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ORIGINAL RESEARCH

Readmissions, Death and Its Associated Predictors in Heart Failure With Preserved Versus Reduced Ejection Fraction

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BACKGROUND: Data on rehospitalizations for heart failure (HF) in Asia are scarce. We sought to determine the burden and predictors of HF (first and recurrent) rehospitalizations and all-cause mortality in patients with HF and preserved versus reduced ejection fraction (preserved EF, ≥50%; reduced EF, <40%), in the multinational ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry.

METHODS AND RESULTS: Patients with symptomatic (stage C) chronic HF were followed up for death and recurrent HF hospitalizations for 1 year. Predictors of HF hospitalizations or all-cause mortality were examined with Cox regression for time to first event and other methods for recurrent events analyses. Among 1666 patients with HF with preserved EF (mean age, 68±12 years; 50% women), and 4479 with HF with reduced EF (mean age, 61±13 years; 22% women), there were 642 and 2302 readmissions, with 28% and 45% attributed to HF, respectively. The 1-year composite event rate for first HF hospitalization or all-cause death was 11% and 21%, and for total HF hospitalization and all-cause death was 17.7 and 38.7 per 100 patient-years in HF with preserved EF and HF with reduced EF, respectively. In HF with preserved EF, consistent independent predictors of these clinical end points included enrollment as an inpatient, Southeast Asian location, and comorbid chronic kidney disease or atrial fibrillation. The same variables were predictive of outcomes in HF with reduced EF except atrial fibrillation, and also included Northeast Asian location, older age, elevated heart rate, decreased systolic blood pressure, diabetes, smoking, and non-usage of beta blockers.

CONCLUSIONS: One-year HF rehospitalization and mortality rates were high among Asian patients with HF. Predictors of outcomes identified in this study could aid in risk stratification and timely interventions.

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Key Words: heart failure ■ ejection fraction ■ outcomes ■ hospitalization

Frequent rehospitalization is a hallmark of chronic heart failure (HF) and is the most common cause of hospitalization among the elderly.[1] Not only are rehospitalizations for HF costly, they also predict further readmissions for HF and all-cause mortality.[2,3] The burden of multiple comorbidities among patients with HF makes complex contributions to the risk of rehospitalization.[4] Early identification of such high-risk patients will inform strategies for preventing HF readmissions, a key priority for clinicians and policy makers to improve quality of care and reduce costs. Therapies and development of new strategies directed at reduction or

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CLINICAL PERSPECTIVE

What Is New?

- One-year heart failure (HF) rehospitalization and mortality rates were high among Asian patients with HF, with overall event rates higher in HF with reduced ejection fraction than HF with preserved ejection fraction.
- In both HF with preserved ejection fraction and HF with reduced ejection fraction, the consistent independent predictors of these clinical end points included enrollment as an inpatient, Southeast Asian location, and comorbid chronic kidney disease.
- In HF with reduced ejection fraction, other variables predictive of outcomes included Northeast Asian location, older age, elevated heart rate, decreased systolic blood pressure, diabetes, smoking and non-usage of beta-blockers.

What Are the Clinical Implications?

- Our findings highlight the growing burden of HF and its separate phenotypes in Asia.
- Predictors of outcomes identified in this study could aid in risk stratification and target limited resources for timely interventions (including therapies and development of new strategies) to reduce or prevent hospitalization and death among patients with HF in Asia.

Nonstandard Abbreviations and Acronyms

ASIAN-HF	Asian Sudden Cardiac Death in Heart Failure
ESC-HF-LT	European Society of Cardiology Heart Failure Long-Term
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
I-PRESERVE	Irbesartan in Heart Failure With Preserved Ejection Fraction
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist

prevention of readmissions following HF hospitalization remain as an important area for continued improvement in health care.

While international geographic differences in HF hospitalizations have been described in global HF trials,[5] few studies have included multinational Asian populations. Indeed, knowledge pertaining to the growing burden of HF in Asia,[6] which is home to more than half of the world's population aged >65 years,[7] is scant. The aging population, accompanied by a large and growing burden of cardiovascular risk factors across the Asian continent, underpin an emerging epidemic of HF in Asia. This poses a major challenge, particularly as the burden of HF is estimated to be highest among the poorer nations that may be least equipped to deal with the onslaught.[8] A better understanding of the burden and predictors of readmissions for HF and its separate phenotypes (HF with preserved versus reduced ejection fraction [HFpEF versus HFrEF]) is important for projection of needs and planned allocation of scarce health care resources.

For this study, we determined the burden and predictors of HF (first and total) rehospitalizations and all-cause mortality in patients with HFpEF (ejection fraction [EF] ≥50%), compared with those with HFrEF (EF <40%), in the multinational cohort of the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry, using various statistical methods and a machine learning approach.

