

Sex and ethnicity modified high 1-year mortality in patients in Singapore with newly diagnosed atrial fibrillation

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ABSTRACT

Introduction: We investigated sex and ethnic differences in the incidence, clinical characteristics and 1-year mortality of patients with newly diagnosed AF in a multiethnic population.

Method: This retrospective cohort study of patients diagnosed with AF from 2008 to 2015 was based on medical claims, casemix and subvention data submitted to the Ministry of Health. Patients with AF were matched with controls without AF for age (3-year bands), sex and ethnicity, and categorised as middle-aged (45–64 years) or elderly (≥65 years) among major ethnic groups in Singapore (Chinese, Malay and Indian).

Results: Among 40,602 adults with AF (elderly 74%), Malays had the highest age-standardised incidence rate of AF, followed by Chinese and Indians; and the rate was higher in men. Despite having the worst cardiovascular risk profile, Indians had the lowest prevalence and incidence of AF. The 1-year mortality rate after newly diagnosed AF was 22–26 deaths per 100 people. Newly diagnosed AF was independently associated with increased 1-year all-cause mortality among middle-aged (adjusted odds ratio [AOR] 9.08, 95% confidence interval [CI] 7.36–11.20) and elderly adults (AOR 3.60, 95% CI 3.40–3.80) compared with those without AF. Sex differences in mortality among patients with AF were limited to elderly adults (men: AOR 1.17, 95% CI 1.11–1.24), while Indians were associated with a 30% increased odds of mortality compared with Chinese regardless of age (middle-aged: AOR 1.27, 95% CI 1.09–1.548 elderly: AOR 1.33, 95% CI 1.22–1.45).

Conclusion: Variations in incidence, clinical profile and 1-year mortality of patients with AF in a nationwide cohort were influenced by sex and ethnicity. Newly diagnosed AF portends a worse prognosis and is a marker of high mortality within the first year.

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Keywords: Atrial fibrillation, ethnic differences, one-year mortality, sex differences

INTRODUCTION

Atrial fibrillation (AF) is the most common clinically significant arrhythmia and is associated with increased risks of stroke, dementia, heart failure (HF) and death.¹ Globally, 33.5 million people were reported to have AF in 2010,² with numbers expected to increase exponentially by 2050.^{3–7} While in part due to ageing populations,⁸ increasing cardiovascular risk factors

and the detection of silent AF further contribute to the growing epidemic.⁹

Apart from modifiable clinical risk factors, non-modifiable factors, including sex and ethnicity, exert varying influences on the prevalence of AF.^{10–22} Significant heterogeneities in AF prevalence were observed within Asian populations.^{23–25} While not fully understood, these differences may be contributed by the

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CLINICAL IMPACT

What is New

- These nationwide data from Singapore highlight significant sex and ethnic differences in the epidemiology, clinical profile and 1-year mortality rate in newly diagnosed atrial fibrillation (AF).
- This study highlights the significant burden of disease AF carries as our population ages.

Clinical Implications

- The high 1-year mortality after diagnosis calls for AF to be regarded as an important marker of poor prognostic outcomes and premature mortality.
- Early aggressive management of AF and underlying comorbidities should be considered in these high-risk patient groups.

complex interactions between genetic and environmental factors.^{26,27} The effects of sex and ethnicity on mortality from AF were, however, more variable, with sex differences not observed^{10–13} but ethnic differences among Asians with HF reported.²⁴

Despite the high prevalence of hypertension, diabetes and HF in Southeast Asia,²⁸ there is a paucity of data on AF characteristics and mortality in this region.^{29–31} Therefore, we investigated sex and ethnic differences in the incidence, clinical characteristics and 1-year mortality of patients with newly diagnosed AF in a nationwide, multiethnic population in Singapore.

METHOD

This retrospective cohort study on newly diagnosed non-valvular AF from 2008 to 2015 included subjects aged ≥ 45 years from the 3 major ethnic groups in Singapore (Chinese 74%, Malay 13% and Indian 9%). The sources of diagnosis data comprised anonymised individual patient-level data from medical claims, casemix and subvention data submitted to the Ministry of Health by primary care clinics (public and private) and public hospitals (emergency departments and inpatient units). These cover more than 95% of Singapore's population with minimal selection bias. It was expected that the majority of AF would be identified through available data sources as most Singapore residents would be treated in public healthcare institutions owing to greater accessibility, extensive coverage and higher subsidy. Ethnicity was

based on registered ethnicity at birth. Housing type served as a surrogate of socioeconomic status, with private housing (condominiums or private houses) corresponding to higher socioeconomic status and public housing of 1- to 2-room flats or studio apartments corresponding to lower socioeconomic status. Identification of AF and other diseases was based on codes from the International Classification of Diseases (ICD) 9th Revision, Clinical Modification (prior to 2012); and ICD 10th Revision, Australian Modification (from 2012) (Supplementary Table S1 in online Supplementary Materials). The survival status of patients was ascertained from the Singapore Registry of Birth and Death. A matched cohort without AF was obtained by matching each patient with AF to a control without AF who was alive in the index year (year of diagnosis of the matched patient) for age (3-year bands), sex and ethnicity. Population numbers were obtained from the Singapore Department of Statistics' mid-yearly population estimates of Singapore residents for the calculation of AF incidence and prevalence. The study complied with the Declaration of Helsinki and patient consent was waived as only anonymised data were obtained from an administrative database.

