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Regional Variation of Mortality in Heart Failure With Reduced and Preserved Ejection Fraction Across Asia: Outcomes in the ASIAN-HF Registry

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Background—Data comparing outcomes in heart failure (HF) across Asia are limited. We examined regional variation in mortality among patients with HF enrolled in the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry with separate analyses for those with reduced ejection fraction (EF; <40%) versus preserved EF ($\geq 50\%$).

Methods and Results—The ASIAN-HF registry is a prospective longitudinal study. Participants with symptomatic HF were recruited from 46 secondary care centers in 3 Asian regions: South Asia (India), Southeast Asia (Thailand, Malaysia, Philippines, Indonesia, Singapore), and Northeast Asia (South Korea, Japan, Taiwan, Hong Kong, China). Overall, 6480 patients aged >18 years with symptomatic HF were recruited (mean age: 61.6 ± 13.3 years; 27% women; 81% with HF and reduced rEF). The primary outcome was 1-year all-cause mortality. Striking regional variations in baseline characteristics and outcomes were observed. Regardless of HF type, Southeast Asians had the highest burden of comorbidities, particularly diabetes mellitus and chronic kidney disease, despite being younger than Northeast Asian participants. One-year, crude, all-cause mortality for the whole population was 9.6%, higher in patients with HF and reduced EF (10.6%) than in those with HF and preserved EF (5.4%). One-year, all-cause mortality was significantly higher in Southeast Asian patients (13.0%), compared with South Asian (7.5%) and Northeast Asian patients (7.4%; $P < 0.001$). Well-known predictors of death accounted for only 44.2% of the variation in risk of mortality.

Conclusions—This first multinational prospective study shows that the outcomes in Asian patients with both HF and reduced or preserved EF are poor overall and worst in Southeast Asian patients. Region-specific risk factors and gaps in guideline-directed therapy should be addressed to potentially improve outcomes.

Clinical Trial Registration—URL: <https://www.clinicaltrials.gov/>. Unique identifier: NCT01633398. (*J Am Heart Assoc.* 2020;9:e012199. DOI: 10.1161/JAHA.119.012199.)

Key Words: epidemiology • heart failure • mortality

Heart failure (HF) is a rapidly growing, global public health problem that imposes a severe burden of morbidity and mortality.¹ Worldwide, >38 million people have HF,² at an estimated cost of US\$100 billion in 2012.³ With explosive

population growth in the past century, Asia is currently home to 4.4 billion people (60% of the world's population), and its population is projected to reach 5.2 billion by 2050. Exponential population growth, urbanization, sedentary lifestyle, and an

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Clinical Perspective

What Is New?

- This study describes large interregional differences in the characteristics and outcomes of patients with heart failure in Asia.
- Heart failure with reduced ejection fraction carries higher mortality than heart failure with preserved ejection fraction in Asia, and patients from Southeast Asia have the poorest outcomes.

What Are the Clinical Implications?

- The results of this study will allow us to target region-specific risk factors and gaps in guideline-directed therapy to improve patient outcomes.

aging population together with increasing rates of obesity, hypertension, and diabetes mellitus, all of which predispose to HF, have contributed to a “tsunami” of cardiovascular disease, including HF, in Asia. Asia is highly heterogeneous, with countries at different stages of economic development. Population-based data suggest that socioeconomically deprived persons are likely to develop HF at an earlier age than affluent individuals.⁴ Limited data from Southeast Asian countries also suggest a higher prevalence of HF compared with other Asian countries.⁵ This is of increasing concern, especially as the burden of HF is predicted to be highest in the poorest countries least equipped to deal with the onslaught.²

Most outcomes data in HF come from European and North American populations, with scant information from Asia, restricted to a few individual Asian countries.^{6,7} In affluent Western populations, 5-year mortality rates in HF patients from population-based studies rival those of major cancers at 50–60%.² The limited data from low- and middle-income countries suggest their mortality rates may be even higher.^{6,8} Furthermore, studies have suggested that Asian patients present with HF on average at least a decade earlier than their white counterparts, with two thirds presenting with multimorbidity.⁹ The INTER-CHF (International Congestive Heart Failure) study recently reported marked regional differences in mortality in patients with HF that persist even after adjustment for known cardiac and noncardiac predictors, suggesting distinctive heterogeneity of the Asian HF phenotype.⁶ Adding to this complexity, HF subtypes (ie, with reduced ejection fraction [rEF] or preserved ejection fraction [pEF]) are heterogeneous syndromes. Epidemiological data on outcomes in these HF subtypes in Asia are scarce, limited to single-center or national data.¹⁰ The degree of regional variation in HF outcomes and the underlying reasons for such variations are uncertain. Research into factors underpinning regional

disparities is necessary to enable targeted action to improve population-level outcomes. We therefore examined the regional variation in all-cause and cause-specific mortality among all patients with HF enrolled in the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry with separate subanalyses in HF patients with rEF (HFrEF) and with pEF (HFpEF).

Methods

Study Population

The study data and materials used to conduct the research cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure because of the legal restrictions imposed by multinational jurisdictions. ASIAN-HF is a prospective observational multinational registry of Asian patients aged >18 years with symptomatic HF (at least 1 episode of decompensated HF in the previous 6 months, resulting in a hospital admission or treatment in an outpatient clinic) recruited from 46 medical centers across 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand), following informed consent.¹¹ Investigation sites (46 in total with >220 investigators; Appendix) 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. Site selection in ASIAN-HF was based on the size of the country, the geographic location of the site within the country, the patient population served, HF patient volume, and availability of expertise in echocardiography. A mix of private and public hospitals and tertiary, university, and cardiovascular specialty hospitals in capital and provincial cities were included. Ethics approvals conforming to the Declaration of Helsinki were obtained from the relevant human ethics committees at all sites. Patients were excluded if they had severe valve disease as the primary cause of HF, had life-threatening comorbidity with life expectancy of <1 year, were unable or unwilling to give consent, or were concurrently participating in a clinical therapeutic trial. Asian patients were recruited in 2 stages: those with HF and rEF (HFrEF; EF <40% on baseline echocardiography) were enrolled between October 1, 2012, and December 31, 2015, with overlapping recruitment of those with HF and pEF (HFpEF; EF ≥50% on baseline echocardiography) between September 9, 2013, and October 31, 2016. Recruitment of patients with HFpEF started later than the recruitment of patients with HFrEF, for funding reasons; however, the delay was only 1 year (October 1, 2012, versus September 9, 2013). For the majority of the recruitment period (until October 6, 2016), there was overlap in recruitment of both types of HF. We do not anticipate that there were substantial shifts in epidemiology or treatment of

