2020 [7]	348	73	149 (42.8)	23.4	226 (64.9)	103 (29.6)	69 (19.8)	103 (29.6)	-	-
HFrEF—AF										
Linssen et al. 2011 [34]	215	71	150 (70)	27	92 (43)	54 (25)	-	85 (40)	3,045	-
Mentz et al. 2012 [35]	1,195	67.4	894 (74.8)	-	856 (71.6)	398 (33.3)	280 (23.4)	812 (68)	4,648	-
Eapen et al. 2014 [38]	13,152	78.8	8,006 (60.9)	-	8,872 (67.5)	4,755 (36.2)	4,154 (31.6)	9,158 (69.6)	-	-
Sartipy et al. 2017 [8]	12,187	74.3	8,933 (73)	26.4	6,912 (57)	3,232 (27)	-	6,787 (56)	3,627	-
Yagawa et al. 2017 [26]	254	77	169 (71)	-	158 (64)	88 (35)	-	-	-	-
Zafrir et al. 2018 [9]	2,110	68.5	1,619 (76.7)	28.6	1,310 (62.2)	756 (35.8)	510 (24.2)	974 (46.5)	3,320	-
Xu et al. 2019 [29]	69	69	54 (78.3)	23.8	28 (40.6)	15 (21.7)	-	32 (46.4)	-	4.90
Son et al. 2020 [7]	921	67.9	589 (64)	23.4	531 (57.7)	327 (35.5)	244 (26.5)	286 (31.1)	-	-
Tan et al. 2020 [51]	1,018	65	805 (79)	24.2	545 (54)	384 (38)	443 (50)	406 (42)	4,110	-
Albert et al. 2021 [55]	1,738	70.1	1,738 (78.4)	30.4	1,475 (84.9)	734 (42.3)	449 (25.9)	1,163 (66.9)	4,419	-
Chouairi et al. 2021 [59]	358	66	260 (72.6)	29.9	-	176 (49.2)	162 (45.3)	203 (57)	4,800	-

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; AF, atrial fibrillation; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CAD, coronary artery disease; NT-proBNP, N-Terminal-pro hormone Brain Natriuretic Peptide; LA, left atrium.