Clinical variables

Patients were stratified into 2 age groups: middle-aged (45–64 years) and elderly (≥ 65 years). An age cut-off of 45 years was chosen as 5% of patients with AF were below 45 years, in order to investigate patients between the 5th and 95th age percentiles. Chronic diseases at baseline were defined as a diagnosis prior to or within 6 months of first diagnosis of AF. The clinical risk factors included hypertension, hyperlipidaemia, renal impairment, end-stage renal failure, ischaemic heart disease (IHD), HF, stroke or transient ischaemic attack, haemorrhagic stroke, systemic embolism, peripheral vascular disease, dementia, depression, hyperthyroidism and cancer. CHA₂DS₂VASc scores were calculated for all patients.³²

Statistical analyses

Crude AF incidence was estimated by the number of newly diagnosed AF patients among people at risk in the same year (with the number of diagnosed AF cases in the previous year removed from the population number in the current year). Crude AF prevalence was estimated by dividing the number of patients diagnosed with AF before and still alive on 1 January of each year by the population number in the same year. To account for the change in population structure over time, adjusted incidence and prevalence rates were calculated

using direct age standardisation and the 2008 resident population as the reference population by 5-year age bands stratified by sex and ethnicity. Crude 1-year mortality was estimated by dividing the number of patients who died in the next calendar year by the number of patients in that year. Baseline characteristics between ethnicities and sexes were compared using the Wilcoxon rank sum test or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. As specific dates of death were unavailable from the National Death Registry (only the years of death were available to prevent re-identification of patients), logistic regression analyses were performed to compare the odds ratios with 95% confidence intervals (CIs) for mortality within 1 year, between the sex and ethnic groups within the cohort of AF patients, and between patients with and without AF. To determine if 2-way interactions existed between age and sex, age and ethnicity, and sex and ethnicity, these interaction terms were included in logistic regression models. All statistical analyses were performed using STATA/SE version 16 (StataCorp, College Station, US), at 5% level of significance.

RESULTS

From 2008 to 2015, a total of 40,602 adults were newly diagnosed with AF. The middle-aged group made up 10,671 (26%) of the patients with a mean age of 57 ± 5 years, 32% women and 76% Chinese; the rest or 29,931 (74%) were in the elderly group with a mean age of 78 ± 8 years, 52% women and 84% Chinese (online Supplementary Fig. S1). Temporal trends in the prevalence and incidence rates of AF are shown in Fig. 1. In both the middle-aged and elderly groups, a linear increase in the age-sex-ethnicity-adjusted prevalence rates was observed from 2008 to 2015 (middle-aged group: 59.9 to 75.2 per 10,000 people; elderly group: 525.4 to 696.5 per 10,000 people). The age-sex-ethnicity-adjusted incidence rate of AF, however, remained fairly constant between 11 and 14 per 10,000 people in the middle-aged group, while the corresponding rate increased from 101.5 to 107.4 per 10,000 people in the elderly group.

Ethnic and sex differences in incidence of AF

Malays had the highest age-standardised incidence rate (ASIR) of AF, followed by Chinese and Indians, while men had a higher ASIR of AF than women in both age groups (Fig. 1). Malay men had the highest ASIR of AF in both age groups, increasing from 20.8 per 10,000 in 2008 to 23.1 per 10,000 in 2015 in middle-aged adults and 124.5 to 155.9 per 10,000 in elderly adults, while Indian women

had the lowest ASIR of AF in both age groups. The ASIR of AF increased from 2008 to 2015 in men of all ethnicities in both age groups, while the ASIR decreased slightly among middle-aged Chinese and Indian women, but increased sharply among Malay elderly women. The temporal trend of AF by sex and ethnicity in both age groups is shown in the online Supplementary Fig. S2.

Ethnic and sex differences in risk profile of AF

Among middle-aged adults, Chinese had the lowest prevalence of hypertension, hyperlipidaemia, diabetes, renal impairment, IHD, HF and peripheral vascular disease compared with Malays and Indians at AF diagnosis ($P < 0.05$) (Table 1). Indian men had the highest prevalence of hyperlipidaemia, diabetes, IHD and vascular disease but the lowest prevalence of hyperthyroidism. Among elderly adults, men had a higher prevalence of IHD, HF, haemorrhagic stroke and cancer (online Supplementary Table S2). When stratified by ethnicity, Indians had the highest prevalence of hypertension, hyperlipidaemia, diabetes and IHD in both men and women (Table 2), while Chinese again had the lowest prevalence of hyperlipidaemia, diabetes, renal impairment, IHD and HF but the highest cancer prevalence ($P < 0.05$) (online Supplementary Table S3). Compared with patients without AF, those with AF had a higher prevalence of chronic conditions including hypertension, hyperlipidaemia, diabetes, IHD, HF, stroke, renal impairment, cancer, depression, dementia and thyrotoxicosis ($P < 0.05$) (online Supplementary Table S4).

Ethnic and sex differences in 1-year mortality

Between 2008 and 2015, the 1-year mortality after AF diagnosis improved but remained high, from 26 to 22 deaths per 100 people (temporal trends stratified by sex, ethnicity and age in Fig. 2). One-year mortality after AF diagnosis was higher in elderly adults but was on the downward trend from 31 to 26 per 100 patients, while remaining fairly constant between 11 and 14 per 100 middle-aged adults (online Supplementary Fig. S3). However, the majority of deaths were non-cardiovascular in both middle-aged and elderly adults (Tables 1 and 2).

Among patients with AF and after adjusting for age, sex, ethnicity, housing type and clinical risk factors, sex differences in 1-year all-cause mortality were limited to elderly adults, with men having a 17% increased odds of mortality compared with women (Table 3). Ethnic differences in 1-year all-cause mortality were observed only between Indians and Chinese, with Indians associated with a 30% increased odds of mortality compared with Chinese in both age groups (Table 3).