METHODS

Study Design

The data and materials used to conduct this research study 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. This cohort study used the precollected records of patients with HFpEF and HFrEF (left ventricular EF ≥50% and left ventricular EF <40%, respectively, on baseline echocardiography) from the ASIAN-HF registry that recruited patients across 10 Asian regions including Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand, between October 2012 and December 2017. ASIAN-HF was originally designed to only include patients with HFrEF (left ventricular EF <40%)[6,9] but in 2013 the study underwent a protocol amendment to also include patients with HFpEF (left ventricular EF ≥50%). Geographic regions were grouped on the basis of the United Nations Regional Groups: Northeast Asia (Hong Kong, Japan, South Korea, Taiwan), South Asia (India), and Southeast Asia (Indonesia, Malaysia, Philippines, Singapore and Thailand). Inclusion and exclusion criteria to the ASIAN-HF had been previously described.[6,9,10]

Among ASIAN-HF patients with HFpEF, 99.5% had structural or functional abnormalities fulfilling the 2016 European Society of Cardiology criteria for diastolic dysfunction (E/e′ ≥13, E′ medial/lateral <9 ms, left atrial enlargement or left ventricular hypertrophy).[10,11]

All patients were followed up at specific time points and recorded as detailed in the study design paper.[9] Vital status was determined by the investigation sites. If the patients were not able to be present physically at the study site, a phone follow-up was performed to acquire information on vital status and hospitalizations, if any (and counterchecked against case report forms). Each outcome event (death or hospitalization) and its cause was independently adjudicated by an independent committee (comprising 3 physicians). Two members of the end point committee independently reviewed, according to prespecified criteria, the data from the case report forms, death certificates, hospital discharge summaries, and any other relevant information requested. Where there is discordance between the 2 adjudicators, arbitration was sought from the third member. One-year follow-up data were used for analysis.

Ethics approval was obtained from the local institutional review committee of each participating center, and all participants gave informed consent. The study conformed to the ethical guidelines in the Declaration of Helsinki.

Primary and Secondary Outcomes

The primary outcome of interest was the composite of HF hospitalizations (unplanned) and all-cause mortality within 1 year from baseline. The primary composite event was analyzed in 2 ways: considering (1) the first HF hospitalization or all-cause death in time-to-first-event analysis, and (2) total HF hospitalization (including first and recurrent hospitalizations) and all-cause death, incorporated as an additional (last) event,[12] in recurrent events analysis.

Secondary outcomes of interest include cause-specific (cardiovascular and noncardiovascular) hospitalizations/readmissions and deaths within 1 year from baseline. A total of 488 (7.4%) patients were lost to follow-up.

Statistical Analysis

Patients with HF were grouped according to numbers of HF hospitalizations (no readmission, 1 HF readmission, and ≥2 readmissions). Differences in baseline characteristics between the groups were presented as follows: Continuous variables were reported using appropriate measures of dispersion and central tendency (means with SDs or medians with ranges) while categorical variables were summarized as number and percentage of the total study population. The outcomes at 1 year were considered within HFpEF and HFrEF subcohorts. Supplementary tests for interaction between HF type and sex (or geographic bloc) on outcomes were performed.

Classical Cox regression analyses for time to first event were used, as well as several models addressing recurrent HF rehospitalization/events including the Andersen-Gill and Prentice, Williams, and Peterson total time and frailty models, as previously reported.[12–14] Recurrent event models take into account the time to event and number of events along the total time scale and apply varying assumptions regarding the baseline hazards and patients' underlying heterogeneity in risks of events. In regression analyses, we used stepwise selection to retain significant (P<0.1) and clinically meaningful predictors in the model.

We also used the random forest[15] as an unsupervised machine learning approach to select features/variables that distinguished patients at higher risk of dying or being hospitalized for HF within 1 year. Using a 10-fold cross-validation approach, a random sample of 80% of the data was used to train the model. The remaining 20% of the data was used to test the model. Model performance was measured by the receiver operating characteristic.

Analyses were performed separately for patients with HFrEF and HFpEF. Appropriate effect measures and 95% CIs for the associations of predictors with outcomes were presented. All tests performed were 2-sided, and P values of <0.05 were considered statistically significant. Statistical analyses were performed using STATA 14.0 (Stata Corp, College Station, TX) or R, A Language and Environment for Statistical Computing, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among a total cohort of 6145 patients (mean age, 62.5±13.2 years; 29.4% women; two-thirds enrolled as outpatients), 1666 had HFpEF (mean age, 68±12 years; 50% women) and 4479 had HFrEF (mean age, 61±13 years; 22% women). Baseline characteristics of the 2 cohorts are shown in Table 1. Overall, of the total patients recruited, 55% had a prior HF hospitalization at baseline; more frequent in HFrEF than HFpEF (61% versus 37%; P<0.001). Patients with HFrEF were also more often enrolled as inpatients (38% versus 29%) and had worse functional status (30% versus 22% in New York Heart Association class III/IV) compared with patients with HFpEF. During 1-year follow-up, the average rate of all-cause readmission per patient was 0.38 (642/1666) and 0.51 (2302/4479) in HFpEF and HFrEF, respectively. The median length of stay (LOS) for all-cause readmissions (excluding baseline hospitalization) was 5 (interquartile range, 3–10) days, and that for a HF readmission was 5 (interquartile range, 3–9) days.