patients with HFrEF or HFpEF during this year that would have biased regional patterns of multimorbidity, although this cannot be entirely excluded. All patients included in the ASIAN-HF registry were required to have a validated clinical diagnosis of HF (based on symptoms and signs according to The Framingham Heart Study criteria with decompensation within 6 months) and left ventricular (LV) EF <40% and \geq 50% for HFrEF and HFpEF, respectively.¹² A previous hospitalization for HF was defined as any previous hospitalization for HF during 6 months before inclusion requiring intravenous or oral diuretic treatment. Patients treated for an episode of decompensation in an outpatient clinic were generally treated with additional or high dosages of oral diuretics for short periods, failing which intravenous diuretics would be administered, usually in a hospital setting. Criteria for recruitment of patients were standardized across sites. Patients with HFpEF and a previously recorded LVEF <50% were excluded. In addition, 99.5% of HFpEF patients had structural or functional abnormalities meeting the 2016 European Society of Cardiology criteria for diastolic dysfunction ($E/e' \geq 13$, E' medial/lateral <9 ms, left atrial enlargement or LV hypertrophy).^{1,13}

The collection and processing of echocardiographic data have been reported previously.¹¹ Echocardiography was performed at each center according to internationally accepted guidelines.¹⁴ Left atrial size, LV diastolic function, stroke volume, and cardiac output were documented in addition to LVEF and LV dimensions. The Cardiovascular Imaging Laboratory of the National University Health System, Singapore, provided oversight and imaging protocol guidelines and quality assurance of the echocardiograms. Echocardiographic measurements were performed at the site level with standardized protocols provided by the echocardiography laboratory in Singapore.

Demographics (including socioeconomic status), clinical signs and symptoms, functional status, date of HF diagnosis, duration of HF, prior cardiovascular procedures or investigations, clinical and lifestyle risk factors, medical history, comorbidities, quality of life, and blood chemistry were documented at recruitment. Standard 12-lead ECG and transthoracic echocardiography were also recorded at baseline. Coronary artery disease was defined as the angiographically documented presence of significant coronary obstruction, history of myocardial infarction, or prior revascularization. Hypertension was defined as any past or current history of hypertension, and diabetes mellitus was defined as having a prior diagnosis of diabetes mellitus. Estimated glomerular filtration rate was calculated using the MDRD (Modification of Diet in Renal Disease) study equation, and chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m². Atrial fibrillation (AF), peripheral arterial vascular disease, previous stroke, and chronic obstructive pulmonary disease were identified by medical history.

Geographic regions were defined according to United Nations classification as follows: Northeast Asia included South Korea, Japan, Taiwan, Hong Kong, and China; South Asia included India; and Southeast Asia included Thailand, Malaysia, Philippines, Indonesia, and Singapore. National income level as defined by the World Bank was used to categorize countries as *high*, *middle*, and *low income*.⁹

All data were captured prospectively in an electronic database, with registry operations and data management handled by Quintiles Outcomes as the contract research organization appointed by the academic executive committee.

Outcomes

The primary outcome of interest was all-cause mortality at 1 year. In all, 5875 (90.7%) patients had outcome data available, whereas 605 (9.3%) patients were lost to follow-up. The cause of death was adjudicated by an independent committee, using the US Food and Drug Administrations standardized event definitions.¹⁵ Two members of the end point committee independently reviewed the death data collected from the case report forms; the third member reviewed cases in which adjudicated causes of death were discordant between the first 2 members. After the third review, if there was still discordance, the events were adjudicated at a meeting of the end point committee. As such, ascertainment of mortality does not vary between sites.

Causes of death were classified as *cardiovascular*, *noncardiovascular*, or *unknown/presumed cardiovascular* in those with insufficient information on cause of death. Specific mode of cardiovascular death was further classified as *sudden death*, *HF death*, *acute myocardial infarction*, *stroke*, *cardiovascular hemorrhage*, or *procedural or other cardiovascular death*.

Statistical Analyses

Standard descriptive statistics were used to describe baseline characteristics by nation and geographic region for patients with HFrEF and HFpEF separately. Differences in the baseline characteristics were assessed with ANOVA and χ^2 tests for continuous and categorical factors, respectively. Univariable and multivariable Cox proportional hazards models were used to assess factors associated with risk of mortality at 1 year, with geographical region as the key factor of interest. We tested for interaction in the univariable models with the specific main effects by geographical region and HF type on 1-year all-cause mortality outcomes and presented stratified results only if interactions were significant. Factors associated with mortality ($P < 0.1$) in univariable models and/or clinically important factors (demographics, clinical signs, concomitant comorbidities, pharmacotherapy, or device therapy) were included for adjustment of the multivariable models. South Asia was

used as the reference region because it had the lowest death rate and the least heterogeneity. Analyses were then repeated and stratified by geographical region (in the presence of significant interaction) to assess differences in the risk factors for 1-year mortality. The Cox proportional hazards assumption was confirmed using log-log plots and the Schoenfeld residuals test. The overall assessment of explained risk and relative importance of a subset of factors in the Cox proportional hazards models was calculated using the explained risk statistic and interpreted similarly to the coefficient of determination R^2 in the normal linear model.¹⁶ Patients who were lost to follow-up or had incomplete data on adjusted risk factors were excluded from survival analysis. All analyses were 2-tailed, and $P < 0.05$ was considered statistically significant. Analyses were performed in Stata v14 (StataCorp), and explained risk statistics were calculated in R software v3.4.1.

Results

Overall, 6480 patients (mean age: 61.6 ± 13.3 years; 27% women; 81% HFrEF) were enrolled from 46 centers across 11 Asian regions. All patients had a documented episode of decompensated HF requiring hospitalization or equivalent outpatient treatment within the 6 months before enrollment. In addition, 42% of patients were enrolled as inpatients recruited after initial treatment of acute symptoms and following stabilization. Vital status was available for 5851 (90.3%) patients who completed 1 year of follow-up. Table 1 describes the baseline characteristics of the entire cohort by HF group and geographic region. Detailed baseline characteristics at a country level are listed in the Appendix.

Demographics

Demographics varied considerably by geographical region. Regardless of ejection fraction, Northeast Asian participants were the oldest, followed by Southeast then South Asian participants. Patients with HFrEF were on average 8 years younger than the patients with HFpEF (Table 1). Among the patients with HFrEF, older cohorts were more likely to be female; 25.2% of patients in Northeast Asia were female, in comparison to 17.7% in Southeast Asia. Approximately half of the patients with HFpEF were women in all 3 regions. The Philippines had the youngest cohort (20% female), aged 55.8 years, in stark contrast to the patients from Hong Kong, who were almost 17 years older (46.8% female) at 72.9 years.