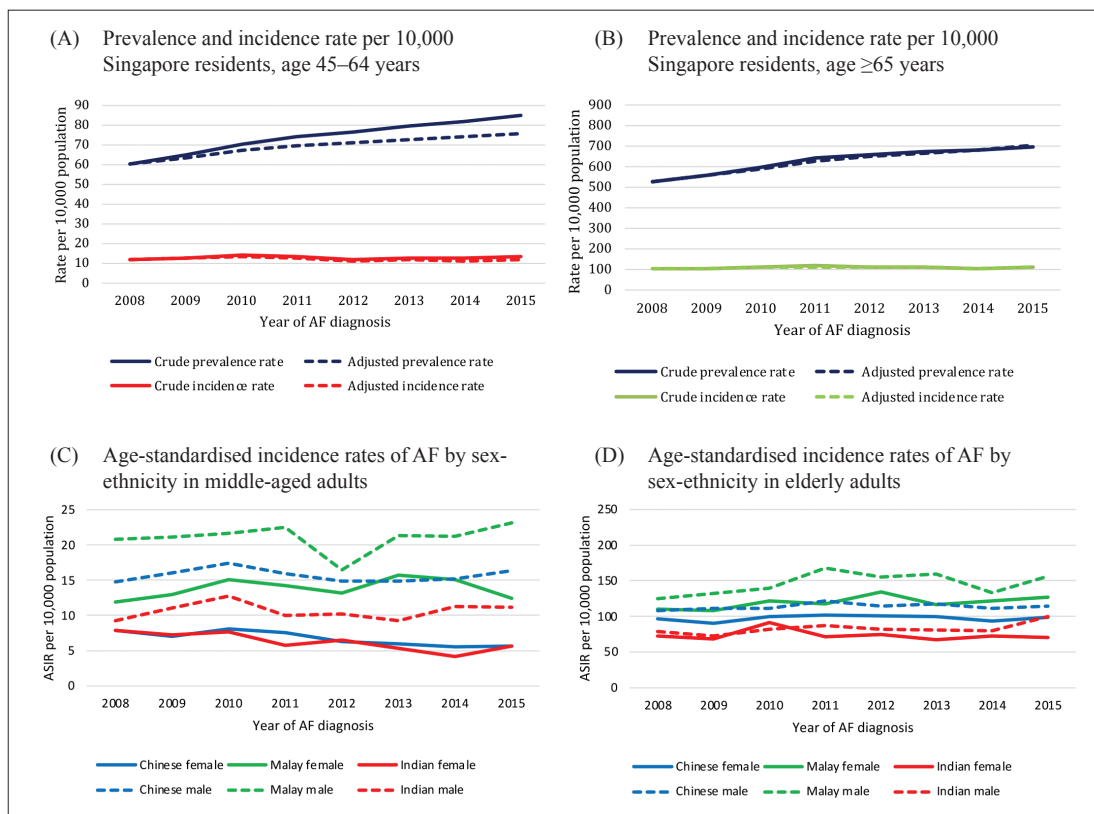


Fig. 1. Crude and age-sex-ethnicity-adjusted (A) prevalence and (B) incidence of atrial fibrillation (AF) in Singapore by age. The prevalence and incidence of AF were almost 10-fold higher in elderly compared with middle-aged adults per 10,000 persons. The age-standardised incidence rate of AF was 10-fold higher in (C) elderly (50–200 per 10,000 persons) compared with (D) middle-aged adults (5–25 per 10,000 persons).

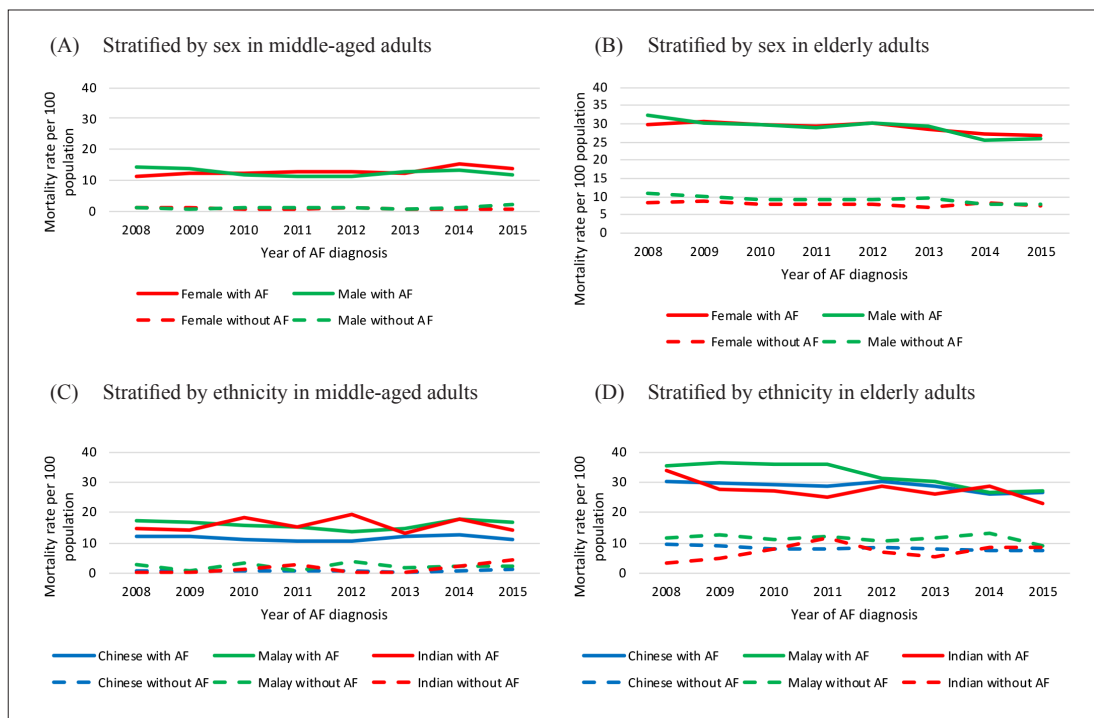


Fig. 2. One-year all-cause mortality rates by age, sex and ethnicity in patients with newly diagnosed atrial fibrillation (AF).

