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ORIGINAL RESEARCH ARTICLE

Ethnic differences in atrial fibrillation among patients with heart failure in Asia

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Abstract

Aims We aimed to characterize ethnic differences in prevalence, clinical correlates, and outcomes of atrial fibrillation (AF) in heart failure (HF) with preserved and reduced ejection fraction (HFpEF and HFrEF) across Asia.

Methods and results Among 5504 patients with HF prospectively recruited across 11 Asian regions using identical protocols in the Asian Sudden Cardiac Death in Heart Failure study (mean age 61 ± 13 years, 27% women, 83% HFrEF), 1383 (25%) had AF defined as a history of AF and/or AF/flutter on baseline electrocardiogram. Clinical correlates of AF were similar across ethnicities and included older age, prior stroke, higher NT-proBNP, and larger left atria. Diabetes was associated with lower odds of AF in HFrEF [adjusted odds ratio (AOR) 0.79, 95% CI 0.66–0.95] and HFpEF (AOR 0.58, 95% CI 0.39–0.84) regardless of ethnicity. Compared with Chinese ethnicity, Japanese/Koreans had higher odds of AF in HFrEF (AOR 1.76, 95% CI 1.40–2.21), while Indians had lower odds in HFrEF (AOR 0.18, 95% CI 0.13–0.24) and HFpEF (AOR 0.28, 95% CI 0.16–0.49) even after adjusting for clinical covariates. Interaction between ethnicity and region was observed among Indians, with Southeast Asian Indians having higher odds of AF (AOR 3.01, 95% CI 1.60–5.67) compared with South Asian Indians. AF was associated with poorer quality of life and increased risk of 1 year all-cause mortality or HF hospitalisation (adjusted hazard ratio 1.39, 95% CI 1.18–1.63) regardless of ethnicity.

Conclusions Among patients with HF across Asia, clinical correlates and adverse outcomes associated with AF are similar across ethnicities; however, there are striking ethnic variations in the prevalence of AF that are not accounted for by known risk factors.

Keywords Atrial fibrillation; Heart failure; Diabetes

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in heart failure (HF) and is associated with an increased risk of stroke, HF hospitalisation and mortality.[1,2] Beyond traditional risk factors, there is growing evidence of ethnic influences on the prevalence of AF in the context of HF.[3–7] A large US registry reported a higher prevalence of AF among white HF patients compared with blacks, Hispanics, and Asians[3]; while a prospective Asia Pacific study showed a distinctly lower prevalence of AF among Singaporean–Asian compared with New Zealand European HF patients.[5] The ethnic differences in AF prevalence in HF, while striking, remain poorly understood.

Asia is geographically vast, with significant heterogeneity among patients with HF not only by region but also by ethnicity.[8] It is unknown if ethnic differences in AF prevalence and clinical correlates within Asia are present. We aimed to characterize ethnic differences in prevalence, clinical correlates, and outcomes of AF in HF with preserved and reduced ejection fraction (HFpEF and HFrEF) across Asia.

Methods

Study population

Participants were identified from the Asian Sudden Cardiac Death in HF (ASIAN-HF) registry (ClinicalTrials.gov Identifier: NCT01633398).[8] In brief, ASIAN-HF is a prospective, observational, multinational registry of Asian patients with symptomatic HF. Consecutive patients were screened in 46 medical centres across 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand) managing both acute and chronic HF. Patients were >18 years and provided written informed consent. Exclusion criteria have previously been described.[8] The study complied with the Declaration of Helsinki, and ethics approvals were obtained at all sites. All patients enrolled in ASIAN-HF had a validated clinical diagnosis of HF by independent site investigators (based on symptoms, signs, and clinical decompensation within 6 months). They were categorized as HFrEF and HFpEF based on left ventricular ejection fraction <40% and ≥50%, respectively. In addition, 99.5% of HFpEF patients had echocardiographic evidence for diastolic dysfunction [E/e′ ≥ 13, e′ medial/lateral <9 ms, left atrial (LA) enlargement, or left ventricular (LV) hypertrophy].[9]

Recruitment of patients in ASIAN-HF was in two phases, through investigation sites which covered a broad spectrum of medical, cardiology, and HF specialty units, admitting patients with acute HF and conducting outpatient follow-up of patients with chronic HF. HFrEF patients were recruited between October 2012 and December 2015; patients with HFpEF were enrolled between September 2013 and December 2017.

Data collection included patient demographics, clinical symptoms, co-morbidities, and medications. Standard 12-lead electrocardiogram (ECG) and transthoracic echocardiography were performed in all patients at baseline. Each centre performed transthoracic echocardiography exams according to internationally accepted guidelines. These assessments included measurements of LV systolic (EF) and diastolic function (E/e′), as well as LA and LV dimension and volumetric quantifications. The Cardiovascular Imaging Core Laboratory of the National University Health System, Singapore, provided oversight and imaging protocol guidelines for quality assurance of echocardiograms. Quality of life (QoL) assessments were based on the Kansas City Cardiomyopathy Questionnaire (KCCQ),[10] made available in local languages in all centres. Quintiles Outcomes, the contract research organisation appointed by the ASIAN-HF academic executive committee, handled all registry operations and data management. ASIAN-HF was an investigator-led study.