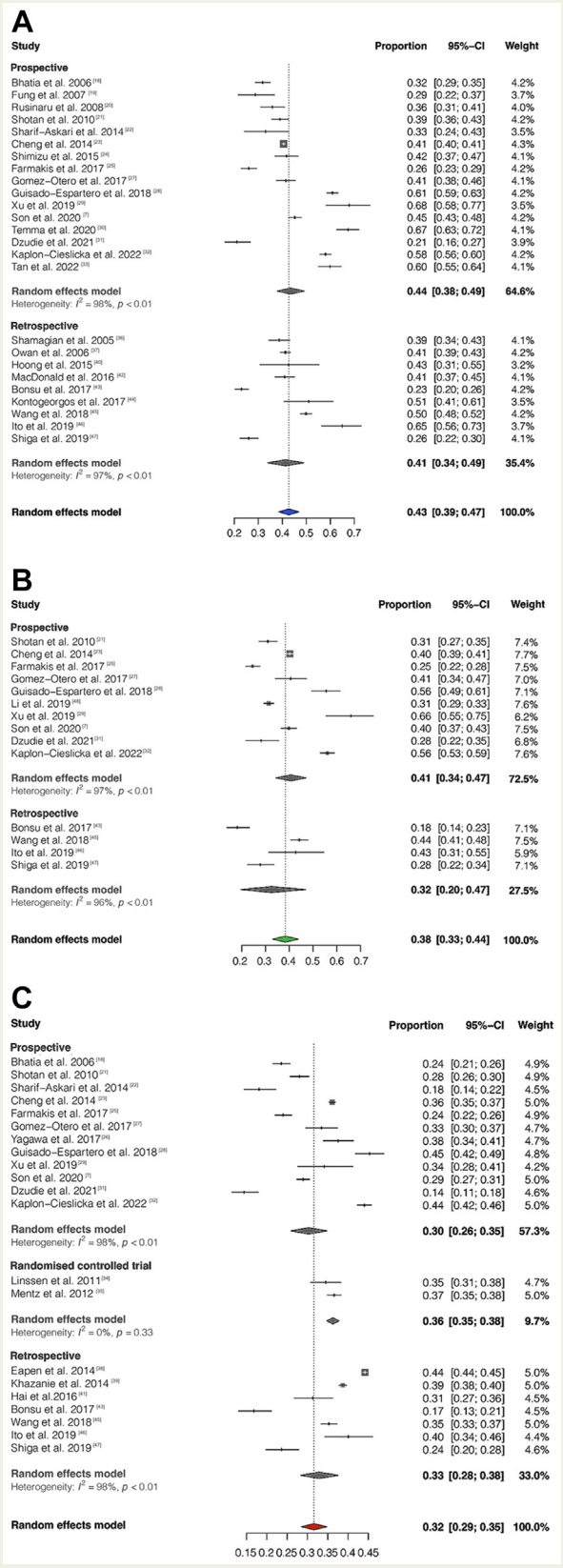

Figure 2 The weighted prevalence of atrial fibrillation (AF) in patients with acute heart failure (HF).
Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.

each HF subtype are summarised in Table 1. The mean age ranged from 71.6–80.2 years for patients with HFpEF and AF, while it ranged from 70.4–76.8 years for patients with HFmrEF and 65–78.8 years for patients with HFrEF.

In terms of left ventricular EF quantification, 35 studies used echocardiography, four studies used multi-modality imaging technique, and 11 studies did not mention the method of measurement (Supplemental Table 2). Of 35 studies used echocardiography, only 11 studies specifically described the use of Simpson's biplane method. The approach to diagnosis AF varied between studies (17 studies used ECG, four studies relied on history, seven studies used a combination of both, and 22 studies did not describe the method) and only seven studies included the types of AF. Although 16 studies reported the presence of cardiovascular implantable electronic device (CIED), ranging from 2.2% to 44.2% of the study population, none of the studies utilised CIED to diagnose AF (Supplemental Table 2).

Prevalence of Atrial Fibrillation in Heart Failure Subtypes

In acute HF patients, the weighted prevalence of AF was 38% [33, 43] (n=14; 12,966 patients; I^2=96.9%) in HFmrEF as compared to 43% [39, 47] (n=25; 35,722 patients; I^2=97.9%) in HFpEF, and 32% [28, 34] (n=21 studies; 78,032 patients; I^2=98.6%) in HFrEF (Figure 2). A similar trend was observed in patients with chronic HF, the weighted prevalence of AF being 41% [21, 62] (n=4; 13,375 patients; I^2=99.8%) in HFmrEF as compared to 46% [39, 54] (n=11; 32,818 patients; I^2=99.3%) in HFpEF, and 34% [26, 42] (n=13; 63,490 patients; I^2=99.8%) in HFrEF (Figure 3). Significant heterogeneity was observed in AF prevalence in all HF subtypes regardless of the chronicity of HF or the study design. The study region was identified as a source of heterogeneity in AF prevalence estimates between studies (Supplemental Table 3). The meta-regression of acute HF samples showed that older age was associated with higher AF prevalence in all HF sub-types. A higher proportion of females was associated with the prevalence of AF in HFpEF and HFrEF samples. Length of follow-up was associated with AF prevalence in all acute HF subtypes (Supplemental Table 4). In chronic HF, meta-regression could not be performed for HFmEF subtype. In other chronic HF subtypes, increasing age, female gender, and follow-up durations were associated with AF prevalence.

The sub-group analysis of AF incidence risk ratio in patients with acute HF showed HFpEF was associated with a 37% increased risk of AF compared to HFrEF (n=15; RR 1.37[1.26, 1.49]; I^2=90%). Analysis between HFpEF and HFmrEF indicated an 8% increased risk of AF in patients with HFpEF (n=13; RR 1.08[1.03, 1.14]; I^2=58%). In comparison to HFrEF, HFmrEF had greater risk of AF with the incidence risk ratio of 1.24[1.15, 1.34] (n=13; I^2=79%), as shown in Supplemental