Comorbidity

Prevalence of comorbidities was high throughout Asia, but marked regional variation was evident. Regardless of HF

group, Southeast Asia had the highest prevalence of diabetes mellitus, stroke, hypertension, CKD, and coronary artery disease despite a relatively low mean age. In both HFrEF and HFpEF, ischemic etiology of HF was twice as common in Southeast Asia as in Northeast and South Asia. In keeping with the higher prevalence of comorbidities, Southeast Asian patients also had the highest body mass index (kg/m^2) at 25.7 and 28.2 in patients with HFrEF and HFpEF, respectively. Between countries, patients from the Philippines had the highest body mass index at 26.9, and those from Japan had the lowest at 23.0. Across all regions, HFpEF patients had higher body mass indexes than those with HFrEF. South Asians had distinctly lower prevalence of AF (4.2% [versus 22.8% average prevalence in other geographical regions] in HFrEF and 7.2% [versus 23.6% average prevalence in other regions] in HFpEF) and chronic obstructive pulmonary disease.

Pharmacological and Device Therapy

Despite the lack of evidence-based HF therapies for HFpEF patients, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and β -blockers were usually prescribed in both HFrEF and HFpEF patients (Table 1). Southeast Asia had the highest rates of ACEI and ARB use (77.3% and 70.2%, respectively) and β -blocker use (81.8% and 78.9%, respectively), whereas mineralocorticoid receptor antagonists were most frequently prescribed in Northeast Asia for 61.7% and 26.6% of HFrEF and HFpEF patients, respectively. Marked variation in pharmacological treatment was observed at the country level—for example, Indonesia had the lowest usage (61.7%) of β -blockers but the highest (85.8%) of ACEIs/ARBs; Japan had highest usage of β -blockers (89.5%) but moderate usage (78.4%) of ACEIs/ARBs. There was wide variability in device implantation across countries and regions, with Japan having the highest rate.

Outcomes

One-year outcome data were available for 93% of patients in South Asia, 86% in Southeast Asia, and 93% in Northeast Asia. One-year crude all-cause mortality for the whole population was 9.6%, with a higher mortality rate for patients with HFrEF than HFpEF (10.6% and 5.4%, respectively; $P < 0.001$). In almost all countries, participants recruited as inpatients had almost twice (13.4% versus 6.8%) the 1-year mortality of those recruited as outpatients. Figures 1 through 3 and Tables 2 and 3 detail 1-year outcomes.

Among patients with HFrEF, Southeast Asia had the highest crude all-cause mortality at 13.6% compared with 8.9% and 8.3% in Northeast Asia and South Asia, respectively. The high mortality in Southeast Asia was largely driven by a