Study definitions

Atrial fibrillation was defined as a documented history of AF based on medical records and/or presence of AF/atrial flutter on baseline 12-lead ECG. Patients with a history of AF and AF on baseline ECG were classified as 'persistent AF'; history of AF without AF on baseline ECG classified as 'paroxysmal AF'; AF on baseline ECG without history of AF classified as 'new-onset AF'; sinus rhythm on baseline ECG without history of AF defined as 'sinus rhythm'. Only 'AF' and 'sinus rhythm' were included in this study; other ECG rhythms were excluded. Diabetes was defined as presence of a prior diagnosis (fasting plasma glucose ≥7 mmol/L, random plasma glucose ≥11.1 mmol/L, or HbA1C ≥6.5%) and/or treatment with antidiabetic medications. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73m^2.

Geographical blocs were defined in accordance with the United Nations Statistics Division subregion classification: Northeast Asia (South Korea, Japan, Taiwan, Hong Kong, and China), South Asia (India), and Southeast Asia (Thailand, Malaysia, Philippines, Indonesia, and Singapore). Ethnicity was defined as self-reported Chinese, Malay, Indian, Japanese/Korean, and indigenous Southeast Asians (others).

Patients were routinely followed up every 6 months at each participating site. The primary outcome of this study is composite all-cause mortality or HF hospitalisation within 1 year. Follow-up data were available in 4973 (90%) patients at 1 year (10% lost to follow-up). An independent outcomes committee adjudicated all outcome events.

Statistical analysis

Baseline characteristics were reported as percentages (%) for categorical variables and mean ± standard deviation or median (lower quartile, upper quartile) for continuous variables. Differences in baseline characteristics were assessed with independent *t*-test (continuous), χ^2 test (categorical), or Mann–Whitney *U* test (non-parametric). Univariable logistic regression was performed for each clinical correlate in its association with AF in each HF type and tested for interaction by ethnicity. The association of other ethnicities with AF compared with Chinese was examined in multivariable analyses adjusting for demographics, clinical correlates, and medications. Chinese and Indians were further stratified to assess

the association of geography with AF. Because of limited availability of LA volume index (LAVI) data, multivariable analyses were repeated with the inclusion of LAVI as sensitivity analyses. To further investigate the effects of diabetes, the association of diabetic medications with AF was evaluated with multivariable analyses. Interactions between diabetes with body mass index (BMI) and LAVI were investigated, and stratification performed if present to evaluate the association of diabetes with AF in the subgroups. Mean KCCQ scores in each domain were adjusted for demographics and clinical factors. The association of AF with primary outcome was performed by multivariable Cox regression analysis in the whole cohort of HF, with testing for interaction by ethnicity and HF type. Kaplan–Meier survival curves of subgroups by ethnicity with and without AF were performed and compared by log-rank test. A P value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS Version 21 (IBM Corporation, NY) or Stata/MP 13.0 (StataCorp LP).

Results

Among 5504 patients from the ASIAN-HF registry included in this study [mean age 61 ± 13 years, 27% women, BMI 25 ± 5 kg/m^2, 4541 (83%) HFrEF, 963 (17%) HFpEF], 1383 (25%) had AF (53% persistent AF, 34% paroxysmal AF, 8% new-onset AF, 5% history of AF but missing ECG data). The prevalence of AF was significantly lower in HFrEF (22%) than