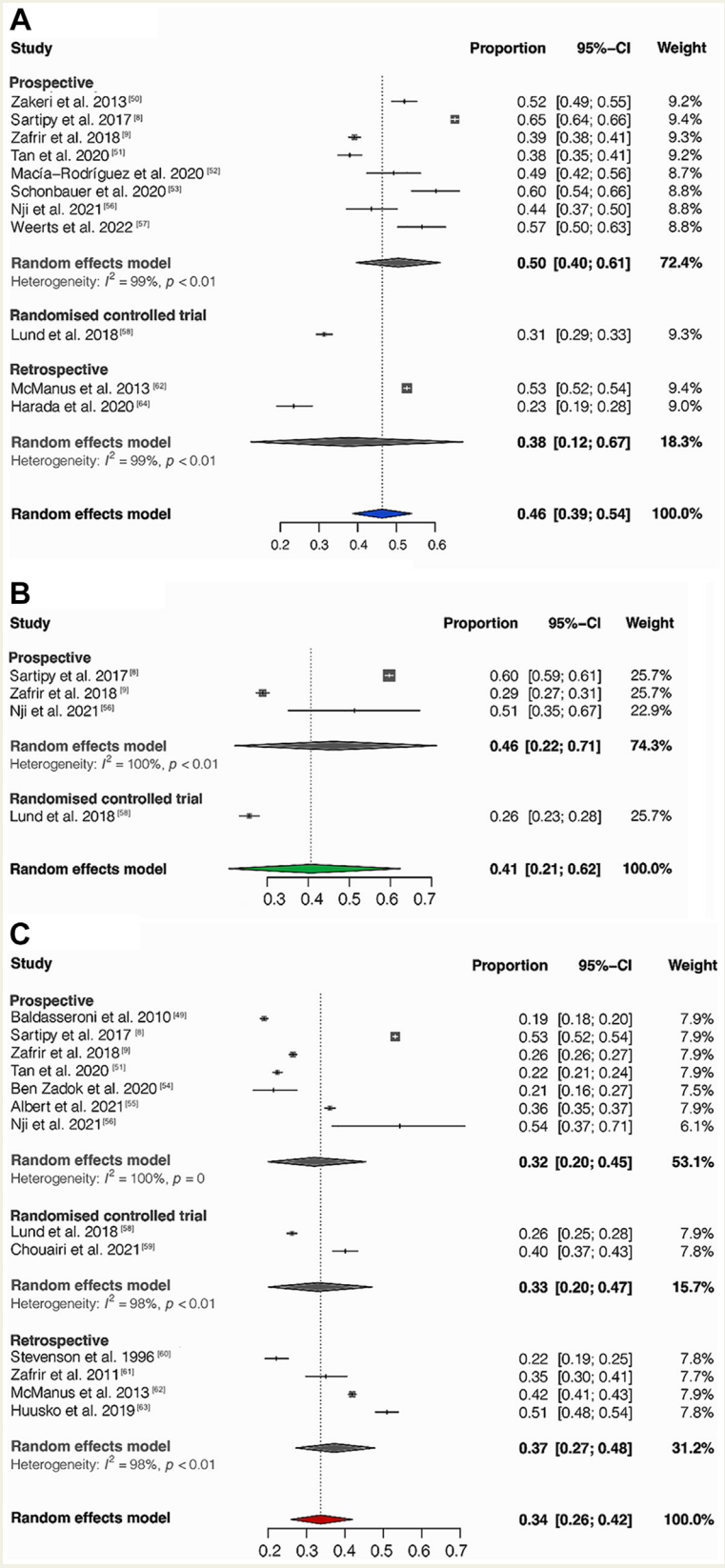

Figure 3 The weighted prevalence of atrial fibrillation (AF) in patients with chronic heart failure (HF).
Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.