Table 1. Continued

	Overall			HFpEF			HFrEF			HFpEF			P Value			
	Northeast Asia	South Asia	Southeast Asia	P Value	Northeast Asia	South Asia	Southeast Asia	Northeast Asia	South Asia	Southeast Asia	P Value	Northeast Asia		South Asia	Southeast Asia	P Value
Smoking, ever	983 (44.7)	291 (17.4)	1362 (53.2)	<0.001	850 (51.3)	280 (19.5)	1231 (57.1)	<0.001	133 (24.5)	11 (4.7)	131 (32.1)	<0.001	131 (32.1)	11 (4.7)	131 (32.1)	<0.001
Alcohol, ever	727 (33.0)	245 (14.7)	725 (28.3)	<0.001	633 (38.2)	234 (16.3)	650 (30.2)	<0.001	94 (17.3)	11 (4.7)	75 (18.4)	<0.001	75 (18.4)	11 (4.7)	75 (18.4)	<0.001
CKD	771 (40.3)	381 (37.0)	1160 (54.0)	<0.001	564 (39.0)	336 (36.5)	931 (52.6)	<0.001	207 (44.3)	45 (41.3)	229 (60.4)	<0.001	229 (60.4)	45 (41.3)	229 (60.4)	<0.001
ECG rhythm																
Sinus rhythm	1084 (54.4)	1228 (78.8)	1812 (74.0)	<0.001	854 (53.6)	1079 (80.0)	1556 (75.6)	<0.001	230 (57.4)	149 (71.0)	256 (65.8)	<0.001	230 (57.4)	149 (71.0)	256 (65.8)	<0.001
AF/flutter	408 (20.5)	61 (3.9)	362 (14.8)		280 (17.5)	45 (3.3)	272 (13.2)		128 (31.9)	16 (7.6)	90 (23.1)		128 (31.9)	16 (7.6)	90 (23.1)	
Other rhythms/unknown	501 (25.1)	269 (17.3)	273 (11.2)		458 (28.8)	224 (16.6)	230 (11.2)		43 (10.7)	45 (21.4)	43 (11.1)		43 (10.7)	45 (21.4)	43 (11.1)	
Left bundle-branch block	200 (10.0)	283 (18.1)	244 (10.0)	<0.001	190 (11.9)	274 (20.3)	230 (11.2)	<0.001	10 (2.5)	9 (4.3)	14 (3.6)	<0.001	10 (2.5)	9 (4.3)	14 (3.6)	0.440
Medication or device use																
ACEI	862 (40.0)	639 (40.9)	1336 (54.1)	<0.001	780 (47.4)	616 (43.7)	1177 (56.4)	<0.001	82 (16.2)	23 (14.9)	159 (41.5)	<0.001	82 (16.2)	23 (14.9)	159 (41.5)	<0.001
ARB	741 (34.4)	517 (33.1)	613 (24.8)	<0.001	472 (28.7)	459 (32.6)	492 (23.6)	<0.001	269 (53.1)	58 (37.7)	121 (31.6)	<0.001	269 (53.1)	58 (37.7)	121 (31.6)	<0.001
ACEI or ARB	1546 (71.8)	1134 (72.6)	1882 (76.2)	0.002	1203 (73.0)	1053 (74.7)	1613 (77.3)	0.011	343 (67.7)	81 (52.6)	269 (70.2)	<0.001	343 (67.7)	81 (52.6)	269 (70.2)	<0.001
β-Blocker	1682 (78.1)	990 (63.3)	2010 (81.3)	<0.001	1353 (82.1)	914 (64.9)	1708 (81.8)	<0.001	329 (64.9)	76 (49.4)	302 (78.9)	<0.001	329 (64.9)	76 (49.4)	302 (78.9)	<0.001
Mineralocorticoid receptor antagonist	1151 (53.4)	868 (55.5)	1203 (48.7)	<0.001	1016 (61.7)	832 (59.0)	1150 (55.1)	<0.001	135 (26.6)	36 (23.4)	53 (13.8)	<0.001	135 (26.6)	36 (23.4)	53 (13.8)	<0.001
Loop diuretic	1519 (70.5)	1242 (79.5)	2092 (84.7)	<0.001	1241 (75.3)	1157 (82.1)	1788 (85.6)	<0.001	278 (54.8)	85 (55.2)	304 (79.4)	<0.001	278 (54.8)	85 (55.2)	304 (79.4)	<0.001
Diuretic	1586 (73.6)	1268 (81.1)	2106 (85.2)	<0.001	1256 (76.3)	1169 (83.0)	1795 (86.0)	<0.001	330 (65.1)	99 (64.3)	311 (81.2)	<0.001	330 (65.1)	99 (64.3)	311 (81.2)	<0.001
Digoxin	523 (24.3)	500 (32.0)	532 (21.5)	<0.001	486 (29.5)	488 (34.6)	489 (23.4)	<0.001	37 (7.3)	12 (7.8)	43 (11.2)	<0.001	37 (7.3)	12 (7.8)	43 (11.2)	0.110
Ivabradine	34 (1.6)	316 (20.2)	144 (5.8)	<0.001	34 (2.1)	303 (21.5)	134 (6.4)	<0.001	0 (0.0)	13 (8.4)	10 (2.6)	<0.001	0 (0.0)	13 (8.4)	10 (2.6)	<0.001
Device therapy																
None	1702 (77.4)	1559 (93.2)	2339 (91.3)	<0.001	1209 (73.0)	1336 (93.0)	1952 (90.6)	<0.001	493 (90.8)	223 (94.1)	387 (94.9)	<0.001	493 (90.8)	223 (94.1)	387 (94.9)	0.015
ICD only	133 (6.0)	46 (2.7)	103 (4.0)		115 (6.9)	38 (2.6)	101 (4.7)		18 (3.3)	8 (3.4)	2 (0.5)		18 (3.3)	8 (3.4)	2 (0.5)	
Pacemaker only	72 (3.3)	16 (1.0)	48 (1.9)		45 (2.7)	12 (0.8)	30 (1.4)		27 (5.0)	4 (1.7)	18 (4.4)		27 (5.0)	4 (1.7)	18 (4.4)	
Biventricular pacer only	57 (2.6)	17 (1.0)	19 (0.7)		55 (3.3)	15 (1.0)	19 (0.9)		2 (0.4)	2 (0.8)	0 (0.0)		2 (0.4)	2 (0.8)	0 (0.0)	
Biventricular pacer and ICD	236 (10.7)	35 (2.1)	54 (2.1)		233 (14.1)	35 (2.4)	53 (2.5)		3 (0.6)	0 (0.0)	1 (0.2)		3 (0.6)	0 (0.0)	1 (0.2)	
Sociodemographics																
Education																
None/primary education	664 (30.8)	460 (27.5)	630 (35.6)	<0.001	398 (24.5)	386 (27.1)	556 (35.1)	<0.001	266 (49.8)	74 (29.8)	74 (39.8)	<0.001	266 (49.8)	74 (29.8)	74 (39.8)	<0.001
Secondary education	697 (32.3)	485 (29.0)	729 (41.2)		578 (35.6)	430 (30.2)	655 (41.4)		119 (22.3)	55 (22.2)	74 (39.8)		119 (22.3)	55 (22.2)	74 (39.8)	
Preuniversity	374 (17.3)	209 (12.5)	175 (9.9)		294 (18.1)	177 (12.4)	157 (9.9)		80 (15.0)	32 (12.9)	18 (9.7)		80 (15.0)	32 (12.9)	18 (9.7)	

Continued

Table 1. Continued

	Overall				HFREF				HFpEF			
	Northeast Asia	South Asia	Southeast Asia	P Value	Northeast Asia	South Asia	Southeast Asia	P Value	Northeast Asia	South Asia	Southeast Asia	P Value
	Degree or higher	347 (16.1)	451 (26.9)	199 (11.3)		288 (17.8)	402 (28.2)	189 (11.9)		59 (11.0)	49 (19.8)	10 (5.4)
Decline to respond	74 (3.4)	69 (4.1)	35 (2.0)		64 (3.9)	31 (2.2)	25 (1.6)		10 (1.9)	38 (15.3)	10 (5.4)	
Marital status				<0.001					<0.001			<0.001
Single	206 (9.6)	28 (1.7)	146 (8.3)		165 (10.2)	26 (1.8)	139 (8.8)		41 (7.7)	2 (0.8)	7 (3.8)	
Married	1621 (75.2)	1570 (93.8)	1417 (80.2)		1246 (76.8)	1336 (93.7)	1274 (80.6)		375 (70.2)	234 (94.4)	143 (76.9)	
Separated/divorced	82 (3.8)	9 (0.5)	77 (4.4)		66 (4.1)	6 (0.4)	70 (4.4)		16 (3.0)	3 (1.2)	7 (3.8)	
Widowed	204 (9.5)	60 (3.6)	119 (6.7)		115 (7.1)	53 (3.7)	93 (5.9)		89 (16.7)	7 (2.8)	26 (14.0)	
Decline to answer	43 (2.0)	7 (0.4)	8 (0.5)		30 (1.8)	5 (0.4)	5 (0.3)		13 (2.4)	2 (0.8)	3 (1.6)	

Data presented are mean (SD) or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; PAD, peripheral arterial disease.

21.4% mortality rate in Indonesia and 14.3% in the Philippines, despite these 2 countries having the youngest populations. Japan, with a relatively elderly population, had the lowest 1-year mortality rate at 4.4%.

Overall, the most common cause of death among patients with HFREF (54%) was known cardiovascular death, with a further 34% of deaths having a presumed cardiovascular or unknown cause, whereas 12% of deaths were noncardiovascular. Sudden death and HF death accounted for at least 80% of cardiovascular deaths. Among patients with HFpEF, cardiovascular and noncardiovascular deaths accounted for half and a quarter of deaths, respectively.