Table 1 Comparison of baseline characteristics by AF status in HFrEF and HFpEF

	HFrEF			HFpEF		
	Sinus rhythm	AF	P value	Sinus rhythm	AF	P value
n (%)	3523 (78)	1018 (22)		598 (62)	365 (38)	
Characteristics						
Age, years	58 ± 13	65 ± 12	<0.001	66 ± 13	73 ± 10	<0.001
Female sex	785 (22)	213 (21)	0.356	289 (48)	192 (53)	0.198
Heart rate, bpm	80 ± 15	79 ± 19	0.366	76 ± 15	78 ± 16	0.062
SBP, mmHg	119 ± 20	116 ± 19	<0.001	134 ± 23	128 ± 22	<0.001
DBP, mmHg	73 ± 13	70 ± 13	<0.001	73 ± 13	71 ± 13	0.077
BMI, kg/m^2	25.1 ± 5.1	24.4 ± 5.0	<0.001	27.8 ± 6.2	26.3 ± 6.0	0.001
NYHA class III/IV	1118 (34)	342 (37)	0.046	117 (22)	84 (26)	0.266
NTproBNP*, pg/mL	2852 [1205,8040]	4110 [1915,7731]	<0.001	1804 [730,4690]	2808 [1417,5051]	0.081
Echocardiography						
LVEF, %	27 [22,33]	28 [22,34]	0.022	60 [55,65]	60 [55,66]	0.047
E/e'	22 ± 12	20 ± 10	0.011	17 ± 9	18 ± 7	0.41
LVMI, g/m^2	137 ± 47	139 ± 46	0.367	109 ± 38	109 ± 45	0.978
LAVI, ml/m^2	36 ± 18	55 ± 24	<0.001	31 ± 14	52 ± 22	<0.001
Medical history						
Ischaemic heart failure	1769 (53)	406 (42)	<0.001	203 (38)	101 (31)	0.049
Hypertension	1825 (52)	545 (54)	0.319	429 (72)	277 (76)	0.138
Diabetes	1572 (45)	384 (38)	<0.001	313 (52)	159 (44)	0.01
Chronic kidney disease	1113 (41)	443(50)	<0.001	249 (53)	168 (53)	0.895
Prior stroke	187 (5)	119 (12)	<0.001	37 (6)	47 (13)	<0.001
Peripheral arterial disease	110 (3)	46 (5)	0.03	13 (2)	5 (1)	0.8
Chronic respiratory disease	274 (8)	89 (9)	0.31	45 (8)	38 (10)	0.12
Smoking history	1576 (45)	506 (50)	0.004	141 (24)	90 (25)	0.669
Alcohol history	963 (27)	376 (37)	<0.001	84 (14)	73 (20)	0.013
KCCQ*						
Physical limitation score	75 (50–92)	71 (50–90)	0.08	83 (63–95)	75 (54–92)	0.06
Quality of life score	58 (33–75)	58 (33–75)	0.05	75 (50–83)	67 (42–83)	0.04
Social limitation score	69 (38–94)	58 (25–91)	<0.001	83 (58–100)	75 (50–100)	0.27
Total symptom score	75 (53–92)	75 (50–94)	0.54	81 (58–96)	78 (53–93)	0.08
Clinical summary score	72 (54–89)	71 (50–88)	0.21	80 (62–94)	74 (55–91)	0.01
Overall score	68 (47–84)	64 (44–83)	0.02	78 (59–91)	72 (53–88)	0.02
Medications						
ACE-I/ARB	2691 (78)	719 (72)	<0.001	367 (69)	202 (59)	0.004
Beta blocker	2665 (77)	795 (80)	0.076	357 (67)	247 (73)	0.077
MRA	2032 (59)	590 (59)	0.818	103 (19)	91 (27)	0.01
Digoxin	860 (25)	416 (42)	<0.001	11 (2)	74 (22)	<0.001
Diuretic	2852 (82)	851 (85)	0.033	373 (70)	278 (82)	<0.001

ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; KCCQ, Kansas City Cardiomyopathy questionnaire; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure.

Comparison of baseline characteristics among patients with and without AF in HFrEF and HFpEF. Values expressed as mean ± standard deviation or percentage (%). * values are expressed as median (lower quartile, upper quartile).

HFpEF (38%) ($P < 0.001$). Baseline characteristics of patients by in AF and sinus rhythm by HF type are shown in *Table 1*, and baseline characteristics of all HF patients stratified by ethnicity in *Table S1*. Patients with AF (compared with sinus rhythm) were older and more likely to have a history of prior stroke, higher NT-proBNP levels, and larger LA volumes but less likely to have diabetes and ischemic heart disease. Mean heart rate was similar between AF and sinus rhythm in both HFrEF and HFpEF, with similar beta blocker usage between AF and sinus rhythm but higher digoxin use in AF. Japanese/Korean had the largest LA size while Indians had the smallest in AF, regardless of HF type (*Table 2*). Among patients with HFrEF, 1956 (43%) had diabetes (mean duration 9.7 ± 8.1 years, 98% type 2 diabetes, 25% oral hypoglycemic agents, 8% insulin), while 452 (47%) patients with HFpEF had diabetes (mean duration 12.5 ± 8.9 years, 98% type 2 diabetes, 29% oral hypoglycemic agents, 11% insulin).

Prevalence of atrial fibrillation within Asia

The prevalence of AF by ethnicity and geographical region within Asia is shown in *Figure 1*. Compared with Chinese, Indians had lower prevalence of AF in both HFpEF (7% vs. 28%, $P < 0.001$) and HFrEF (17% vs. 42%, $P < 0.001$), while Japanese/Koreans had higher prevalence of AF in HFrEF (47% vs. 28%, $P < 0.001$). Significant ethnic differences were noted in the association with AF by HF type in multivariable models adjusted for demographics, clinical correlates, and medications (*Figure 2*). Ethnic differences persisted in sensitivity analyses after further adjustment for LAVI ($n = 1670$ in HFrEF, $n = 280$ in HFpEF) [Indian: adjusted odds ratio (AOR) in HFrEF 0.25, 95% CI 0.17–0.36, AOR in HFpEF 0.35, 95% CI 0.18–0.68; Japanese/Korean: AOR in HFrEF 3.94, 95% CI 2.81–5.54].