Table 1. Baseline Characteristics of Patients With HFpEF and HFrEF, by Number of HF Hospitalizations in a Year

Baseline characteristics	ASIAN-HF	HFpEF				HFrEF			
		None	1 HF readmission	≥2 HF readmissions	*P* value*	None	1 HF readmission	≥2 HF readmissions	*P* value*
Number of patients	6145	1549	81	36		3935	345	199	
Age, y	62.5 (13.2)	67.5 (12.4)	71.9 (9.8)	70.2 (10.3)	0.004	60.2 (12.9)	62.4 (14.1)	62.9 (11.7)	<0.001
Women	1804 (29.4)	767 (49.5)	46 (56.8)	20 (55.6)	0.350	870 (22.1)	70 (20.3)	31 (15.6)	0.075
Geographic region					<0.001				<0.001
Northeast Asia	1864 (30.3)	709 (45.8)	20 (24.7)	9 (25.0)		991 (25.2)	105 (30.4)	30 (15.1)	
South Asia	1811 (29.5)	451 (29.1)	3 (3.7)	2 (5.6)		1321 (33.6)	27 (7.8)	7 (3.5)	
Southeast Asia	2470 (40.2)	389 (25.1)	58 (71.6)	25 (69.4)		1623 (41.2)	213 (61.7)	162 (81.4)	
Regional income level									<0.001
Low	2063 (33.6)	472 (30.5)	4 (4.9)	3 (8.3)	<0.001	1493 (37.9)	61 (17.7)	30 (15.1)	
Middle	792 (12.9)	85 (5.5)	3 (3.7)	0 (0.0)		667 (17.0)	28 (8.1)	9 (4.5)	
High	3290 (53.5)	992 (64.0)	74 (91.4)	33 (91.7)		1775 (45.1)	256 (74.2)	160 (80.4)	
Ethnicity									<0.001
Chinese	1876 (30.5)	753 (48.6)	39 (48.1)	22 (61.1)	<0.001	850 (21.6)	122 (35.4)	90 (45.2)	
Indian	2075 (33.8)	503 (32.5)	13 (16.0)	4 (11.1)		1476 (37.5)	47 (13.6)	32 (16.1)	
Malay	839 (13.6)	112 (7.2)	21 (25.9)	8 (22.2)		550 (14.0)	92 (26.7)	56 (28.1)	
Japanese/Korean	982 (16.0)	151 (9.7)	7 (8.6)	2 (5.6)		742 (18.9)	67 (19.4)	13 (6.5)	
Thai/Filipino/Others	373 (6.1)	30 (1.9)	1 (1.2)	0 (0.0)		317 (8.1)	17 (4.9)	8 (4.0)	
Enrolled as inpatient	2208 (35.9)	414 (26.7)	47 (58.0)	28 (77.8)	<0.001	1388 (35.3)	193 (55.9)	138 (69.3)	<0.001
NYHA class III/IV	1475 (27.8)	239 (21.1)	26 (33.3)	12 (35.3)	0.007	984 (27.8)	128 (39.8)	86 (45.0)	<0.001
Baseline LVEF, %	31 (24–52)	60 (55–66)	60 (57–65)	60 (55–63)	0.270	28 (22–33)	25 (20–30)	24 (19–31)	<0.001
Body mass index, kg/m^2	25.5 (5.6)	27.1 (5.8)	27.9 (6.8)	28.3 (7.1)	0.260	25.1 (5.4)	25.1 (5.2)	24.9 (5.0)	0.910
Heart rate, bpm	78.6 (15.7)	76.0 (14.8)	74.7 (13.7)	73.4 (12.5)	0.430	79.4 (15.8)	80.8 (16.7)	81.8 (17.1)	0.041
Systolic BP, mm Hg	122.1 (21.2)	132.2 (20.7)	131.7 (25.2)	140.4 (16.6)	0.065	118.3 (20.0)	119.8 (21.4)	114.7 (18.6)	0.014
Diastolic BP, mm Hg	72.4 (12.7)	73.9 (12.8)	68.5 (12.4)	73.9 (12.9)	0.001	72.2 (12.6)	71.2 (12.4)	68.1 (11.7)	<0.001
Coronary artery disease	2825 (46.0)	435 (28.1)	36 (44.4)	18 (50.0)	<0.001	1993 (50.7)	206 (59.7)	137 (68.8)	<0.001
Atrial fibrillation/flutter	1219 (19.9)	366 (23.6)	36 (44.4)	13 (36.1)	<0.001	671 (17.1)	84 (24.3)	49 (24.7)	<0.001
Hypertension	3573 (58.2)	1103 (71.2)	70 (86.4)	33 (91.7)	<0.001	2023 (51.4)	211 (61.3)	133 (66.8)	<0.001
Diabetes	2809 (45.7)	692 (44.7)	56 (69.1)	22 (61.1)	<0.001	1701 (43.2)	189 (54.8)	149 (74.9)	<0.001
Prior stroke	441 (7.2)	102 (6.6)	12 (14.8)	6 (16.7)	0.002	263 (6.7)	37 (10.7)	21 (10.6)	0.003
Peripheral arterial vascular disease	177 (2.9)	23 (1.5)	5 (6.3)	2 (5.7)	0.002	111 (2.8)	18 (5.2)	18 (9.0)	<0.001
COPD	481 (7.8)	120 (7.7)	10 (12.3)	3 (8.3)	0.330	289 (7.3)	42 (12.2)	17 (8.5)	0.005
Chronic kidney disease (eGFR<60)	2305 (47.4)	536 (47.1)	62 (77.5)	28 (77.8)	<0.001	1358 (43.9)	204 (62.8)	117 (60.9)	<0.001

(*Continued*)