Table 1. Characteristics of patients by sex and ethnicity among middle-aged adults (age 45–64 years)

	Women				Men			
	Chinese (n=2434)	Malay (n=805)	Indian (n=204)	P ^a	Chinese (n=5645)	Malay (n=1194)	Indian (n=389)	P ^a
Age, years								
Median (IQR)	58 (54–62)	58 (54–61)	59 (53–62)	0.114 ^b	58 (54–62)	57 (53–61)	58 (54–61)	<0.001 ^b
Mean (SD)	57 (5)	57 (5)	57 (5)		57 (5)	57 (5)	57 (5)	
Housing type, no. (%)								
Public (studio apartments)	182 (7.5)	146 (18.1)	27 (13.2)	<0.001 ^{b,c}	552 (9.8)	162 (13.6)	46 (11.8)	<0.001 ^{b,c,d}
Public (small apartments)	628 (25.8)	210 (26.1)	49 (24.0)		1270 (22.5)	284 (23.8)	106 (27.3)	
Public (medium apartments)	800 (32.9)	270 (33.5)	67 (32.8)		1718 (30.4)	444 (37.2)	110 (28.3)	
Public (large apartments)	537 (22.1)	165 (20.5)	52 (25.5)		1333 (23.6)	278 (23.3)	95 (24.4)	
Private (condominiums)	172 (7.1)	7 (0.9)	6 (2.9)		449 (8.0)	16 (1.3)	21 (5.4)	
Private (houses)	115 (4.7)	7 (0.9)	3 (1.5)		323 (5.7)	10 (0.8)	11 (2.8)	
Place of notification, no. (%)								
Inpatient	1289 (53.0)	567 (70.4)	130 (63.7)	<0.001 ^{b,c,d}	3443 (70.0)	881 (73.8)	290 (74.6)	<0.001 ^{b,c,d}
Public clinic	642 (26.4)	116 (14.4)	38 (18.6)		1111 (19.7)	132 (11.1)	37 (9.5)	
Emergency department	390 (16.0)	117 (14.5)	31 (15.2)		856 (15.2)	162 (13.6)	42 (10.8)	
Private clinic	113 (4.6)	5 (0.6)	5 (2.5)		235 (4.2)	19 (1.6)	20 (5.1)	
CHA ₂ DS ₂ -VASc score								
Median (IQR)	2 (1–4)	3 (2–5)	3 (2–5)	<0.001 ^{b,c}	2 (1–3)	2 (1–4)	3 (2–4)	<0.001 ^{b,c,d}
Mean (SD)	2.6 (1.5)	3.5 (1.6)	3.4 (1.7)		2.0 (1.6)	2.5 (1.6)	2.7 (1.6)	
0	680 (27.9)	92 (11.4)	29 (14.2)		1091 (19.3)	148 (12.4)	41 (10.5)	
≥2	1754 (72.1)	713 (88.6)	175 (85.8)	<0.001 ^{b,c}	3347 (59.3)	865 (72.5)	301 (77.4)	<0.001 ^{b,c}

Table 1. Characteristics of patients by sex and ethnicity among middle-aged adults (age 45–64 years) (Cont'd)

	Women				Men			
	Chinese (n=2434)	Malay (n=805)	Indian (n=204)	P ^a	Chinese (n=5645)	Malay (n=1194)	Indian (n=389)	P ^a
Diagnosis prior to or within 6 months after first AF, no. (%)								
Hypertension	1426 (58.6)	623 (77.4)	149 (73.0)	<0.001 ^{b,c}	3682 (65.2)	848 (71.0)	279 (71.7)	<0.001 ^{b,c}
Hyperlipidaemia	1168 (48.0)	571 (70.9)	144 (70.6)	<0.001 ^{b,c}	3188 (56.5)	809 (67.8)	290 (74.6)	<0.001 ^{b,c,d}
Diabetes	657 (27.0)	449 (55.8)	119 (58.3)	<0.001 ^{b,c}	1859 (32.9)	561 (47.0)	214 (55.0)	<0.001 ^{b,c,d}
Renal impairment	345 (14.2)	245 (30.4)	45 (22.1)	<0.001 ^{b,c,d}	819 (14.5)	289 (24.2)	84 (21.6)	<0.001 ^{b,c}
End-stage renal failure	200 (8.2)	125 (15.5)	21 (10.3)	<0.001 ^b	368 (6.5)	115 (9.6)	32 (8.2)	0.001 ^b
Ischaemic heart disease	579 (23.8)	300 (37.3)	83 (40.7)	<0.001 ^{b,c}	2455 (43.5)	668 (56.0)	265 (68.1)	<0.001 ^{b,c,d}
Chronic heart failure	436 (17.9)	255 (31.7)	60 (29.4)	<0.001 ^{b,c}	1116 (19.8)	402 (33.7)	126 (32.4)	<0.001 ^{b,c}
Stroke/transient ischaemic attack	315 (12.9)	138 (17.1)	28 (13.7)	0.012 ^b	893 (15.8)	176 (14.7)	65 (16.7)	0.551
Haemorrhagic stroke	76 (3.1)	30 (3.7)	4 (2.0)	0.447	243 (4.3)	53 (4.4)	20 (5.1)	0.732
Systemic embolism	14 (0.6)	8 (1.0)	4 (2.0)	0.051 ^c	39 (0.7)	12 (1.0)	7 (1.8)	0.042 ^c
Vascular disease	69 (2.8)	53 (6.6)	14 (6.9)	<0.001 ^{b,c}	217 (3.8)	67 (5.6)	38 (9.8)	<0.001 ^{b,c,d}
Dementia	2 (0.1)	6 (0.8)	0	0.011 ^b	14 (0.3)	2 (0.2)	1 (0.3)	0.904
Depression	62 (2.6)	19 (2.4)	11 (5.4)	0.044 ^{c,d}	100 (1.8)	25 (2.1)	9 (2.3)	0.594
Hyperthyroidism	217 (8.9)	61 (7.6)	9 (4.4)	0.055 ^c	190 (3.4)	57 (4.8)	5 (1.3)	0.003 ^{b,c,d}
Cancer	210 (8.6)	51 (6.3)	16 (7.8)	0.116 ^b	349 (6.2)	49 (4.1)	19 (4.9)	0.015 ^b
All-cause deaths within 1 year from diagnosis of AF, no. (%)	274 (11.3)	132 (16.4)	36 (17.7)	<0.001 ^{b,c}	651 (11.5)	186 (15.6)	58 (14.9)	<0.001 ^{b,c}
Cardiovascular deaths within 1 year from diagnosis of AF, no. (%)	91 (3.7)	51 (6.3)	15 (7.4)	0.001 ^{b,c}	252 (4.5)	103 (8.6)	22 (5.7)	<0.001 ^b