Only Chinese and Indians were represented in more than one geographical bloc, with striking geographical variations present in subgroup analyses. Among 1659 Indians, 141 (8%) had AF (16% Southeast Asia vs. 7% South Asia, $P < 0.001$). Southeast Asian Indians were three times as likely to have AF compared with South Asian Indians, even after adjusting for clinical covariates (AOR 3.01, 95% CI 1.60–5.67), with no interaction by HF type ($p_{interaction} = 0.15$). Among 1837 Chinese, 577 (31%) had AF, with lower prevalence of AF in Southeast Asia than Northeast Asia (29% vs. 34%, respectively, $P = 0.03$). Southeast Asian Chinese were less likely to have AF compared with Northeast Asian Chinese with no interaction by HF type ($p_{interaction} = 0.50$), but this was attenuated after adjusting for differences in baseline characteristics (as above) (AOR 0.95, 95% CI 0.72–1.27).

Clinical correlates of atrial fibrillation by heart failure type

The clinical correlates of AF in HFrEF and HFpEF were similar across ethnicities (no significant interaction by ethnicity, *Figure 2*). Diabetes was consistently associated with lower odds of AF in both HFrEF (AOR 0.79, 95% CI 0.66–0.95) and HFpEF (AOR 0.58, 95% CI 0.39–0.84) in multivariable analyses. Adjusting for age, sex, ethnicity, and BMI, anti-diabetic medications were not associated with AF (*Table S2*). The association between diabetes and AF was modified by BMI in patients with HFrEF ($p_{interaction}$ in HFrEF = 0.001, $p_{interaction}$ in HFpEF = 0.27). Among obese (BMI $\geq$ 30 kg/m^2) patients with HFrEF, diabetes was not associated with AF (OR 1.39, 95% CI 0.92–2.10); whereas in non-obese patients with HFrEF, diabetes was associated with lower risk of AF (OR 0.69, 95% CI 0.59–0.81).

Association of atrial fibrillation with quality of life

Patients with AF had poorer QoL based on KCCQ indices in both HFrEF and HFpEF, with lowest overall score in HFrEF (*Table 1*). Adjusted for demographics, clinical confounders and education, patients with AF had lower social limitation scores but similar overall summary scores without HF type interactions in all domains (*Table S3*). Ethnic variation was noted only for social limitation ($p_{interaction}$ for ethnicity = 0.009), such that Indians with AF had lower social limitation scores (adjusted β coefficient − 12.4, $P < 0.001$), a difference not observed in the other ethnicities.

Table 2 Comparison of LAVI by ethnicity

	Chinese	Indian	Malay	Japanese/Korean	Others	*P* value
HFrEF						
AF	56.8 ± 22.1	39.2 ± 19.9	39.6 ± 20.7	63.3 ± 26.9	47.5 ± 17.8	<0.001
SR	44.8 ± 17.0	28.1 ± 16.6	36.2 ± 16.7	44.2 ± 17.4	36.1 ± 16.9	<0.001
HFpEF						
AF	54.8 ± 22.6	42.4 ± 18.0	41.5 ± 18.2	59.2 ± 21.6	NA	0.02
SR	36.7 ± 13.5	25.9 ± 13.6	25.6 ± 8.8	39.7 ± 14.8	24.1 ± 6.8	<0.001

Comparsion of LAVI in patients with and without AF in HFrEF and HFpEF stratified by ethnicity.
AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVI, left atrial volume indexed by body surface area; SR, sinus rhythm.

Figure 1 Prevalence of atrial fibrillation by ethnicity and geographical region in within Asia. Prevalence of AF by ethnicity (upper panel) and geographical region (lower panel), classified by HFpEF (blue) and HFrEF (red). AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