Associations With Mortality

Table 4 demonstrates the variables associated with 1-year mortality in the entire ASIAN-HF cohort. In unadjusted analyses, multiple variables were associated with death. After adjustment, clinical and demographic features associated with death within 1 year included enrollment as an inpatient (hazard ratio [HR]: 1.49; 95% CI, 1.19–1.86), HFpEF (HR: 0.54; 95% CI, 0.37–0.80), New York Heart Association (NYHA) class III/IV (HR: 1.99; 95% CI, 1.60–2.47), body mass index (HR: 0.95; 95% CI, 0.93–0.97), systolic blood pressure (HR: 0.90; 95% CI, 0.85–0.95), AF (HR: 1.33; 95% CI, 1.05–1.67), and CKD (HR: 1.58; 95% CI, 1.27–1.97). Treatment with an ACEI/ARB and treatment with a β -blocker were both independently associated with better survival, with HRs of 0.61 (95% CI, 0.50–0.76) and 0.66 (95% CI, 0.52–0.83), respectively. However, use of mineralocorticoid receptor antagonists was not associated with outcomes, and use of diuretics was associated with worse outcomes (HR: 1.96; 95% CI, 1.37–2.82). There were a number of interactions with regional status in the univariable models. AF was associated with poor prognosis in South Asian patients (HR: 2.79; 95% CI, 1.31–5.94) and Northeast Asian patients (HR: 1.55; 95% CI, 1.07–2.25) but not in Southeast Asian patients, in whom it was not significantly associated with mortality. There was also a significant interaction between enrollment as an inpatient and region. Inpatient enrollment was associated with higher mortality than outpatient enrollment in Northeast and South Asia but not in Southeast Asia. Southeast Asia had almost double the adjusted risk of mortality of the other 2 regions (HR: 1.94; 95% CI, 1.42–2.66). The relationship between geographical region and outcomes was not significantly affected by HF type ($P_{interaction}=0.075$), such that Southeast Asia had higher risk of mortality compared with South and Northeast Asia for both HFREF and HFpEF.

Table 5 shows the contribution of each demographic, clinical, medication/device, and regional variable that contributed to the relative amount of the risk of death at 1 year. These known variables accounted for only 44.8% of the risk of

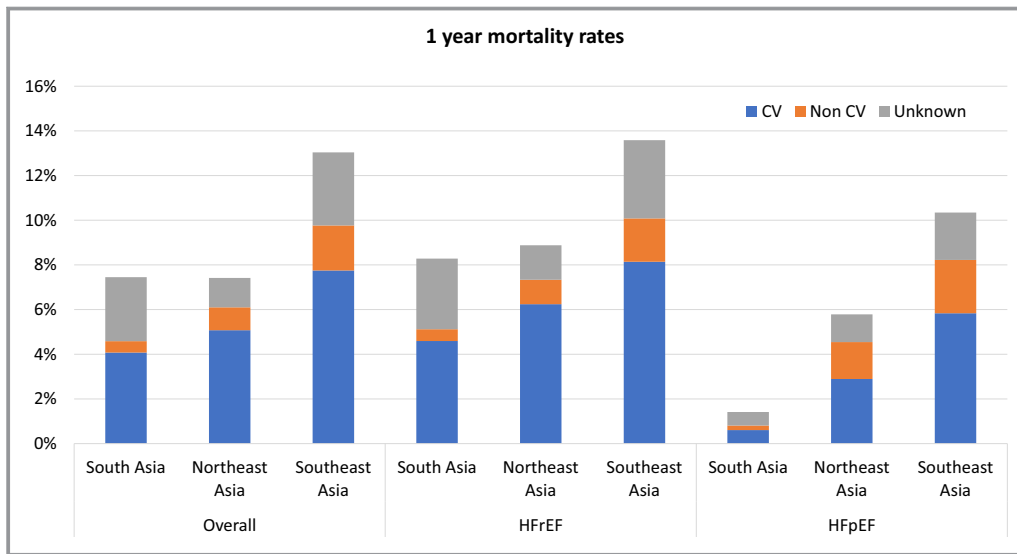


Figure 1. One-year mortality and cause of death by region and heart failure group. CV indicates cardiovascular; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

death and consisted of 3.9% demographic, 21.9% clinical, 7.0% medication/device, and 5.8% regional variables. The relative contributions were similar in HFrEF, comprising 3.8% demographic, 18.2% clinical, 7.8% medication/device, and 5.3% regional variables. In HFpEF, however, known variables accounted for 49.0% of the risk of death, mostly contributed by demographics and region.

Discussion

The ASIAN-HF study is the first multinational prospective registry to present outcomes data for patients with HF by regions and HF subtypes across Asia. Crude 1-year all-cause mortality was 9.6% in the overall cohort. However, we

observed significant regional differences in patient characteristics, treatment, and mortality. Asian patients with HFrEF had worse 1-year outcomes than those with HFpEF, despite being significantly younger. Patients from the lowest income countries presented at the youngest ages but had the poorest outcomes. Southeast Asia had the highest rate of comorbidities, and patients from this region were almost twice as likely to die during the first year of follow-up in comparison to patients from South and Northeast Asia. Despite the considerable regional variations in demographics, comorbidity, and treatment, these measured factors explain less than half of the interregional variation in mortality, with unmeasured factors accounting for the bulk of the varying mortality risk. Notably, region was as or more important than demographics in predicting mortality in both HFrEF and HFpEF patients.

Few other studies have explored the outcomes of patients with HF in Asia at national and regional levels.¹⁰ The INTER-CHF study was a prospective HF cohort study conducted in 108 centers worldwide.⁶ In addition to enrolling patients from the Middle East, Africa, and South America, INTER-CHF also enrolled 2660 patients from 4 Asian countries: China, India, Malaysia, and the Philippines. Unlike ASIAN-HF, INTER-CHF did not report outcomes in the different HF subtypes. The 1-year mortality rate in Southeast Asia (Malaysia and Philippines) in INTER-CHF was 15%, which is comparable to the mortality in our own Southeast Asian cohort (covering 5 countries) at 13%. However, the INTER-CHF mortality rates for China (7.3%) and India (23.3%) do not accord with our data; this is attributed to marked differences in patient characteristics of both studies. In ASIAN-HF, we found almost double the mortality rate in China (13.6%) and a far lower mortality

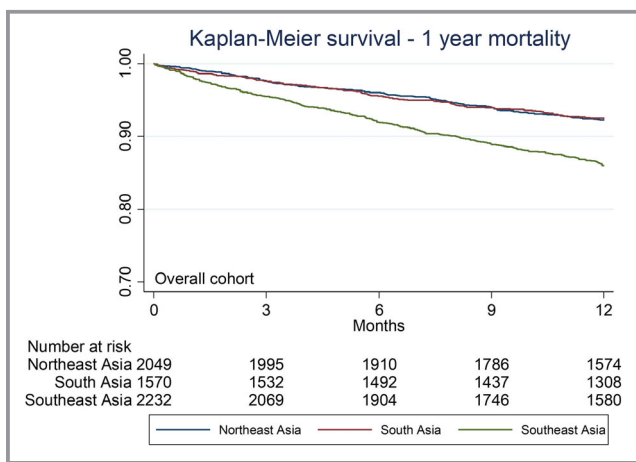


Figure 2. Kaplan–Meier curves for mortality by region.