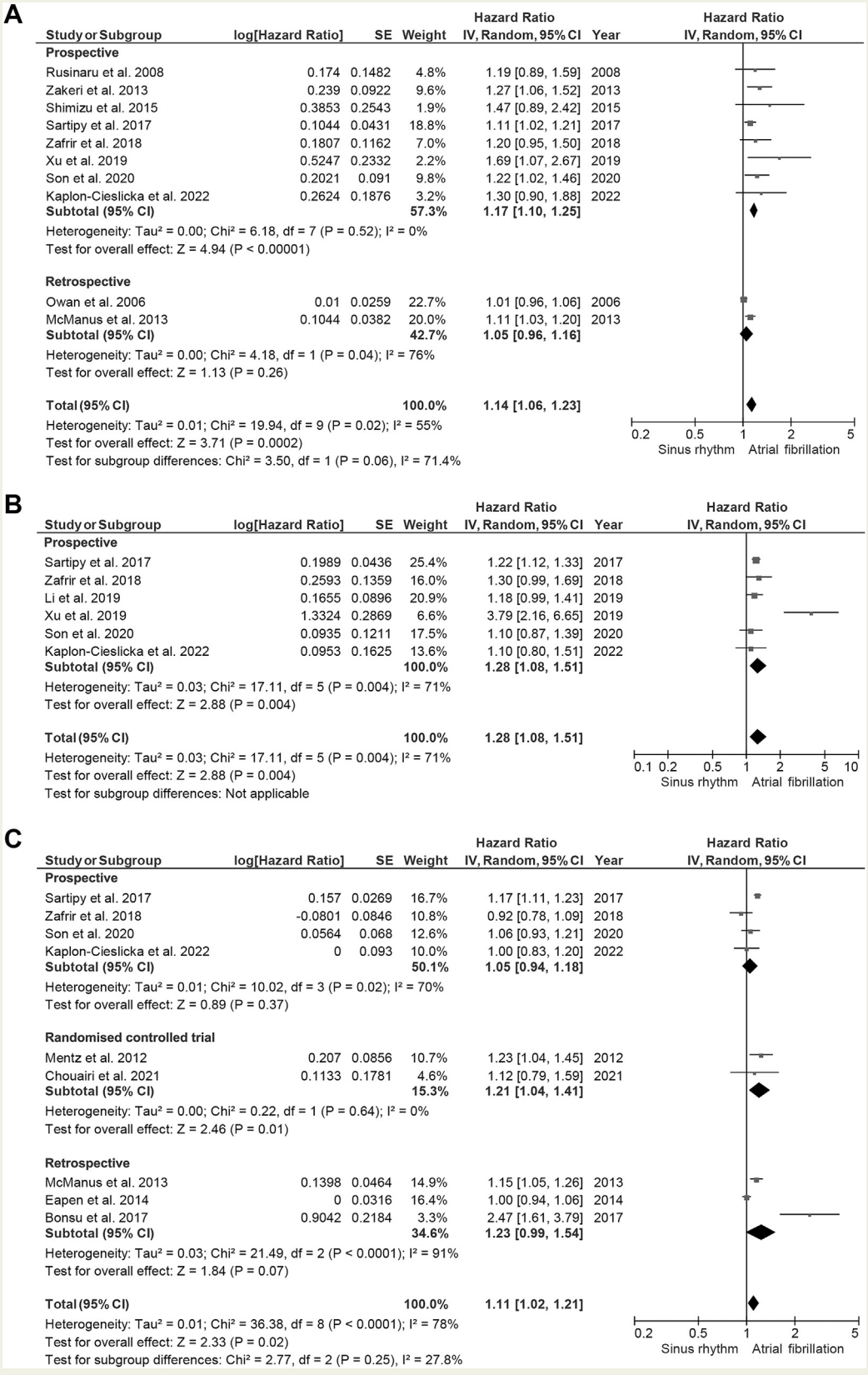

Figure 4 Hazard ratio of all-cause mortality in atrial fibrillation (AF) and heart failure (HF) subtypes.