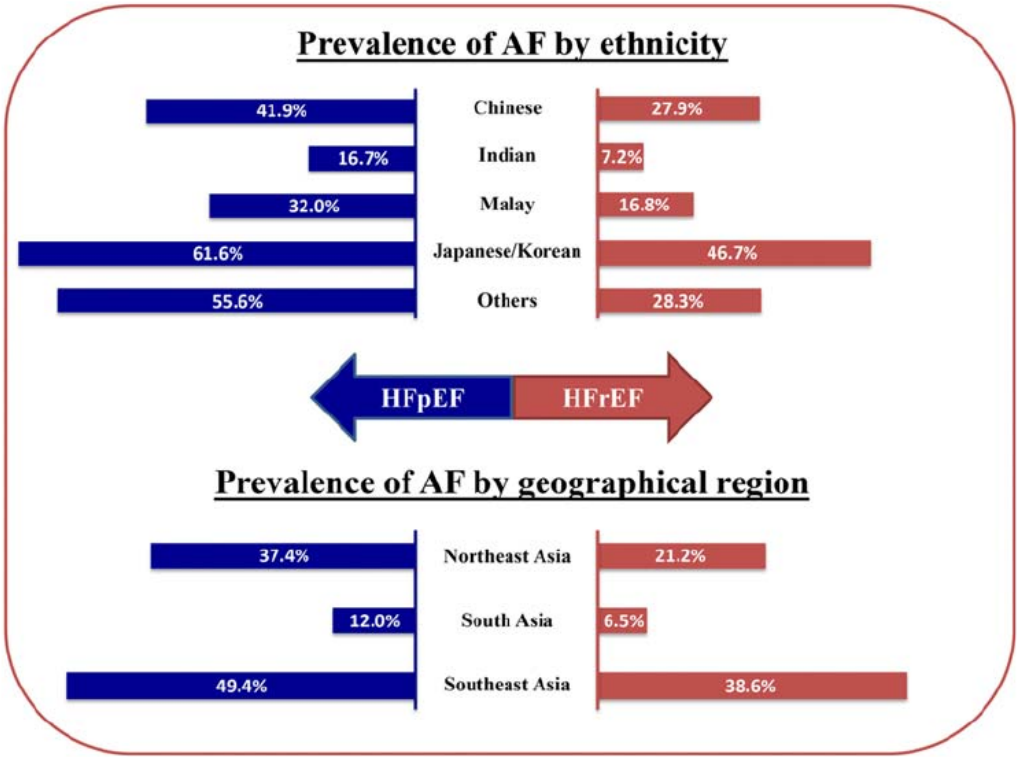
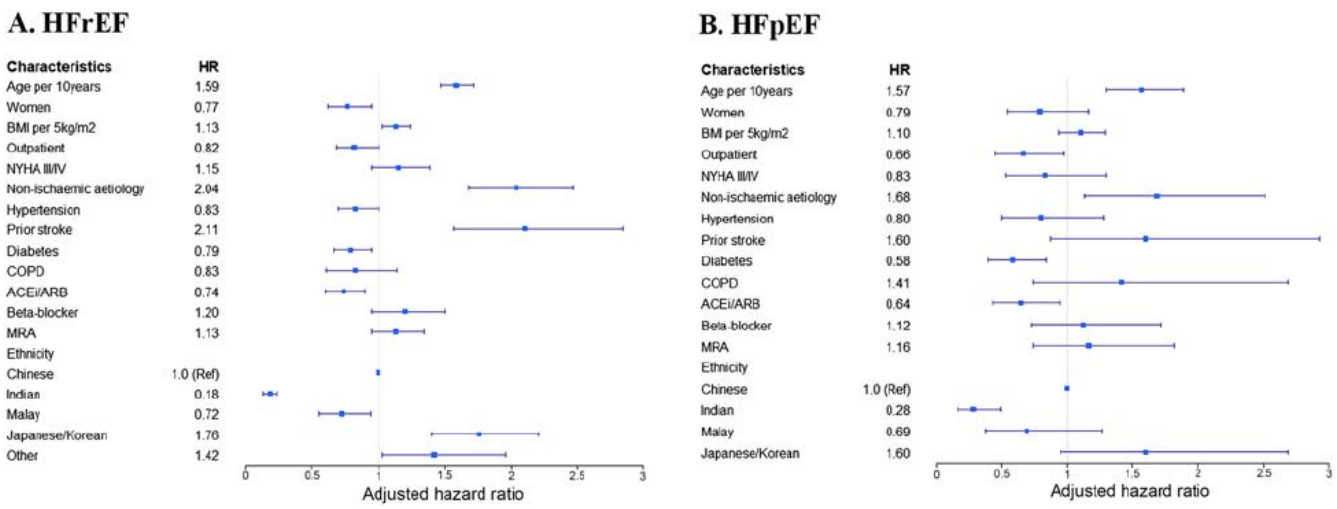


Figure 2 Association of clinical correlates with atrial fibrillation in (A) HFrEF and (B) HFpEF. Multivariable analysis of the association of clinical correlates including ethnicity (Chinese as reference ethnic race) with atrial fibrillation in (A) HFrEF and (B) HFpEF. ACE-I, angiotensin-converting enzyme inhibitor; AOR, adjusted odds ratio; ARB, angiotensin receptor-II blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association functional class; MRA, mineralocorticoid receptor antagonist.