Table 1. Continued

Baseline characteristics	ASIAN-HF	HFpEF				HFrEF			
		None	1 HF readmission	≥2 HF readmissions	*P* value*	None	1 HF readmission	≥2 HF readmissions	*P* value*
Anemia	1928 (46.9)	468 (57.0)	53 (72.6)	25 (71.4)	0.010	1142 (42.2)	136 (46.9)	104 (55.6)	0.001
Ever smoked	2266 (36.9)	285 (18.4)	19 (23.5)	11 (30.6)	0.100	1628 (41.4)	196 (56.8)	127 (63.8)	<0.001
Ever had alcohol	1457 (23.7)	180 (11.6)	16 (19.8)	8 (22.2)	0.017	1086 (27.6)	99 (28.7)	68 (34.2)	0.130
ACEI or ARB	4501 (75.9)	968 (66.3)	48 (60.8)	23 (63.9)	0.580	3053 (78.5)	261 (75.7)	148 (74.7)	0.250
Beta blockers	4575 (76.1)	940 (64.4)	56 (70.9)	28 (77.8)	0.130	3112 (80.0)	277 (80.3)	162 (81.8)	0.810
MRA	2946 (49.0)	303 (20.8)	14 (17.7)	10 (27.8)	0.470	2303 (59.2)	207 (60.0)	109 (55.1)	0.480
Diuretics	4767 (79.3)	942 (64.5)	64 (81.0)	34 (94.4)	<0.001	3225 (82.9)	317 (91.9)	185 (93.4)	<0.001
Statin	3929 (65.3)	919 (62.8)	64 (80.0)	25 (69.4)	0.006	2532 (65.0)	234 (67.8)	155 (77.9)	<0.001
Outcomes									
All-cause death at 1 y	559 (9.1)	68 (4.4)	11 (13.6)	6 (16.7)	<0.001	371 (9.4)	64 (18.6)	39 (19.6)	<0.001

Data presented are means (SD) and number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; 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; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and NYHA, New York Heart Association.

**P*-values for test of differences among 3 groups (no readmission, 1 HF readmission, and ≥2 HF readmissions).

Of the patients with HFpEF (versus HFrEF) who were readmitted for HF, 5% (versus 8%) and 2% (versus 4%) had 1 readmission and ≥2 readmissions, respectively (Figure 1). The median number of HF readmissions over a year was 1 in both HFrEF and HFpEF subcohorts. The median cumulative length of stay (LOS; ie, total number of days in hospital over all readmissions) attributable to HF over the 1-year follow-up was 7 (interquartile range, 4–17) days. However, marked variation in LOS was evident across the Asian countries, with longest median LOS for a single readmission in Japan (11 [interquartile range, 6–24] days) and shortest (4–5 days) in most Southeast Asian countries (Singapore, Malaysia, Thailand, Indonesia).

Among patients with HFpEF, those who had ≥2 HF readmissions were older, located in Southeast Asia or a region with higher national income, enrolled as an inpatient, and carried a higher burden of comorbidity (including coronary artery disease, atrial fibrillation/flutter, hypertension, diabetes or chronic kidney disease [CKD], anemia), as compared with those who did not have any readmissions over a year (Table 1). While the prescription of evidence-based HF medications (angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, beta blocker or mineralocorticoid receptor antagonists) did not differ between groups, those with ≥2 readmissions were more frequently prescribed diuretics.

Among patients with HFrEF, as compared with patients who were not readmitted over a year, those experiencing ≥2 HF readmissions had similar characteristics as those with HFpEF and had ≥2 HF readmissions, except for lower systolic blood pressures, higher heart rates, and were more likely to be past or current smokers.

Outcomes and Associated Predictors

Over the 1-year follow up, there were 85 (5%) deaths in HFpEF compared with 474 (11%) deaths in HFrEF (*P*<0.001; Table 2). Of these, deaths were attributable to cardiovascular causes in ≈50% of patients with HFpEF compared with ≈75% patients with HFrEF (*P*<0.001). Crude 1-year death rates were higher in Southeast Asia as compared with South Asia (11% versus 3% and 14% versus 8% in HFpEF and HFrEF, respectively; *P*=0.036). Within the 2 HF phenotypes, death rates were similar in men and women (*P*=0.776; Table S1).

Of 642 and 2302 readmissions in patients with HFpEF and HFrEF, 287 (45%) and 1583 (69%) were attributed to cardiovascular causes, while HF accounted for 181 (28%) and 1044 (45%) rehospitalizations, respectively (Table 2). Hospitalizations were more frequently observed in patients from Southeast Asia compared with South and Northeast Asia in both HFpEF and HFrEF; driven by a higher proportion