AF: atrial fibrillation; IQR: interquartile range; SD: standard deviation

^a The *P* value indicates whether there is statistically significant difference across the 3 ethnicities while the superscript letters indicate pairwise comparisons^b Statistically significant difference between Chinese and Malays, *P*<0.05^c Statistically significant difference between Chinese and Indians, *P*<0.05^d Statistically significant difference between Malays and Indians, *P*<0.05

Table 2. Characteristics of patients by sex and ethnicity among elderly adults (age ≥65 years)

	Women			P ^a	Men			P ^a
	Chinese (n=13,171)	Malay (n=1736)	Indian (n=664)		Chinese (n=12,043)	Malay (n=1627)	Indian (n=690)	
Age, years								
Median (IQR)	80 (74–87)	76 (71–82)	77 (72–82)	<0.001 ^{b,c}	76 (70–82)	76 (70–82)	77 (71–83)	0.039 ^d
Mean (SD)	81 (8)	77 (7)	77 (7)		77 (8)	76 (7)	77 (8)	
Housing type, no. (%)								
Public (studio apartments)	1384 (10.5)	289 (16.7)	70 (10.5)	<0.001 ^{b,d}	1359 (11.3)	251 (15.4)	116 (16.8)	<0.001 ^{b,c,d}
Public (small apartments)	3518 (26.7)	514 (29.6)	152 (22.9)		3258 (27.1)	523 (32.2)	162 (23.5)	
Public (medium apartments)	3842 (29.2)	535 (30.8)	193 (29.1)		3344 (27.8)	474 (29.1)	171 (24.8)	
Public (large apartments)	2571 (19.5)	356 (20.5)	155 (23.3)		2301 (19.1)	339 (20.8)	130 (18.8)	
Private (condominiums)	786 (6.0)	13 (0.8)	42 (6.3)		740 (6.1)	17 (1.0)	42 (6.1)	
Private (houses)	1070 (8.1)	29 (1.7)	52 (7.8)		1041 (8.6)	23 (1.4)	69 (10.0)	
Place of notification, no. (%)								
Inpatient	9911 (75.3)	1427 (82.2)	508 (76.5)	<0.001 ^{b,d}	9096 (75.5)	1332 (81.9)	545 (79.0)	<0.001 ^{b,c,d}
Public clinic	1606 (12.2)	152 (8.8)	77 (11.6)		1678 (13.9)	176 (10.8)	67 (9.7)	
Emergency department	1214 (9.2)	138 (8.0)	60 (9.0)		924 (7.7)	100 (6.2)	57 (8.3)	
Private clinic	440 (3.3)	19 (1.1)	19 (2.9)		345 (2.9)	19 (1.2)	21 (3.0)	
CHA ₂ DS ₂ VASc score								
Median (IQR)	6 (4–7)	6 (4–7)	6 (5–7)	<0.001 ^{c,d}	4 (3–5)	5 (3–6)	5 (4–6)	<0.001 ^{b,c,d}
Mean (SD)	5.6 (1.7)	5.6 (1.7)	5.9 (1.6)		4.2 (1.7)	4.5 (1.7)	4.8 (1.6)	
0	0	0	0		0	0	0	
≥2	13,171 (100.0)	1736 (100.0)	664 (100.0)	Not applicable	11,571 (96.1)	1579 (97.1)	675 (97.8)	0.013 ^e

Table 2. Characteristics of patients by sex and ethnicity among elderly adults (age ≥65 years) (Cont'd)