Association of atrial fibrillation with outcomes

Over a follow-up period of 1 year, 982 (20%) patients either died or were hospitalized for HF (24% AF vs. 18% sinus rhythm, $P < 0.001$). AF was associated with increased primary outcome (OR 1.42, 95% CI 1.24–1.63), without interaction by HF type ($p_{interaction} = 0.39$). Similar associations were observed for all-cause mortality (12% AF vs. 9% sinus rhythm, $P < 0.001$) and HF hospitalizations (16% AF vs. 11% sinus rhythm, $P < 0.001$). In separate multivariable models, AF increased the risk of all-cause mortality (adjusted HR 1.61, 95% CI 1.27–2.06) and HF hospitalisations accounting for death as competing risk (adjusted HR 1.24, 95% CI 1.02–1.52), both without interaction by HF type ($p_{interaction} > 0.05$).

Although Kaplan–Meier survival curves by ethnicity appeared to show that the association of AF with poor survival was stronger in Chinese and Indians compared with Malays and Japanese/Koreans (*Figure 3*), formal ethnic interaction testing was non-significant ($p_{interaction} = 0.08$). These associations among Chinese and Indians persisted even after adjusting for age, sex, BMI, NYHA class, enrolment type, HF type, HF aetiology, diabetes, hypertension, stroke, and CKD but not was present in Malays, Japanese/Koreans, and indigenous Southeast Asians (Chinese: AHR 1.51, 95% CI 1.21–1.88; Indian: AHR 2.26, 95% CI 1.26–4.06; Malay: AHR 1.16, 95% CI 0.81–1.65; Japanese/Korean: AHR 0.93, 95% CI 0.58–1.49; Others: AHR 1.44, 95% CI 0.60–3.50). In the total cohort of HF patients, AF independently increased the risk of the composite outcome of 1 year all-cause mortality or HF hospitalisation in multiple models of multivariable adjustments (*Table 3*).

Discussion

The prospective multinational ASIAN-HF study provides novel findings on the ethnic differences in prevalence of AF among patients with HF recruited across Asia using identical protocols and extends upon previous studies in several important ways: (i) it is the first multinational study on ethnic differences and clinical correlates of AF in Asia; (ii) by having large numbers of adjudicated outcomes and comprehensive QoL data; and (iii) having good representation of different ethnicities in Asia from countries at divergent economic levels. Indians had the lowest prevalence of AF regardless of HF type, while Japanese/Korean with HFrEF had the highest prevalence of AF. Interestingly, the association with AF differed according to geographical locations among the same ethnicity, with Southeast Asian Indians having higher odds of AF compared with Northeast Asian Indians. Clinical

Figure 3 Kaplan–Meier survival curves of patients with AF vs. sinus rhythm by ethnicity. Kaplan–Meier survival curves of the association of AF with primary composite event of HF hospitalisation and all-cause mortality among Chinese, Indians, Malays and Japanese/Koreans with HF, with separation of survival curves among Chinese and Indians. AF, atrial fibrillation; HF, heart failure.