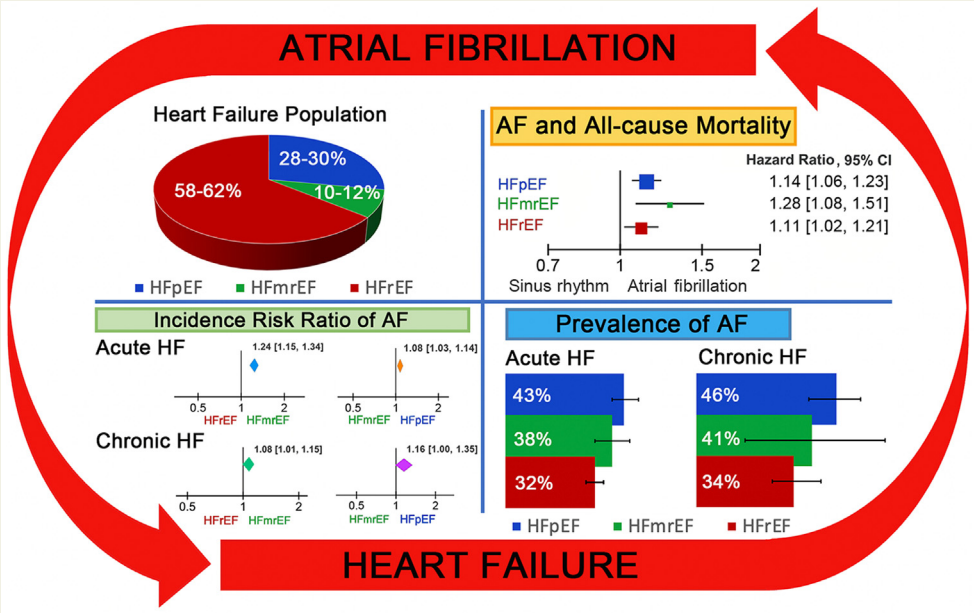

Figure 5 (Central Illustration) Prevalence and Prognostic Implication of Atrial Fibrillation in Heart Failure Subtypes. Abbreviations: HF, heart failure; AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Figure 1. In addition, the sub-group analysis of AF incidence risk ratio in chronic HF patients suggested similar findings with HFpEF had a 32% increased risk of AF compared to HFrEF and had a 16% increased risk compared to HFmrEF. Analysis between HFmrEF and HFrEF in the chronic HF population indicated an 8% increased risk of AF in patients with HFmrEF (Supplemental Figure 2). The meta-regression in acute HF samples showed that age, female gender, and follow-up durations were differentially associated with AF incidence and no consistent patterns were found (Supplemental Table 5).

Atrial Fibrillation and All-Cause Mortality in Heart Failure Subtypes

Atrial fibrillation was associated with an increase in all-cause mortality across all HF subsets. Our analysis suggested that AF increased the risk of all-cause mortality by 14% compared to those in sinus rhythm (n=10; HR 1.14[1.06, 1.24]; I^2=55%) in HFpEF. This increased risk of mortality was consistent regardless of the study design. The presence of AF in HFmrEF patients likewise increased the risk of all-cause mortality (n=6; HR 1.28[1.08, 1.51]; I^2=71%). The risk of all-cause mortality for patients with AF and HFrEF was also increased by 11% (n=9; HR 1.11[1.02, 1.21]; I^2=80%). Only the sub-analysis from the RCT sub-studies indicated that AF increased the risk of all-cause mortality in the HFrEF group (n=2; HR 1.21[1.04, 1.41]). The sub-analysis of either prospective or retrospective studies showed AF was not associated with an increased risk of all-cause mortality in HFrEF patients (n=4; HR 1.05[0.94, 1.18], and n=3 studies, HR 1.23[0.99, 1.54], respectively), though considerable heterogeneity was observed in the pooled HR of all HF subtypes (Figures 4 and 5).

Assessment of Bias

There was no significant risk of biases in all studies based on the modified NOS scores. All included studies were well representative of the relevant cohort, with most of them having an adequate sample size (Supplemental Table 6). Egger's tests suggested an absence of publication bias in the meta-analysis for AF prevalence in HFpEF and HFmrEF groups ($p>0.05$), regardless of the chronicity of HF. However, Egger's test suggested publication bias in the Acute HF–HFrEF group ($p<0.01$), but not in the Chronic HF–HFrEF group ($p>0.05$). Egger's test showed a significant risk of publication bias in the HFpEF group ($p<0.01$) for all-cause mortality. In contrast, analyses of all-cause mortality in HFmrEF and HFrEF groups did not show a significant risk of bias ($p>0.05$ for both).