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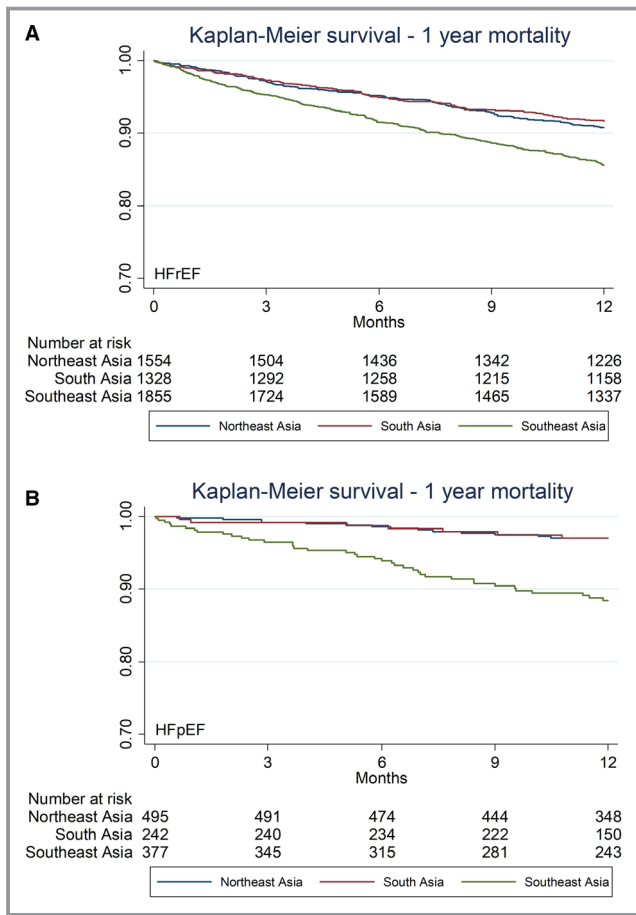


Figure 3. Kaplan–Meier curves for mortality by heart failure group. **A**, Heart failure with reduced ejection fraction (HFrEF). **B**, Heart failure with preserved ejection fraction (HFpEF).

rate in India (7.7%). The mortality variation in China may well be explained by the differing proportions of patients with HFrEF and inpatients in each study; in INTER-CHF, 27% of Chinese patients had HFrEF and 35% were recruited as inpatients. In contrast, the corresponding proportions of China’s participants in ASIAN-HF were 98.8% with HFrEF and 91.3% recruited as inpatients. Higher mortality in the INTER-CHF population from India may be partly explained by a sicker population, with patients more likely to be enrolled as inpatients, to have more NYHA III/IV class HF, and to use fewer ACEIs/ARBs and β -blockers compared with ASIAN-HF participants.

The SWEDHE-HF (Swedish Heart Failure) registry had enrollment criteria similar to the ASIAN-HF registry, so it is a useful comparator to represent non-Asian populations. Crude 1-year mortality rates for patients with EF <40% (n=23 400) and EF \geq 50% (n=9640) were 15% and 17%, respectively. These rates are higher than those in the ASIAN-HF cohort but may partly reflect the older age of the Swedish cohort, with a mean age of 72 years for HFrEF and 77 years for HFpEF patients, in comparison to mean ages of 60 and

Table 2. One-Year Mortality Rates

	Overall		HFrEF				HFpEF						
	All-Cause Death	Cardiovascular Death	Non Cardiovascular Death	Unknown/Presumed Cardiovascular Deaths	All-Cause Death	Cardiovascular Death	Non Cardiovascular Death	Unknown/Presumed Cardiovascular Deaths					
ASIAN-HF	5851	341 (60.9)	74 (13.2)	145 (25.9)	4737	500 (10.6)	270 (54.0)	60 (12.0)	170 (34.0)	1114	60 (5.4)	32 (53.3)	14 (23.3)
By geographical region													
South Asia	1570	64 (54.7)	8 (6.8)	45 (38.5)	1328	110 (8.3)	61 (55.5)	7 (6.4)	42 (38.2)	242	7 (2.9)	3 (42.9)	3 (42.9)
Northeast Asia	2049	104 (68.4)	21 (13.8)	27 (17.8)	1554	138 (8.9)	97 (70.3)	17 (12.3)	24 (17.4)	495	14 (2.8)	7 (50.0)	4 (28.6)
Southeast Asia	2232	173 (59.4)	45 (15.5)	73 (25.1)	1855	252 (13.6)	151 (59.9)	36 (14.3)	65 (25.8)	377	39 (10.3)	22 (56.4)	8 (20.5)
By enrollment status													
Inpatient	2472	215 (64.9)	42 (12.7)	74 (22.4)	2062	297 (14.4)	198 (66.7)	33 (11.1)	66 (22.2)	410	34 (8.3)	17 (50.0)	8 (23.5)
Outpatient	3379	126 (55.0)	32 (14.0)	71 (31.0)	2675	203 (7.6)	111 (54.7)	27 (13.3)	65 (32.0)	704	26 (3.7)	15 (57.7)	6 (23.1)

ASIAN-HF indicates Asian Sudden Cardiac Death in Heart Failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Table 3. One-Year Cause-Specific Mortality Rates