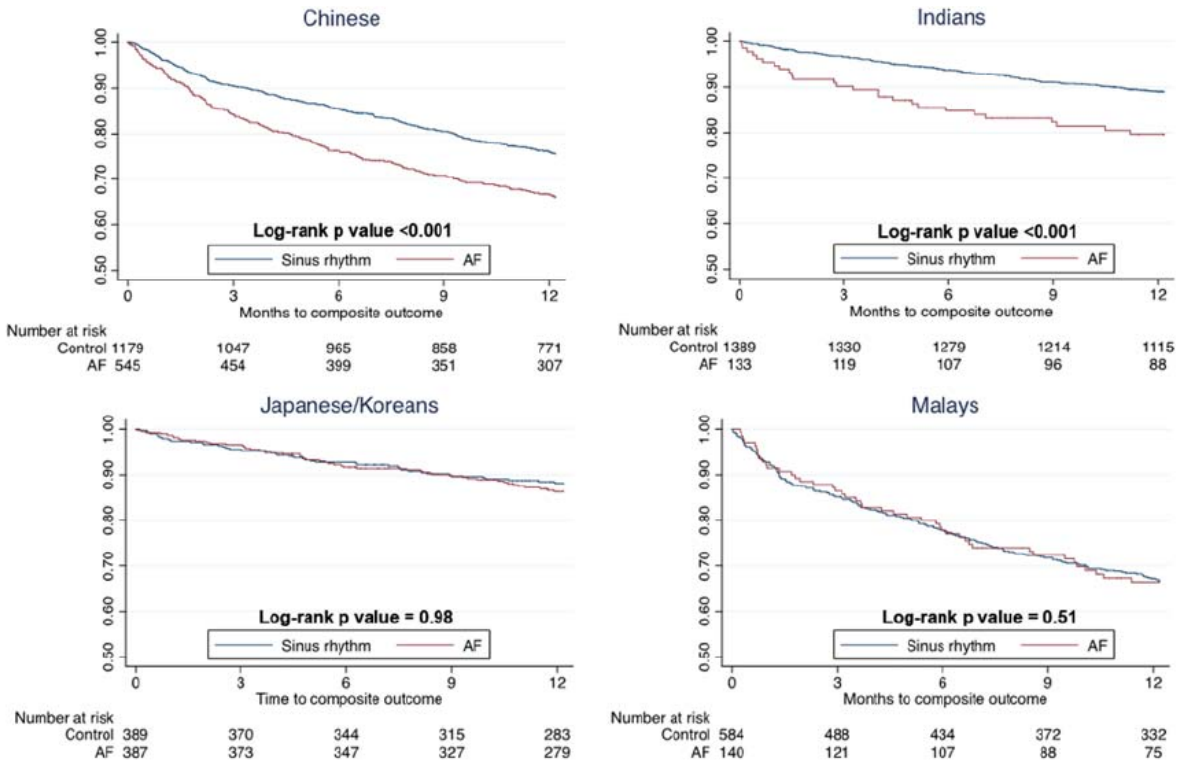


Table 3 Association of AF with 1 year primary composite endpoint of HF hospitalisation or all-cause mortality

	Hazard ratio	95% CI	*P* value
Crude AF	1.42	1.24–1.63	<0.001
AF + Age	1.34	1.16–1.54	<0.001
Model A	1.31	1.13–1.52	<0.001
Model B	1.38	1.18–1.63	<0.001

Association of AF with primary composite endpoint of HF hospitalisation or all-cause mortality in multivariable adjustment models.
Model A: adjusted for age, sex, BMI, NYHA, ethnicity, and enrolment type.
Model B: Model A + HF type, HF aetiology, hypertension, diabetes, stroke, chronic kidney disease.
AF, atrial fibrillation; BMI, body mass index; HF, heart failure; NYHA, New York Heart Association functional class

correlates and adverse outcomes associated with AF were similar across ethnicities.

Ethnic variations among Asian-heart failure patients

Although the SHOP-PEOPLE study previously reported a lower prevalence of AF among Asian patients with HF, it was not powered to detect differences between the three major ethnic races within Singapore and significant heterogeneity exists within Asian ethnicities.[5] The ASIAN-HF study offers a unique opportunity for ethnic and interregional comparisons among a large contemporary cohort of Asian patients recruited simultaneously across multiple Asian countries using identical study procedures. We report a prevalence of 25% of AF in HF within Asia, consistent with prior observations of 16–42% among Asian HF patients.[11,12] Additionally, we found ethnic differences in the prevalence of AF within Asia by HF type. In HFrEF, Japanese/Korean patients had the highest prevalence of AF, while Indians had the lowest prevalence of AF in both HFpEF and HFrEF. The significance of ethnicity was previously demonstrated among Asian women in the Women's Health Initiative,[13] while South Asians in the United Kingdom had lower AF prevalence, attributed to inherent genetic differences that render atria morphologically and physiologically distinct.[6,14] Ethnic variations in our study were independent of traditional AF risk factors. Furthermore, although ethnic differences in LA size may precede AF development, ethnic variations notably among Japanese/Koreans and Indians in AF prevalence persisted in sensitivity analyses after adjustment for LAVI, highlighting contributory roles of factors that remain unaccounted for. The development of AF is often multifactorial and the role of 'nature versus nurture' remains of great interest. Although non-shared environmental factors play a larger contributory role, genetic and shared environmental factors also participate in the pathogenesis of AF.[7] An interesting observation from our study was the differential AF associations among Indians in geographically separate locations. Local dietary habits, living conditions, and levels of physical activity may differ vastly in different regions of Asia. Singapore is an advanced economy with 'westernized' lifestyle, whereas the World Health Organization classifies India as a lower income region. The adoption of the 'western' lifestyle may explain the tripled odds of AF among Southeast Asian Indians (i.e. Singapore, Malaysia) compared with South Asian Indians (i.e. India). Indeed, the RACE-3 study highlighted the significance of lifestyle factors on AF, with exercise and dietary restrictions complementing HF medications in AF reduction.[15] Nonetheless, the lower prevalence of AF among Indians is consistent with previous studies[6,14] and suggests an intrinsic effect of Indian ethnicity, compared with other ethnicities, on AF. Ethnic variations in AF are thus likely a result of complex interactions between genetic and environmental factors that are population specific, suggesting the need for targeted therapy among different populations.