Discussion

The meta-analysis comprised over 126,720 and 109,683 patients with acute HF and chronic HF, respectively. The major findings were:

1. 10%–12% of all patients were classified as HFmrEF subtype.
2. The prevalence of AF was intermediate for HFmrEF between HFpEF and HFrEF. Meta-regression showed age is the common determinant for AF prevalence across all HF subtypes.
3. An increase in the all-cause mortality rate among patients with AF was also observed in all HF subtypes. The increased risk of all-cause mortality was noted only in the sub-analysis of the randomised control trials in the HFrEF group.

Universal Classification of Heart Failure Subtypes and Atrial Fibrillation

The 2021 Consensus Statement provided a universal definition and classification for heart failure and emphasised HFmrEF as a subtype, HF mimickers and clinical trajectory [11]. Heart failure biomarkers such as NTproBNP can be elevated in patients with AF. The ESC 2021 Heart failure guidelines recommend a higher cut-off for diagnosing HFpEF in the presence of AF [10]. Similarly, the diastolic function is difficult to assess in patients with AF. AF and HF share risk factors that may promote fluid overload and mimic HF. These features may lead to overdiagnosis of HFpEF in patients with AF [65,66]. However, the poor prognosis associated with AF and HFpEF in our meta-analysis suggests an appropriate diagnosis of HFpEF in the included studies. Also, one in 10 patients with HF will be classified as HFmrEF subtype. Previous studies have shown transition between HF subtypes and different clinical trajectories with respect to response to medical treatment. The current meta-analysis provides evidence towards the different AF prevalence in different HF subtypes and similarly increased mortality in all subtypes.

Differences in Prevalence and Possible Mechanism

This meta-analysis showed that the AF prevalence in the HFmrEF group is intermediate between HFpEF and HFrEF groups. The mechanisms by which AF prevalence was significantly greater with increasing EF remain uncertain, especially with the emerging HFmrEF subtype. In a previous study where the HF population was dichotomised only into HFpEF and HFrEF, left atrium (LA) remodelling differed among these two HF subtypes [67]. They observed substantial LA stiffness in HFpEF while eccentric LA remodelling in HFrEF [67,68]. However, AF may beget HFpEF through AF related LA dilatation, impaired atrial function, atrioventricular annular remodelling and atrial fibrosis [65]. AF and HFpEF also share common risk factors and comorbidities, such as advanced age, hypertension, obesity and sleep apnoea which may provide the substrate for developing both conditions simultaneously [65,69].

HFmrEF is the newly emerging HF subtype and is increasingly receiving attention. Few studies have reported that the characteristics of patients with HFmrEF are similar to HFpEF as they were older, more likely female and had more comorbidities compared with HFrEF [70]. However, the prevalence of coronary artery disease in patients with HFmrEF is high, resembling HFrEF [58,70]. Thus, HFmrEF comprises a heterogeneous population that can resemble either HFpEF or HFrEF. HFmrEF may occur as deterioration from HFpEF, as a recovery from HFrEF, or even as the first presentation of HF, which can progress in either direction [71]. Therefore, it is not unexpected to observe the 'intermediate' prevalence of AF in this group. Our meta-analysis demonstrated that older age was associated with the prevalence of AF across all HF sub-types. Also, the meta-analysis suggested that a higher proportion of females were associated with the prevalence of AF in HFpEF and HFrEF that could not be corroborated in HFmrEF. Analysis by follow-up duration provided mixed results, with longer follow-up durations associated with lower AF prevalence in acute HF, though higher AF prevalence in chronic HF.

Increase in All-Cause Mortality and Possible Mechanism

Our analysis indicated that the presence of AF was associated with an increase in all-cause mortality across all HF subtypes. Patients with both AF and HFpEF may have a more advanced atrial and ventricular remodelling compared to those with either AF or HFpEF only [72]. Several longitudinal studies reported that the development of AF after the diagnosis of HFpEF was associated with a worse prognosis. In the same way, patients who develop HFpEF after the diagnosis of AF also have an increased risk of death [72]. Combination of AF and HFpEF results in significant haemodynamic consequences and worsening cardiac function through diffuse ventricular fibrosis, impaired relaxation, shorter diastolic filling time, loss of atrial systole, elevated filling pressure, and chronotropic dysregulation [9,73,74].