	Women				Men			
	Chinese (n=13,171)	Malay (n=1736)	Indian (n=664)	P ^a	Chinese (n=12,043)	Malay (n=1627)	Indian (n=690)	P ^a
Diagnosis prior to or within 6 months after first AF, no. (%)								
Hypertension	11,468 (87.1)	1517 (87.4)	607 (91.4)	0.005 ^{c,d}	10,006 (83.1)	1350 (83.0)	615 (89.1)	<0.001 ^{c,d}
Hyperlipidaemia	9050 (68.7)	1268 (73.0)	545 (82.1)	<0.001 ^{b,c,d}	8110 (67.3)	1163 (71.5)	557 (80.7)	<0.001 ^{b,c,d}
Diabetes	5729 (43.5)	972 (56.0)	430 (64.8)	<0.001 ^{b,c,d}	4780 (39.7)	808 (49.7)	428 (62.0)	<0.001 ^{b,c,d}
Renal impairment	3410 (25.9)	622 (35.8)	193 (29.1)	<0.001 ^{b,d}	3329 (27.6)	627 (38.5)	217 (31.5)	<0.001 ^{b,c,d}
End-stage renal failure	804 (6.1)	160 (9.2)	36 (5.4)	<0.001 ^{b,d}	703 (5.8)	121 (7.4)	40 (5.8)	0.038 ^b
Diagnosis prior to first AF, no. (%)								
Ischaemic heart disease	5960 (45.3)	878 (50.6)	424 (63.9)	<0.001 ^{b,c,d}	6039 (50.2)	968 (59.5)	485 (70.3)	<0.001 ^{b,c,d}
Chronic heart failure	4138 (31.4)	658 (37.9)	295 (44.4)	<0.001 ^{b,c,d}	3228 (26.8)	625 (38.4)	244 (35.4)	<0.001 ^{b,c}
Stroke/transient ischaemic attack	3981 (30.2)	493 (28.4)	177 (26.7)	0.053 ^c	3353 (27.8)	432 (26.6)	187 (27.1)	0.521
Haemorrhagic stroke	680 (5.2)	105 (6.1)	35 (5.3)	0.300	728 (6.1)	102 (6.3)	34 (4.9)	0.439
Systemic embolism	121 (0.9)	23 (1.3)	11 (1.7)	0.059	114 (1.0)	23 (1.4)	6 (0.9)	0.193
Vascular disease	766 (5.8)	130 (7.5)	55 (8.3)	0.001 ^{b,c}	769 (6.4)	101 (6.2)	84 (12.2)	<0.001 ^{c,d}
Dementia	914 (6.9)	100 (5.8)	31 (4.7)	0.018 ^c	500 (4.2)	76 (4.7)	43 (6.2)	0.024 ^c
Depression	620 (4.7)	59 (3.4)	40 (6.0)	0.011 ^{b,d}	354 (2.9)	35 (2.2)	23 (3.3)	0.153
Hyperthyroidism	435 (3.3)	67 (3.9)	17 (2.6)	0.251	193 (1.6)	25 (1.5)	10 (1.5)	0.938
Cancer	1375 (10.4)	133 (7.7)	45 (6.8)	<0.001 ^{b,c}	1750 (14.5)	122 (7.5)	52 (7.5)	<0.001 ^{b,c}
All-cause deaths within 1 year from diagnosis of AF, no. (%)	3758 (28.5)	556 (32.0)	182 (27.4)	<0.007 ^{b,d}	3419 (28.4)	526 (31.7)	186 (27.0)	0.014 ^{b,d}
Cardiovascular deaths within 1 year from diagnosis of AF, no. (%)	1345 (10.2)	260 (15.0)	72 (10.8)	<0.001 ^{b,d}	1109 (9.2)	233 (14.3)	74 (10.7)	<0.001 ^{b,d}

AF: atrial fibrillation; IQR: interquartile range; SD: standard deviation

^a The *P* value indicates whether there is statistically significant difference across the 3 ethnicities while the superscript letters indicate pairwise comparisons^b Statistically significant difference between Chinese and Malays, *P*<0.05^c Statistically significant difference between Chinese and Indians, *P*<0.05^d Statistically significant difference between Malays and Indians, *P*<0.05

Table 3. Odds ratio of 1-year all-cause mortality and cardiovascular mortality among patients with atrial fibrillation stratified by age group

	Age 45–64 years		Age ≥65 years	
	OR (95% CI)	AOR (95% CI) ^a	OR (95% CI)	AOR (95% CI) ^a
All-cause mortality				
Sex				
Female	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
Male	0.96 (0.86–1.08)	1.06 (0.92–1.21)	0.97 (0.93–1.02)	1.17 (1.11–1.24)
Ethnicity				
Chinese	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
Malay	1.43 (1.15–1.79)	1.15 (0.89–1.48)	0.93 (0.83–1.05)	1.01 (0.89–1.15)
Indian	1.48 (1.30–1.69)	1.27 (1.09–1.48)	1.18 (1.09–1.27)	1.33 (1.22–1.45)
Interaction between age and sex				
Age and male sex	<i>P</i> =0.413	<i>P</i> =0.437	<i>P</i> =0.698	<i>P</i> =0.278
Interaction between age and ethnicity				
Age and Malay	<i>P</i> =0.199	<i>P</i> =0.389	<i>P</i> =0.065	<i>P</i> =0.415
Age and Indian	<i>P</i> =0.963	<i>P</i> =0.759	<i>P</i> =0.085	<i>P</i> =0.111
Interaction between sex and ethnicity				
Male sex and Malay	<i>P</i> =0.310	<i>P</i> =0.625	<i>P</i> <0.001	<i>P</i> <0.001
Male sex and Indian	<i>P</i> =0.529	<i>P</i> =0.482	<i>P</i> =0.038	<i>P</i> =0.124
Cardiovascular mortality				
Sex				
Female	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
Male	1.17 (0.98–1.40)	1.04 (0.85–1.26)	0.88 (0.82–0.95)	0.99 (0.92–1.07)
Ethnicity				
Chinese	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
Malay	1.63 (1.18–2.25)	0.95 (0.67–1.35)	1.11 (0.94–1.31)	0.96 (0.81–1.15)
Indian	1.99 (1.66–2.39)	1.36 (1.11–1.67)	1.58 (1.43–1.74)	1.54 (1.38–1.71)
Interaction between age and sex				
Age and male sex	<i>P</i> =0.201	<i>P</i> =0.139	<i>P</i> =0.005	<i>P</i> =0.033
Interaction between age and race				
Age and Malay	<i>P</i> =0.854	<i>P</i> =0.922	<i>P</i> =0.974	<i>P</i> =0.298
Age and Indian	<i>P</i> =0.046	<i>P</i> =0.049	<i>P</i> =0.095	<i>P</i> =0.121
Interaction between sex and race				
Male sex and Malay	<i>P</i> =0.820	<i>P</i> =0.189	<i>P</i> =0.118	<i>P</i> =0.062
Male sex and Indian	<i>P</i> =0.244	<i>P</i> =0.270	<i>P</i> =0.517	<i>P</i> =0.694