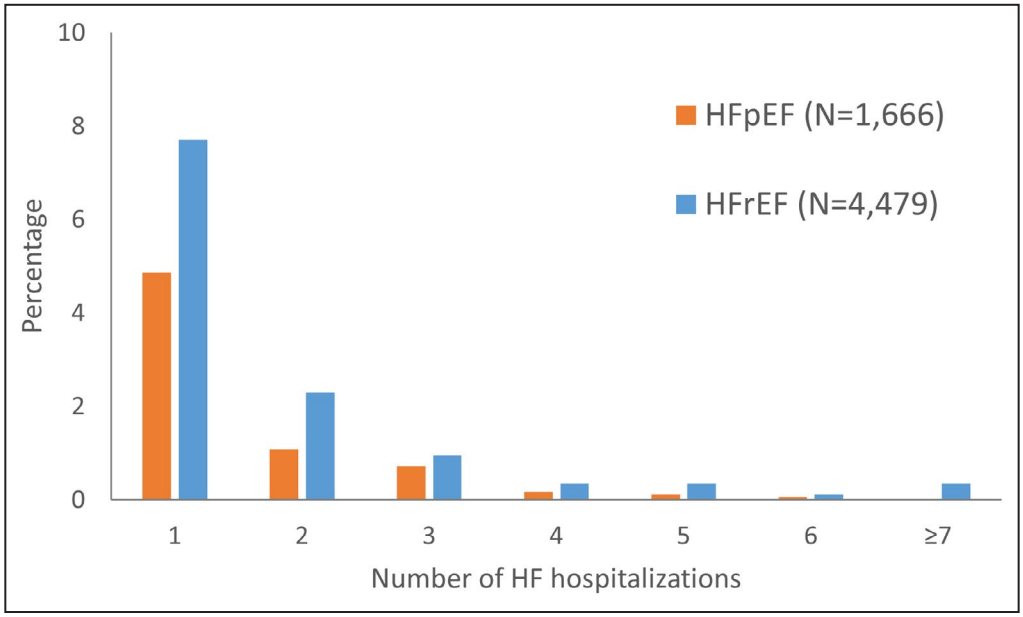

Figure 1. Distribution of the number of heart failure hospitalizations per patient in HFpEF vs HFrEF.
HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

of inpatient recruitment in Southeast Asia (Table S1). The median cumulative LOS did not differ between HFpEF and HFrEF for all-cause, cardiovascular, or HF hospitalizations (P=0.54, 0.99, and 0.34, respectively). Among HFrEF cases, fewer women had incurred HF readmissions than men (18% versus 23%; P=0.001), while in HFpEF, rates were similar in men and women (13% versus 11%; P=0.385).

Composite of First HF Hospitalization or All-Cause Death, Analyzed as Time to First Event

The 1-year composite of HF hospitalization or all-cause death rate was 11% (185/1666) and 21% (916/4479) in HFpEF and HFrEF, respectively (P<0.001; Table 2). The hazards of the composite event were 1.4 to 2.9 times higher in patients with HFpEF enrolled from Southeast Asia as inpatients, in patients with a history of atrial fibrillation or CKD, and when diuretics were prescribed (Table 3). In contrast, the hazards of the composite event in HFrEF were higher in patients from Southeast and Northeast Asia (versus South Asia); those enrolled as inpatients; and those with a higher heart rate, lower systolic blood pressure, history of diabetes, CKD, smoking, or a prescription of diuretics at baseline. Use of guideline-mandated medications (including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers or beta blockers) was associated with lower hazards of the composite event in HFrEF. This association was absent in HFpEF. After multivariable correction, including age, sex, geographic location, NYHA class, prior HF hospitalization, and comorbidities, patients with HFpEF remain at a lower risk for the composite event (hazard ratio [HR]=0.76; 95% CI, 0.62–0.93).

In sensitivity analyses, among those who were enrolled as in-patients, patients with HFpEF and HFrEF had similar risks for the composite event (HR=0.83; 95% CI, 0.64–1.05). Increased duration in the initial LOS at enrollment (per day) was associated with a slightly higher composite event in both HFpEF (HR=1.02; 95% CI, 1.01–1.03) and HFrEF (HR=1.01; 95% CI, 1.00–1.01). Women with HFrEF and diabetes (HR=2.88; 95% CI 2.09–3.98) or CKD (HR=3.09; 95% CI, 2.14–4.48) had higher risks of the composite event as compared with men with HFrEF and diabetes (HR=1.69; 95% CI, 1.46–1.95) or CKD (HR=1.87; 95% CI, 1.60–2.18).

Composite of Total (First and Recurrent) HF Hospitalization and All-Cause Death

The event rate (total HF hospitalization and all-cause death) was 17.7 and 38.7 per 100 patient-years in HFpEF and HFrEF respectively. In HFpEF, analyses of total (first and recurrent) HF hospitalization and all-cause death using the Andersen-Gill and Prentice, Williams, and Peterson total time and frailty models identified the following independent predictors of events: Southeast Asian versus South Asian location; enrollment as an inpatient; a history of chronic kidney

Table 2. Outcomes in Patients With HFpEF (Versus HFrEF)

Outcomes at 1 y	HFpEF	HFrEF	*P* value
Number of patients	1666	4479	
Number of deaths	85 (5.1)	474 (10.6)	<0.001
Number of cardiovascular deaths	46 (2.8)	353 (7.9)	<0.001
All-cause hospitalizations			
Patients with ≥1 readmission	329 (19.7)	1088 (24.3)	<0.001
Patients with ≥2 readmissions	145 (8.7)	448 (10.0)	0.125
Total readmissions	642	2302	
Cumulative length of stay, d*	8 (4–19)	9 (4–23)	0.539
Cardiovascular hospitalizations			
Patients with ≥1 readmission	182 (10.9)	856 (19.1)	<0.001
Patients with ≥2 readmissions	66 (4.0)	301 (6.7)	<0.001
Total readmissions	287	1583	
Cumulative length of stay, d*	8 (4–16)	8 (4–18)	0.989
HF hospitalizations			
Patients with ≥1 readmission	117 (7.0)	544 (12.1)	<0.001
Patients with ≥2 readmissions	36 (2.2)	199 (4.4)	<0.001
Total readmissions	181	1044	
Cumulative length of stay, d*	7 (4–17)	8 (4–20)	0.340
Composite of first HF hospitalization or all-cause death	185 (11.1)	916 (20.5)	<0.001
Recurrent HF hospitalization(s) and all-cause death			
Patients with ≥1 event	185 (11.1)	913 (20.4)	<0.001
Patients with ≥2 events	47 (2.8)	263 (5.9)	<0.001
Total events	266	1516	
Rate per 100 patient-year	17.7	38.7	

Data presented are number (percentage). HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

*Values are median (interquartile range).

disease, atrial fibrillation, or coronary artery disease; and use of diuretics (Table 3).