The adverse prognosis associated with AF in patients with HFrEF was driven by the RCT sub-studies in our meta-analysis. Neither the prospective nor retrospective studies showed increased all-cause mortality with AF. A possible explanation of this observation is indication bias with patients recruited to RCTs having a more advanced HF stage [35,59]. The clinical trajectory in patients with AF and HFrEF may be predominantly determined by the severity of HF rather than AF alone, unlike AF in HFpEF.

Although the HFmrEF cohort constitutes patient with demographics intermediate between HFpEF and HFrEF, the presence of AF in this cohort seemed to have a stronger impact on all-cause mortality than the presence of AF in either HFrEF or HFpEF. One potential explanation is HFmrEF had a generally better prognosis than HFrEF [75,76]; as such its clinical trajectory may not necessarily be influenced by the severity of HF alone. Furthermore, HFmrEF patients are like HFpEF patients in that they were older and had more comorbidities compared with HFrEF [70]. As a result, the presence of AF in this cohort could give rise to similar haemodynamic sequalae, like AF in HFpEF.

What the Study Adds

The results of this meta-analysis support HFmrEF as a distinct clinical entity. The underlying pathophysiology and its relationship with AF need to be further explored. Nonetheless, AF is common in HF patients and clinicians should have high index of suspicion, especially in HFpEF and HFmrEF. This study showed AF adversely influences prognosis in HF patients regardless of HF subtypes. Hence, attempts should be made to achieve and maintain sinus rhythm, particularly in

HFmrEF, as the presence of AF in this cohort might play an important role in its long-term prognosis.

Limitations

Substantial statistical and methodological heterogeneity is potentially the most significant limitation of this meta-analysis. This is partly attributable to differences in the inclusion criteria for acute or chronic HF (Supplemental Table 2). In studies with acute HF, not all studies utilised Framingham criteria to diagnose acute decompensated HF. Likewise, studies with chronic HF recruited patients in different clinical settings, involving inpatient, outpatient, or both. Differences in the left ventricular EF quantification might also contribute to methodological heterogeneity. Meta-regression identified age, female gender, and follow-up duration as sources of heterogeneity in AF prevalence and AF incidence. Moreover, geographical differences in AF and HF also exist, and our analysis confirmed the study region was associated with heterogeneity in AF prevalence. Different study regions are likely to exhibit diversities in the ethnicity, gender majority, or socioeconomic status between study cohorts, which has previously been shown to influence AF prevalence [77,78]. The other possible explanation of this heterogeneity is the variance in the diagnosis or detection of AF. Not all studies elaborated the method of identifying the presence of AF. Even in those studies that described the method, the timing of electrocardiogram varied, and the presence of AF might not necessarily be adjudicated. Most studies also did not report the type of AF. Another limitation of our meta-analysis is the discrepancy between the modified NOS and Egger's test in the AF prevalence of Acute HF—HFrEF group and the pooled HR of all-cause mortality for the HFpEF group. This discrepancy could be attributable to the inclusion of both large registry databases and smaller prospective or retrospective cohort studies.

Conclusions

The meta-analyses demonstrate that the AF prevalence was intermediate for HFmrEF compared to HFpEF and HFrEF, with determinants shared with either HF subtypes. The coexistence of AF and all subtypes of heart failure predicted increased all-cause mortality. The meta-analysis highlights the potential difference in prevalence but similar poor prognosis in patients with coexisting AF and HF.

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Conflict of Interest Disclosures

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Author Contributions

All authors have met the criteria for authorship and agree with the manuscript's content. Authors R.M., J.M., K.B.F. and D.A.M. had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: J.M. and R. M.

Acquisition of data: J.M. and K.B.F.

Analysis and interpretation of data: J.M., K.B.F. D.A.M., P.J.T. and R.M.

Drafting of manuscript: J.M. and R.M.

Critical revision of the manuscript for important intellectual content: J.M., K.B.F., D.A.M., P.J.T., S.K. and R.M.

Statistical analysis: J.M., D.A.M., K.B.F., P.J.T.

Study supervision: R.M.

Appendices

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.10.1016/j.hlc.2023.02.009.

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