AOR: adjusted odds ratio; CI: confidence interval; OR: odds ratio

^a Adjusted for age, sex, ethnicity, housing type, hypertension, diabetes, renal impairment, end-stage renal failure, ischaemic heart disease, chronic heart failure, stroke/transient ischaemic attack, haemorrhagic stroke, systemic embolism, peripheral vascular disease, dementia, depression, hyperthyroidism and cancer

Table 4. Odds ratio of 1-year all-cause mortality in patients with atrial fibrillation compared with those without atrial fibrillation (reference) in subgroups of patients stratified by age group, sex and ethnicity

	Age 45–64 years		Age ≥65 years	
	OR (95% CI)	AOR (95% CI) ^a	OR (95% CI)	AOR (95% CI) ^a
Overall	15.72 (12.95–19.08)	9.08 (7.36–11.20)	5.22 (4.98–5.48)	3.60 (3.40–3.80)
Interaction between age and sex				
Age and male sex	<i>P</i> =0.272	<i>P</i> =0.281	<i>P</i> =0.127	<i>P</i> =0.023
Interaction between age and ethnicity				
Age and Malay	<i>P</i> =0.778	<i>P</i> =0.800	<i>P</i> =0.024	<i>P</i> =0.342
Age and Indian	<i>P</i> =0.813	<i>P</i> =0.527	<i>P</i> =0.003	<i>P</i> =0.012
Interaction between sex and ethnicity				
Male sex and Malay	<i>P</i> =0.308	<i>P</i> =0.614	<i>P</i> <0.001	<i>P</i> <0.001
Male sex and Indian	<i>P</i> =0.619	<i>P</i> =0.550	<i>P</i> =0.001	<i>P</i> =0.015
Sex				
Female	19.56 (13.49–28.37)	11.29 (7.58–16.79)	5.73 (5.36–6.13)	3.83 (3.54–4.14)
Male	14.31 (11.40–17.97)	8.22 (6.41–10.54)	4.75 (4.44–5.07)	3.37 (3.11–3.64)
Ethnicity				
Chinese	20.09 (15.46–26.11)	12.32 (9.32–16.29)	5.36 (5.09–5.65)	3.75 (3.53–3.99)
Malay	10.10 (7.31–13.95)	5.75 (3.97–8.33)	4.36 (3.83–4.95)	2.83 (2.43–3.28)
Indian	14.11 (7.07–28.17)	5.50 (2.52–12.02)	5.67 (4.48–7.19)	3.26 (2.46–4.33)

AOR: adjusted odds ratio; CI: confidence interval; OR: odds ratio

^a Adjusted for housing type, hypertension, diabetes, renal impairment, end-stage renal failure, ischaemic heart disease, chronic heart failure, stroke/transient ischaemic attack, haemorrhagic stroke, systemic embolism, peripheral vascular disease, dementia, depression, hyperthyroidism and cancer

With respect to cardiovascular mortality, Indians were noted to have 36% and 54% increased odds of 1-year mortality in the middle-aged and elderly groups, respectively, compared with Chinese in the corresponding groups (Table 3). Age, diabetes, IHD, renal impairment, HF, stroke/transient ischaemic attack, haemorrhagic stroke, systemic embolism, peripheral vascular disease, depression and cancer were associated with all-cause mortality in both age groups, while end-stage renal failure and dementia were also associated with all-cause mortality among elderly adults (online Supplementary Table S5).

The presence of AF in patients conferred a substantially higher risk of mortality compared with matched patients without AF (28% vs 7%, *P*<0.001), with a 9-fold increased odds of mortality among middle-aged adults (adjusted odds ratio [AOR] 9.08, 95% CI 7.36–11.20) and a greater than 3-fold increased odds of mortality among elderly adults (AOR 3.60, 95% CI 3.40–3.80) within a year of diagnosis after adjusting for clinical risk factors (Table 4). Interactions in all-cause mortality were present only among elderly

adults and were between age and sex (*P* for age and male = 0.023), age and ethnicity (*P* for age and Indian = 0.012), and sex and ethnicity (*P* for male and Malay <0.001; *P* for male and Indian = 0.015). Among middle-aged adults, AF affected mortality differently in the sex and ethnic categories. AF conferred a greater increase in mortality in women than in men; while Chinese also had a greater increase in mortality compared with Malays and Indians (Table 4). In the elderly population, the increased odds of mortality associated with AF were generally 2- to 3-fold higher across the sexes and ethnicities.

DISCUSSION

In this nationwide multiethnic cohort, we found significant sex and ethnic differences in the incidence, clinical profile and 1-year all-cause mortality among patients with newly diagnosed AF. Despite having the worst cardiovascular risk profile, Indians had the lowest incidence of AF. The development of AF conferred substantially higher risk of mortality within a year of diagnosis compared with no development of AF, with a

mortality rate of up to 22–26 per 100 people. Mortality in newly diagnosed AF was influenced by sex and ethnicity, particularly among elderly men and Indians who were more susceptible.

Prevalence and incidence of AF

The prevalence of AF in Asia is approximately 1% but with significant geographical variations.^{2,5-7,9} We found an almost 10-fold higher prevalence of AF in elderly adults compared with middle-aged adults, a finding consistent with known age-related effects.^{2,8} Within the Asia-Pacific region, the prevalence of AF in Singapore mirrors that of Australia and New Zealand (1.4–4.9%) and is higher than those of other Southeast Asian countries (<2%).^{5,29-31} Based on national population data, we report a prevalence of 0.6% among middle-aged adults and 7% in elderly adults, and a steady temporal increase in the prevalence of AF. The higher rates of AF observed in Singapore are not unexpected and are likely due to an ageing population with increased life expectancy, a higher burden of cardiovascular disease and increasing detection of AF.²⁸ Additionally, Singapore is a high-income country, and the adoption of lifestyles similar to those in affluent Western nations may partly account for AF rates closer to those of Western nations.⁵ Despite the steady incidence of AF, mortality rates were on the downward trend from 2010, possibly explained by rapid improvements in the standard of living, healthcare access and increasing emphasis on cardiovascular risk factor prevention and management, as well as the increasing longevity of population in Singapore.