Diabetes-atrial fibrillation paradox

Although diabetes is a well-recognized risk factor for AF, the paradoxically protective effect of diabetes on AF was reported in Swedish-HF, SHOP-PEOPLE, and GWTG-HF.[1,5,16] We now extend this paradoxical association for the first time to a larger cohort across Asia in both HFrEF and HFpEF. The exact mechanisms remain unknown, although we have previously thought it unlikely to be an effect of collider bias.[17] Separately, diabetic medications had been reported to decrease the risk of AF. Modulation of electrical and mechanical properties of pulmonary veins and atria by dipeptidyl peptidase-4 inhibitors, inhibition of inflammation and oxidation by metformin and reduction of proarrhythmic substrates via inhibition of ATP-sensitive potassium channels by glibenclamide and tolbutamide have been suggested to confer protective benefits against AF.[18–20] However, antidiabetic medications did not exhibit the same relationship with AF after adjusting for patient demographics in our study. The absence of treatment effect in our study is likely because of different cardiac substrates, with HF patients more likely to have undergone structural and electrical remodelling, while prior studies were in animals or populations with largely structurally normal hearts. Biological plausibility for the diabetes-AF paradox remains unproven, but previous studies have shown diabetes to be associated with inward remodelling effects in the paradoxical protection against aortic aneurysms, smaller LV volumes and more concentric LV remodelling.[21–24] The protection from outward remodelling has been attributed to advanced glycation end-product (AGE) cross links, with AGE cross link breaker treatment leading to LV dilatation.[25] Given our previous finding of smaller LAVI in diabetes

regardless of AF or HF subtype,[5] diabetic protection against atrial outward remodelling may plausibly confer a lower risk of AF. In non-HF cohorts, BMI was acknowledged as a residual confounding factor in the increased risk of AF with diabetes.[26] An increased association with AF was found among obese patients but absent among patients with normal weight.[27] Similarly, two Japanese studies, with mean BMI within normal ranges (22–25 kg/m^2) did not demonstrate an association between diabetes and AF.[28,29] When stratified by BMI, the diabetes-AF paradox was only observed in non-obese patients with HFrEF, and not in obese patients in whom the obesity-associated higher odds of AF may have masked any diabetes-related lower odds of AF. The exact mechanisms by which obesity and diabetes interact in predisposing to AF remains unknown, although interestingly, the Look AHEAD trial did not find a reduction in AF among diabetic patients even with modest weight reduction.[30] It should be noted however, that the mean BMI in Look AHEAD (36 kg/m^2) was much higher than in ASIAN-HF (25 kg/m^2), and the modest weight loss of 6% in Look AHEAD might have been insufficient to reduce the risk of AF.

Association of atrial fibrillation with outcomes

AF portends a poorer prognosis in HF. We found a direct association of AF with death or HF hospitalisation regardless of HF type, consistent with the Swedish-HF registry.[1] Data on ethnic differences in outcomes with AF in the context of HF are conflicting. Higher in-hospital mortality in black compared with white, Hispanic, and Asian-American HF patients with AF were noted,[3] but ethnic differences were not observed between black and white patients in the GWTG-HF registry[4] or Asian and white patients in the Asia-Pacific SHOP-PEOPLE study.[5] Although ethnic interactions with primary outcome were not statistically significant, the distinct separation in Kaplan–Meier survival curves by AF among Chinese and Indians persisted even after adjusting for demographics and clinical co-morbidities. Exact mechanisms underlying these observations are uncertain and deserve further study.

Limitations

We acknowledge the potential of selection bias from site selection and variations in patient willingness to participate in a prospective registry. Site selection in ASIAN-HF was based on the size and geographical location within the country, patient population, and availability of expertise in echocardiography. Efforts were made to ensure protocol standardisation and adherence, including region-specific language translations, on-site investigator training and regular monitoring, and centralized database management in order to maintain quality data and minimize missing data. Ethnicity was self-reported, with the potential for misclassification. The number of indigenous Southeast Asian patients with HFpEF was too small to allow for meaningful comparisons. We recognize the differences in healthcare systems and cultural barriers to healthcare access within Asia, which may potentially affect the AF and HF burden in our study. Duration of AF and the incidence of AF during the course of follow-up were unavailable. Analyses of AF prevalence were cross-sectional and do not allow ascertainment of temporal relationships between AF and other clinical factors. Moreover, patients with asymptomatic paroxysmal AF may have been undetected, although the inclusion of these patients will unlikely attenuate the strong relationships with AF seen in our study.

Conclusions

Among patients with HF across Asia, clinical correlates and adverse outcomes associated with AF are similar across ethnicities; however, there are striking ethnic variations in the prevalence of AF that are not accounted for by known risk factors.

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Conflict of interest

CSPL is supported by a Clinician Scientist Award from the National Medical Research Council Singapore. CSPL has received research support from Boston Scientific, Medtronic, and Vifor Pharma, and has consulted for Bayer, Novartis, Takeda, Merck, Astra Zeneca, Janssen Research & Development, LLC and Menarini. She has served on the Clinical Endpoint Committee for DC Devices. AMR has received research support from Boston Scientific, Bayer, Astra Zeneca, Medtronic, Roche Diagnostics, Abbott Laboratories, Thermo Fisher, Critical Diagnostics and has consulted for Bayer, Novartis, Merck, Astra Zeneca, Roche Diagnostics. The other authors have no conflict of interests to declare.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of all heart failure patients stratified by ethnicity.

Table S2. Association of anti-diabetic drugs with AF in HF (n = 2428)

Table S3. Adjusted mean KCCQ domains scores

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