	Overall			HF _r EF			HF _p EF		
	South Asia	Northeast Asia	Southeast Asia	South Asia	Northeast Asia	Southeast Asia	South Asia	Northeast Asia	Southeast Asia
No. of cardiovascular deaths	64	104	173	61	97	151	3	7	22
Specific cause of cardiovascular death									
Sudden death	41 (64.0)	43 (41.3)	49 (28.3)	41 (67.2)	41 (42.3)	47 (31.1)	0 (0.0)	2 (28.6)	2 (9.1)
HF death	18 (28.1)	52 (50.0)	41 (23.7)	17 (27.9)	47 (48.4)	39 (25.8)	1 (33.3)	5 (71.4)	2 (9.1)
AMI death	4 (6.3)	5 (4.8)	14 (8.1)	3 (4.9)	5 (5.2)	11 (7.3)	1 (33.3)	0 (0.0)	3 (13.6)
Stroke death	1 (1.6)	2 (1.9)	7 (4.0)	0 (0.0)	2 (2.1)	6 (4.0)	1 (33.3)	0 (0.0)	1 (4.6)
Cardiovascular hemorrhage death	0 (0)	1 (1.0)	4 (2.3)	0 (0.0)	1 (1.0)	2 (1.3)	0 (0.0)	0 (0.0)	2 (9.1)
Procedure death	0 (0)	1 (1.0)	2 (1.2)	0 (0.0)	1 (1.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other cardiovascular death	0 (0)	0 (0)	56 (32.4)	0 (0.0)	0 (0.0)	44 (29.1)	0 (0.0)	0 (0.0)	12 (55.5)

Data are shown as n (%) except as noted. AMI indicates acute myocardial infarction; HF, heart failure; HF_pEF, heart failure with preserved ejection fraction; HF_rEF, heart failure with reduced ejection fraction.

68 years, respectively, in ASIAN-HF participants. Other notable differences in the populations were a far higher proportion of patients with AF in the Swedish cohort, at 51% in those with HF_rEF and 63% in those with HF_pEF. In addition, the Swedish cohort had a higher proportion of female participants, with 29% of HF_rEF patients and 55% of HF_pEF patients being female.¹⁷

We previously described the interregional differences in clinical and echo characteristics and outcomes of patients with HF_pEF in the ASIAN-HF population. We found that in patients with HF_pEF, Southeast Asian patients had the highest rate of comorbidities and LV hypertrophy and the poorest outcomes. We extend this study in a number of ways by (1) presenting mortality rates for HF_rEF and comparing these with HF_pEF, (2) investigating differences in adjudicated causes of death in patients with HF_rEF and HF_pEF, and (3) studying differences in predictors of clinical outcomes between patients with HF_rEF and HF_pEF from Asia. A similar pattern of comorbidity clustering occurs in HF_rEF patients, with particularly high rates of comorbidities and mortality in Southeast Asia. Mortality rates are almost double in HF_rEF patients despite their being significantly younger.

After multivariable analysis we found that the relationship between certain key factors and mortality was modified by regional status. Enrollment as an inpatient was associated with significantly worse outcomes in Northeast and South Asia but not in Southeast Asia. This may reflect that inpatients in Southeast Asia may not be as sick as inpatients in Northeast and South Asia, or perhaps be due to disproportionately higher enrollment of inpatients from Singapore and Malaysia, where there is good tertiary care. Interestingly, in patients from South Asia, AF was associated with a far greater risk of death than in other regions. This result is particularly

intriguing, given the markedly lower prevalence of AF in the South Asian population, and further study is warranted.

At a national level, Indonesia had the highest rate of all-cause death at 22.6%, with the second highest in Hong Kong at 19.8%—an interesting finding, given that Indonesia had the youngest population in the cohort (mean age: 57 years) and Hong Kong had the oldest (mean age: 79 years). It is notable that Indonesia also had the highest rates of coronary artery disease (62%) and smoking (66.4%) and a high prevalence of CKD but the lowest uptake of implantable cardioverter-defibrillators and cardiac resynchronization therapy—defibrillators and β -blockers. The finding of poor outcomes in young patients in Asia was reported previously from a subgroup analysis of the PARADIGM-HF trial that compared patient characteristics and outcomes among different global geographic regions, including 1487 patients with HF_rEF from the Asia Pacific region.¹⁸ Patients in the Asia Pacific region were on average 10.5 years younger than their western European counterparts at enrollment and had one of the highest rates of all-cause mortality and cardiovascular death globally, before and after adjustment for clinical characteristics. Poorer outcomes in younger Southeast Asian populations may reflect later presentation and more advanced disease but also the lower life expectancy seen in lower income countries such as Indonesia and the Philippines, which have vast geographic spread and less developed healthcare infrastructure.

We found marked divergence in both drug and device utilization across Asia. Device utilization in Northeast Asia was more than 3-fold that seen in Southeast and South Asia, with particularly high rates of device usage in Japan. The disparity in device utilization across geographical regions was recently described in a pan-Asian analysis from ASIAN-HF.¹⁹

Table 4. Variables Associated With All-Cause Mortality At 1 Year

	Univariable Analysis		Multivariable Analysis		Interaction With Region			
	HR (95% CI)	P Value	HR (95% CI)	P Value	<i>P</i> _{interaction}	Northeast Asia	South Asia	Southeast Asia
Demographic variables								
Age, per 10 y	1.13 (1.06–1.21)	<0.001	1.07 (0.98–1.18)	0.148	0.002	1.08 (0.93–1.26)	0.94 (0.77–1.15)	1.17 (1.02–1.33)
Female	0.81 (0.67–0.99)	0.038	0.97 (0.74–1.27)	0.834
Enrolled as inpatient	2.12 (1.79–2.51)	<0.001	1.47 (1.17–1.84)	0.001	0.001	1.88 (1.21–2.93)	1.86 (1.11–3.12)	1.20 (0.89–1.62)
HF hospitalization in past 6 mo	1.87 (1.59–2.21)	<0.001	1.47 (1.20–1.80)	<0.001	0.062
Clinical variables								
HFpEF	0.51 (0.39–0.67)	<0.001	0.55 (0.37–0.83)	0.004
NYHA class III/IV	2.26 (1.91–2.68)	<0.001	1.93 (1.54–2.42)	<0.001
Body mass index, kg/m ²	0.94 (0.93–0.96)	<0.001	0.95 (0.93–0.97)	<0.001
Heart rate, per 5 bpm	1.02 (1.00–1.05)	0.074	1.02 (0.99–1.05)	0.201
Systolic BP, per 10 mm Hg	0.89 (0.86–0.93)	<0.001	0.91 (0.86–0.97)	0.002
Diastolic BP, per 10 mm Hg	0.87 (0.81–0.93)	<0.001
Duration of HF, y	1.20 (1.11–1.31)	<0.001	1.16 (1.04–1.29)	0.006
Ischemic etiology of HF	1.64 (1.38–1.95)	<0.001
Coronary artery disease	1.53 (1.30–1.81)	<0.001	1.14 (0.91–1.42)	0.265
AF	1.44 (1.19–1.74)	<0.001	1.35 (1.06–1.71)	0.013	0.019	1.55 (1.07–2.25)	2.79 (1.31–5.94)	1.15 (0.84–1.57)
Hypertension	1.11 (0.94–1.31)	0.218
Prior stroke	1.38 (1.03–1.85)	0.029	0.99 (0.70–1.40)	0.975
PAD	2.28 (1.63–3.20)	<0.001	1.41 (0.92–2.17)	0.117
COPD	1.33 (1.01–1.74)	0.039	0.88 (0.63–1.24)	0.479
Diabetes mellitus	1.37 (1.16–1.61)	<0.001	1.06 (0.85–1.31)	0.621
Renal artery stenosis	2.34 (1.29–4.26)	0.005
Cancer	1.12 (0.73–1.73)	0.607
Smoking, ever	1.33 (1.13–1.57)	0.001	0.99 (0.78–1.25)	0.930
Alcohol, ever	1.05 (0.87–1.27)	0.596
CKD	1.97 (1.64–2.37)	<0.001	1.57 (1.26–1.97)	<0.001
Left bundle-branch block	0.96 (0.74–1.25)	0.758
Medications/device use								
ACEI or ARB	0.55 (0.46–0.65)	<0.001	0.61 (0.49–0.75)	<0.001
β-Blocker	0.63 (0.52–0.75)	<0.001	0.66 (0.52–0.83)	<0.001
Mineralocorticoid receptor antagonist	0.89 (0.75–1.05)	0.161	0.90 (0.72–1.11)	0.325
Diuretic	2.01 (1.54–2.64)	<0.001	1.87 (1.30–2.69)	0.001
Digoxin	1.35 (1.13–1.62)	0.001
ICD/CRT-D	0.92 (0.69–1.22)	0.558	0.75 (0.53–1.08)	0.119