In contrast, in HFrEF, the predictors of total HF hospitalization and all-cause death included Southeast/Northeast Asian versus South Asian location, enrollment as an inpatient, chronic kidney disease, older age, elevated heart rate, decreased systolic blood pressure, a history of diabetes, smoking, and nonusage of beta blockers.

Feature Selection by Random Forest

The random forest algorithm was able to discriminate patients with events in HFpEF (receiver operating characteristic=0.73) and HFrEF (receiver operating characteristic=0.70) using a similar combination of features: body mass index, age at baseline, systolic blood pressure, and heart rate (Figure 2), along with moderately important features including Singapore or Southeast Asian location and enrollment as inpatients. These variables with higher importance values were consistent with those identified in the regression models, and have significant impact on the risk of dying or being hospitalized for HF within 1 year.

DISCUSSION

Among a multinational cohort (two-thirds enrolled as outpatients) in the ASIAN-HF registry, the 1-year composite event rate for first HF hospitalization or all-cause death was 11% and 21%, and the composite event rate for total HF hospitalization and death was 17.7 and 38.7 per 100 patient-year in HFpEF and HFrEF respectively. All-cause readmissions occurred in a fifth of patients with HFpEF and a quarter of patients with HFrEF, and were mainly attributed to cardiovascular causes with a median cumulative LOS (of 8 days), which did not differ between the 2 HF subgroups. Morbidity burden attributed to HF accounted for nearly half of total readmissions (45%) in HFrEF; whereas, in HFpEF, the majority of admissions (72%) were not HF related.

Overall outcome rates in ASIAN-HF (predominantly enrolled from outpatients) were lower compared with registries from Western populations (eg, Get With The Guidelines), although comparable with that reported in the ESC-HF-LT (European Society of Cardiology Heart Failure Long-Term) registry[16] and to other Asian studies (eg, from Korea and Japan).[17–21] Outcomes in patients with HFpEF in ASIAN-HF were also comparable with those in key HFpEF trials such as TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist)[22] and I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction)[23] (1-year composite outcome rate of 11% versus 15% and 13%, respectively). Of note, the real-world patients from ASIAN-HF with HFpEF were of similar age compared with the White populations in TOPCAT[22] and I-PRESERVE[23] trials, but notably had relatively high prevalence of comorbidities, particularly CKD, diabetes, and hypertension.

The following independent predictors of adverse events were identified: in HFpEF, enrollment as an inpatient, Southeast Asian location, a history of CKD or atrial fibrillation, and use of diuretics. Advancing age was weakly associated with events among those with HFpEF. In HFrEF, beside those predictors identified in HFpEF (with exception of atrial fibrillation), additional predictors of adverse events included older age, elevated heart rate, lower systolic blood pressure, a history of diabetes, coronary artery disease, smoking, and nonusage of beta blockers. Thus, adverse outcomes reflected the burden of comorbidities, and

Table 3. Independent Predictors of Outcomes in Patients With HFpEF (Versus HFrEF)