Clinical profile

Regardless of age, women consistently had lower prevalence and incidence of AF. Sex differences in baseline characteristics among elderly adults with AF in Singapore were consistent with previous reports¹⁰⁻¹⁸ and have been attributed to the protective effect of oestrogen on atrial electrophysiological properties, while body mass index had varying effects on atrial mechanical function by sex.^{16,33,34} In contrast, disparities in AF risk factors did not correspond to the observed rates of AF among the major ethnic groups in Singapore. Despite the higher prevalence of cardiovascular disease in Indians and Malays compared with Chinese regardless of age or sex, Indians had the lowest rates of AF while Malays had the highest, with higher rates of AF even among Malay women than among Indian men. Low rates of AF among Indians were previously reported within and outside Asia and were attributed to genetic variations. These variations might lead to atrial structural and electrophysiological properties that result

in Indians being less susceptible to AF.²⁴⁻²⁶ Differences in AF rates between Malays and Chinese are likely a reflection of the higher cardiovascular risk profile among Malays, while differences in local dietary habits and activity levels may also contribute, with the effects of lifestyle modifications on maintenance of sinus rhythm being highlighted previously in a study.³⁵ The higher prevalence of inpatient diagnoses of AF among Malays may also suggest a worse comorbid status. Despite shared environmental factors within the same country, ethnic differences in AF rates in this population are likely multifactorial, involving clinical risk factors, genetic susceptibility, lifestyle and socioeconomic status.^{9,27}

One-year mortality after newly diagnosed AF

The 1-year mortality rate of 22–26 per 100 person-years is far higher than the previously reported rate of 18 per 1,000 patient-years in a meta-analysis,³⁶ but is similar to that in the Framingham Heart Study, which reported a lower 1-year mortality rate of 11–15% among younger patients aged 55–64 years and a graded increase per decade in those aged above 65 years.³⁷ The lower mortality previously reported may be due to survival bias, as those studies included patients with known AF who were likely to have survived past the first year of diagnosis compared with our cohort with newly diagnosed AF. Hence, those studies may have included more patients with fewer comorbidities who were generally in better health. For example, patients in our study when compared with those in the Framingham study had higher rates of diabetes (41.9% vs 11.3%), hypertension (80.2% vs 58.4%), myocardial infarction (47.1% vs 28.0%), HF (28.5% vs 21.8%) and stroke (25.2% vs 14.0%).³⁷ Another reason for the high mortality may be that over two-thirds of our patients were first diagnosed with AF during hospital admissions and not during outpatient clinic encounters; hence, a higher-risk cohort was selected compared to previous studies, with AF possibly picked up at later stages of the disease. The majority of the initial presentations during hospital admissions were likely multifactorial, considering the lack of a systematic community screening programme for AF. Furthermore, most Singapore residents prefer to seek medical care at public hospitals, especially through emergency departments, in order to have easy access to highly subsidised acute care. Hence, AF is often only diagnosed when acutely unwell patients seek emergency care.

Notably, more than half of the deaths in our study were non-cardiovascular in nature, and the predictive effects of AF on mortality were independent of cardiovascular

risk factors. AF may be more of a risk marker than a risk factor in this population, occurring in patients at high risk of mortality from other causes. This view is further supported by excess mortality in men within 30 days of AF diagnosis in the Framingham Heart Study, suggesting the role of AF as a marker of terminal illness.³⁷ Our study extends current evidence by demonstrating ethnic-specific mortality risks among patients with shared environments. Despite having the lowest incidence of AF, Indians had a 30% increased 1-year mortality after diagnosis of AF regardless of age. Although the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study demonstrated higher adjusted 1-year mortality rates in India compared with Southeast Asia,³⁸ the higher mortality rate in Indians compared with Chinese in this study was among patients who lived in the same country with less environmental differences. Given the genetic basis that potentially renders Indians less susceptible to AF,²⁵⁻²⁷ it is possible that the development of AF among Indians may indicate more advanced stages of systemic disease with an increased likelihood of early mortality. The significantly increased mortality within a year of AF diagnosis, especially among certain patient subgroups, suggests that AF should be considered a marker of poor prognostic outcomes and a harbinger of early mortality. Early aggressive management of AF and underlying comorbidities should be considered in these high-risk patient groups.

Strengths and limitations

The large study population and long study period provide statistically stable estimates and trends. However, we acknowledge the possibility of underestimation or overestimation of the number of AF cases as cases included in this study were based on coded diagnoses submitted by healthcare institutions rather than direct inspection of 12-lead electrocardiograms. Furthermore, ethnic differences in perceptions of healthcare access and thresholds to seeking medical attention might potentially impact the incidence of newly diagnosed AF, although we think it is likely a small effect due to the lack of significant geographical and financial barriers to healthcare in Singapore. Newly diagnosed AF does not imply new-onset AF and may have been detected only late in the course of the disease. However, it is not possible to reliably ascertain the date of AF onset, with current guidelines recommending opportunistic screening for AF only in elderly patients ≥ 65 years of age.⁹ Data collection was made primarily for an administrative database on disease prevalence within Singapore, which precluded in-depth analyses on

treatment efficacy and differences in cardiac structure and function. Specific dates of death were unavailable, and only a small proportion of patients would have a lag in death certification and these lags are not expected to affect the time to death significantly. The retrospective nature of this study allowed only inferences to be drawn about the association between AF and death, and may be affected by unknown confounders despite our comprehensive adjustment of clinical covariates in the multivariable models.

CONCLUSION

Among patients from a multiethnic population, variations in incidence, clinical profile and 1-year mortality of patients with AF were influenced by age, sex and ethnicity. Newly diagnosed AF portends a worse prognosis and is a marker of high mortality within the first year.

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