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy–defibrillator; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; PAD, peripheral arterial disease.

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Table 5. Explained Risk Analysis

1-y Mortality	Overall*		HF _r EF*		HF _p EF†	
	Value (%)	SE (%)	Value (%)	SE (%)	Value (%)	SE (%)
Demographic variables+clinical variables+ medication or device use+region	44.8	2.9	42.7	3.2	49.0	7.9
Only demographic variables	3.9	1.6	3.8	1.7	20.4	9.7
Only clinical variables	21.9	3.2	18.2	3.2	11.5	7.8
Only medications/device use	7.0	2.0	7.8	2.2
Only region	5.8	1.9	5.3	2.0	21.8	8.8

HF_pEF indicates heart failure with preserved ejection fraction; HF_rEF, heart failure with reduced ejection fraction.

*Adjusted for demographic variables (age, sex, inpatient enrollment), clinical variables (New York Heart Association class, body mass index, heart rate, systolic blood pressure, duration of heart failure, coronary artery disease, atrial fibrillation, prior stroke, peripheral arterial disease, chronic obstructive pulmonary disease, diabetes mellitus, smoking, chronic kidney disease), medication or device use (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β -blocker, mineralocorticoid receptor antagonist, diuretic, implantable cardioverter-defibrillator/cardiac resynchronization therapy–defibrillator) and regional variables.

†Adjusted for demographic (age, inpatient enrollment), clinical (New York Heart Association class, body mass index, duration of heart failure), and regional variables.

The ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) study²⁰ previously reported low rates of guideline-directed medical therapy and very low rates of implantable cardioverter-defibrillator utilization in a small group of patients (n=439) from the Asia Pacific region (India, Singapore, Israel, Philippines, Turkey, Taiwan). Implantable cardioverter-defibrillator usage was 5.7% in Asia Pacific in comparison to 38% in North America, and patients from the Asia Pacific region had the highest 1-year all-cause mortality rate at 26.7%, in comparison to 7.3% in North America. The largest driver of regional differences in mortality was sudden cardiac death, with a 10.3% 1-year rate of sudden cardiac death in Asia compared with 1.6% in North America.

The clear interregional differences in mortality seen in ASIAN-HF were only partly explained by differences in patient demographics, comorbidities, and treatment. These measured variables account for less than half of the variation in mortality risk after multivariable adjustment. The majority of regional variation in mortality arises from unmeasured factors that likely include differences in healthcare infrastructure, delayed presentation to healthcare facilities, access to and delivery of health care, and the quality of healthcare, as shown by the poorest countries having the greatest mortality. Other important variables such as genetic, cultural, and environmental factors may also be operative. Consequently, efforts at unraveling and addressing these unmeasured factors, including improvements in national and regional healthcare infrastructure and organization, may have great potential for enhancing survival outcomes in Asian HF patients. With pharmacological management and device therapy explaining only 7% of variation in the risk of mortality in the fully adjusted model in chronic patients with HF, primary prevention of HF through attention to its key risk factors or antecedents (eg. coronary artery disease, hypertension, diabetes mellitus, and CKD) is key to reducing the burden of HF in Asia.

Limitations

There is a potential bias in site selection (with a clear bias to reputable, academically inclined centers with expertise in echocardiography and resources to devote to research activities) and willingness of patients to participate in a prospective registry. Priority was given to sites that could provide high-quality data with as little missing data as possible. Therefore, the experience of our centers likely represents the best practice achievable in our multinational observational registry. Our results may therefore underestimate the true outcome burden of HF across Asia. Underreporting bias is also a possibility. To minimize this, every effort was made to ensure protocol standardization and adherence, including on-site investigator training, regular monitoring (both in person and remote), and centralized database management. Variation in reporting of cause of death across the different sites precluded the ascertainment of the cause of death in a significant proportion of cases, with subsequent substantial percentage variation in the category of death with unknown cause. However, in the absence of official pan-Asian population-based data, ASIAN-HF provides the best information available on HF to date across a broad swathe of Asia.

Conclusions

These first multinational prospective outcomes data on patients with HF across 11 Asian regions show that patients from Southeast Asia (particularly low-income countries with the youngest patients) had the poorest outcomes regardless of LVEF. Region-specific risk factors and gaps in guideline-directed therapy should be addressed, along with exploration of potential regional differences in healthcare systems, access to device therapy, and genetic and environmental factors.

Appendix

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Authors' Contributions

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors critically reviewed and contributed to the intellectual content of the article. Lam, MacDonald, and Anand were involved with the conception of the study. Initial data preparation was done by Tay, who performed the statistical analyses. MacDonald drafted the article. Teng contributed to part of the draft article and undertook revisions of the final article. Lam, MacDonald, Richards, Ling, and Anand provided the clinical expertise. Lam, MacDonald, and Yap adjudicated all mortality and causes of death. All authors have read and approved the final version of the article.

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