	Cox regression		Andersen-Gill model		PWP-TT		Frailty	
	Hazards ratio (95% CI)	*P* value	Hazards ratio (95% CI)	*P* value	Hazards ratio (95% CI)	*P* value	Hazards ratio (95% CI)	*P* value
HFpEF								
Age, y	1.02 (1.00–1.04)	0.012	1.01 (1.00–1.03)	0.154	1.01 (0.99–1.02)	0.252	1.02 (1.00–1.04)	0.046
Geographic region								
South Asia	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Northeast Asia	0.94 (0.44–2.03)	0.884	1.60 (0.70–3.68)	0.266	1.20 (0.57–2.48)	0.633	1.64 (0.71–3.80)	0.246
Southeast Asia	2.93 (1.45–5.92)	0.003	3.51 (1.70–7.27)	0.001	1.96 (1.01–3.80)	0.046	4.56 (2.09–9.95)	<0.001
Enrolled as inpatient	2.24 (1.59–3.15)	<0.001	2.77 (1.79–4.28)	<0.001	2.20 (1.52–3.19)	<0.001	3.43 (2.29–5.14)	<0.001
Atrial fibrillation/flutter	1.41 (1.02–1.95)	0.039	1.37 (0.97–1.92)	0.072	1.42 (1.05–1.92)	0.023	1.54 (1.01–2.35)	0.045
Coronary artery disease			1.52 (1.08–2.14)	0.017	1.38 (1.03–1.85)	0.029	1.71 (1.15–2.55)	0.009
Chronic kidney disease (eGFR <60)	2.56 (1.75–3.76)	<0.001	2.60 (1.71–3.95)	<0.001	2.15 (1.46–3.17)	<0.001	2.70 (1.76–4.15)	<0.001
Peripheral arterial vascular disease	1.93 (0.98–3.83)	0.059						
Ever smoked	1.40 (0.99–1.99)	0.059						
Diuretics	1.68 (1.09–2.59)	0.019	2.15 (1.37–3.37)	0.001	1.95 (1.29–2.96)	0.002	2.39 (1.44–3.97)	0.001
HFrEF								
Age, y	1.01 (1.00–1.02)	<0.001	1.01 (1.00–1.03)	0.009	1.01 (1.00–1.02)	0.018	1.01 (1.00–1.02)	0.050
Geographical region								
South Asia	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Northeast Asia	1.95 (1.49–2.56)	<0.001	2.36 (1.74–3.20)	<0.001	1.65 (1.26–2.18)	<0.001	2.29 (1.63–3.23)	<0.001
Southeast Asia	3.53 (2.79–4.48)	<0.001	4.97 (3.73–6.64)	<0.001	2.93 (2.29–3.75)	<0.001	4.97 (3.64–6.79)	<0.001
Enrolled as inpatient	1.60 (1.39–1.86)	<0.001	1.72 (1.41–2.09)	<0.001	1.44 (1.23–1.69)	<0.001	1.91 (1.53–2.37)	<0.001
Heart rate, bpm	1.01 (1.00–1.01)	0.019	1.01 (1.00–1.02)	<0.001	1.01 (1.00–1.01)	0.001	1.01 (1.00–1.02)	0.002
Systolic blood pressure, mm Hg	0.99 (0.99–1.00)	<0.001	0.99 (0.98–1.00)	0.011	0.99 (0.99–1.00)	<0.001	0.99 (0.98–0.99)	<0.001
Coronary artery disease	1.28 (1.10–1.50)	0.002	1.18 (0.96–1.45)	0.111	1.15 (0.95–1.39)	0.161	1.34 (1.06–1.71)	0.016
Diabetes	1.45 (1.25–1.69)	<0.001	1.79 (1.48–2.16)	<0.001	1.51 (1.28–1.79)	<0.001	1.85 (1.47–2.33)	<0.001
Peripheral arterial vascular disease	1.43 (1.08–1.90)	0.012			1.47 (1.09–1.99)	0.011	1.80 (1.08–3.00)	0.024
Chronic kidney disease (eGFR <60)	1.46 (1.26–1.70)	<0.001	1.46 (1.20–1.77)	<0.001	1.37 (1.15–1.64)	<0.001	1.76 (1.39–2.21)	<0.001
Ever smoked	1.35 (1.16–1.56)	<0.001	1.44 (1.17–1.78)	0.001	1.33 (1.13–1.56)	<0.001	1.83 (1.46–2.28)	<0.001
Beta blockers	0.65 (0.55–0.77)	<0.001	0.60 (0.43–0.83)	0.003	0.69 (0.57–0.82)	<0.001	0.49 (0.38–0.65)	<0.001
ACEI or ARB	0.78 (0.67–0.92)	0.002			0.78 (0.66–0.93)	0.005	0.59 (0.46–0.76)	<0.001
Diuretics	1.80 (1.42–2.28)	<0.001	1.88 (1.41–2.50)	<0.001	1.70 (1.32–2.19)	<0.001	2.09 (1.51–2.89)	<0.001
Statin	0.79 (0.67–0.92)	0.004			0.74 (0.63–0.88)	0.001	0.64 (0.50–0.82)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; and PWP-TT, Prentice, Williams, and Peterson total time.

the consistency of our findings using multiple well-established statistical methods suggests that comorbidities may play an important role in the progression of disease regardless of HF phenotype.

Our findings are consistent with prior studies and extend prior observations to Asia.[24–27] Older age and atrial fibrillation have been found to be associated with increased risk of HF readmissions in patients with either reduced or preserved ejection fraction. In a large US study using Medicare data, Aranda et al[28] reported that patients who were readmitted more frequently more often had diabetes, peripheral vascular

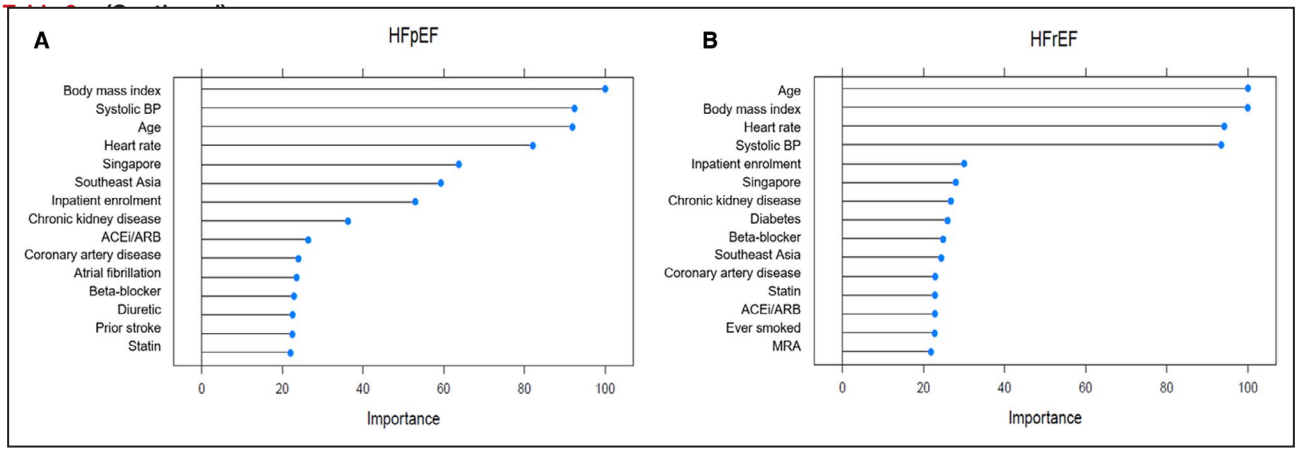

Figure 2. Random forest feature selection in (A) HFpEF vs (B) HFrEF.
Higher importance value of the variable reflects how much the model accuracy decreases if that certain variable was dropped. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and MRA, mineralocorticoid receptor antagonist.

disease, and/or a history of stroke when compared with HF patients free from readmission after their index hospitalization. The consistent relationship between diabetesand increased rehospitalization rates in HF with reduced or preserved ejection fraction has been demonstrated in several other studies. Similarly, there is a wealth of data suggesting that worsening renal function or renal insufficiency is an independent predictor of rehospitalization in HF.[29,30]

Our results also highlight the heterogeneity across the Asian continent, not dissimilar to that observed in other regions of the world.[5] We observed marked variation both in mortality and morbidity associated with HF across both geographic region and subpopulation. Patients from Southeast Asia sustained the worst outcomes compared with other geographic regions. Countries in Asia comprise an assortment of diverse countries at different stages of economic development and diverse health care systems. The high event rates in Southeast Asia may be driven by the excess mortality observed in Indonesia (with highest percent of prior myocardial infarction and smoking), or more frequent hospitalizations in Singapore.[6,31] Differences in clinical practice, thresholds for hospital admissions, and health care systems (eg, reimbursement patterns, access to health care facilities, quality of cardiac care programs, LOS) may in part explain the observed geographic variation in outcomes across Asia. Notably, at the patient level, those from Southeast Asia, despite being significantly younger than those in Northeast Asia, had a higher comorbidity burden, particularly driven by a higher prevalence of diabetes, CKD, CAD, hypertension, and obesity.[31]

The ASIAN-HF registry is the first prospective pan-Asian multinational study of patients with HFpEF and HFrEF across Asia incorporating adjudicated outcomes. This study is the most recent and comprehensive report of follow-up of all recruited patients in ASIAN-HF, including updated numbers of patients, hospitalization, and mortality events since the database was completed and locked in March 2020. The use of a variety of analytical methods (including exploratory [unsupervised machine learning] and conventional regression analyses) for recurrent events beyond the classical time-to-first-event analyses allows greater insight and statistical power to consider the true burden of HF hospitalizations.

However, there are inevitable residual inadequacies in such modeling reflecting residual confounding by unknown and unmeasured factors. Similarly, the lack of discriminate ability with the random forest approach may also reflect the effect on the variation in event rates from unmeasured factors such as genetic, cultural, or socioeconomic factors and differences in health care systems across the region. By design, ASIAN-HF did not include patients with EF in the midrange of 40% to 50%, and patients from China were excluded from this analysis because of the recent restriction from Office of Human Genetic Resources Administration, so we cannot draw conclusions for these groups of patients. We acknowledge potential variation between inter- and intra-regions in socioeconomics, health care delivery, and other factors that cannot be fully accounted for. We lack data about emergency department presentations and outpatient observation stays were not accounted for, hence underestimating the true burden of re-presentations to hospitals.

In conclusion, rehospitalizations and mortality among Asian patients with HF are common, with overall event rates higher in HFrEF than HFpEF. Independent predictors of events identified in this study may aid in risk stratification and targeting of limited resources for prevention of hospitalization and death among patients with HF in Asia.

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Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Outcomes in patients with HFpEF (vs HFrEF), stratified by sex and geographical bloc.

Outcomes at 1 year	HFpEF	HFrEF	p-value
Number of patients			
By sex			<0.001
Men	833 (50%)	3508 (78.3%)	
Women	833 (50%)	971 (21.7%)	
By geographical bloc			<0.001
Northeast Asia	738 (44.3%)	1126 (25.1%)	
South Asia	456 (27.4%)	1355 (30.3%)	
Southeast Asia	472 (28.3%)	1998 (44.6%)	
Number of deaths			
By sex			0.776*
Men	46 (5.5%)	388 (11.1%)	
Women	39 (4.7%)	86 (8.9%)	
By geographical bloc			0.036*
Northeast Asia	22 (3.0%)	78 (6.9%)	
South Asia	13 (2.9%)	109 (8.0%)	
Southeast Asia	50 (10.6%)	287 (14.4%)	
All-cause hospitalizations			
Patients with ≥1 readmission			
By sex			<0.001*
Men	142 (17.1%)	881 (25.1%)	
Women	187 (22.5%)	207 (21.3%)	
By geographical bloc			<0.001*
Northeast Asia	129 (17.5%)	345 (30.6%)	
South Asia	24 (5.3%)	89 (6.6%)	
Southeast Asia	176 (37.3%)	654 (32.7%)	
HF hospitalizations			
Patients with ≥1 readmission			
By sex			0.028*
Men	51 (6.1%)	443 (12.6%)	
Women	66 (7.9%)	101 (10.4%)	
By geographical bloc			<0.001*
Northeast Asia	29 (3.9%)	135 (12.0%)	
South Asia	5 (1.1%)	34 (2.5%)	
Southeast Asia	83 (17.6%)	375 (18.8%)	
Composite of 1st HF hospitalization or all-cause death			
By sex			0.022*
Men	86 (10.3%)	748 (21.3%)	
Women	99 (11.9%)	168 (17.3%)	
By geographical bloc			<0.001*
Northeast Asia	46 (6.2%)	192 (17.1%)	

South Asia	18 (4.0%)	135 (10.0%)
Southeast Asia	121 (25.6%)	589 (29.5%)

Data presented are number (percentage).

*p for interaction (sex x HF group, or geographical bloc x HF group)