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ORIGINAL RESEARCH

Prevalence and Prognostic Significance of Frailty in Asian Patients With Heart Failure

Insights From ASIAN-HF

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ABSTRACT

BACKGROUND Frailty is common in patients with heart failure (HF) and can adversely impact outcomes.

OBJECTIVES This study examined the prevalence of frailty among Asian patients with HF, its association with 1-year outcomes, and if race-ethnicity, HF subtypes, and sex modify this relationship.

METHODS In the multinational ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry, a baseline frailty index (FI) was constructed using a cumulative deficits approach with 48 baseline variables, and patients were followed for the 1-year primary outcome of all-cause death or HF hospitalization.

RESULTS Among 3,881 participants (age 61 ± 13 years, 27% female), the mean FI was 0.28 ± 0.11, and 69% were frail (FI >0.21). Higher FI was associated with older age, Malay ethnicity, and Southeast Asian residency. While comorbidities were more frequent in frail patients (by definition), body mass index was not different across frailty classes. Compared with FI class 1 (<0.21, nonfrail), FI class 2 (0.21-0.31) and FI class 3 (>0.31) had increased risk of the 1-year composite outcome (hazard ratios of 1.84 [95% confidence interval (CI): 1.42-2.38] and 4.51 [95% CI: 3.59-5.67], respectively), even after multivariable adjustment (adjusted hazard ratios of 1.49 [95% CI: 1.13-1.97] and 2.69 [95% CI: 2.06-3.50], respectively). Race-ethnicity modified the association of frailty with the composite outcome ($P_{interaction}$ = 0.0097), wherein the impact of frailty was strongest among Chinese patients. The association between frailty and outcomes did not differ between men and women ($P_{interaction}$ = 0.186) or for HF with reduced ejection fraction versus HF with preserved ejection fraction ($P_{interaction}$ = 0.094).

CONCLUSIONS Most Asian patients with HF are frail despite relatively young age. Our results reveal specific ethnic (Malay) and regional (Southeast Asia) predisposition to frailty and highlight its prognostic importance, especially in Chinese individuals. (ASIAN HF Registry, A Prospective Observational Study [ASIANHF]; NCT01633398)
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ABBREVIATIONS AND ACRONYMS

aHR = adjusted hazard ratio

CI = confidence interval

EF = ejection fraction

FI = frailty index

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire

NYHA = New York Heart Association

VAS = visual analog scale

Frailty is a complex condition characterized by increased vulnerability to stressors and exaggerated declines in physical reserves and functions across multiple physiological systems (1). Its prevalence gradually increases with age and is associated with high risk for adverse health outcomes, including mortality, institutionalization, falls, and frequent hospitalization (2,3). Frailty commonly coexists with heart failure (HF) (4-8), attributable to shared risk factors and pathophysiology, such as high comorbidity burden and aging, culminating in accelerated functional decline (9). Further, it is also plausible that HF causes frailty as a consequence of hemodynamic alterations in HF that could induce tissue hypoxia with resulting inflammation, promoting skeletal muscle apoptosis and sarcopenia (10).

The world's fastest-aging populations are in Asia (11). Asian populations comprise an eclectic mix of ethnicities with cultural, genetic, and sociocultural differences. Asian patients with HF are also a decade younger and have smaller body size and generally lower muscle mass compared with their Western counterparts (12-14). Thus, the prevalence, and clinical correlates, of frailty may be unique to this region. Notably, defining frailty is challenging, and there is currently no gold standard or frailty assessment tool that has been validated in Asian HF populations (15).

Data regarding frailty among Asian patients with HF are sparse. For this study, we aimed to: 1) construct a frailty index (FI) using the accumulation-of-deficits approach (2); 2) determine the prevalence of frailty among Asian patients with HF; and 3) examine the association of frailty with 1-year outcomes. Furthermore, recognizing that among individuals with HF, women have been reported to be predisposed to frailty to a greater extent than men (partially reflecting their lower muscle mass) (16), and that the prevalence of frailty was higher among patients with heart failure with preserved ejection fraction (HFpEF) than heart failure with reduced ejection fraction (HFrEF) (15), we also aimed to identify if the relationship between frailty and 1-year outcomes was modified by ethnicity, HF subtypes, or sex.

METHODS

STUDY POPULATION. The ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry is the first prospective multinational Asian registry of patients with symptomatic HF (stage C), including patients with HF and reduced ejection fraction (EF) (<40%) (12), and patients with preserved EF (EF ≥50%) (14,17). Participants were enrolled across 10 Asian regions, including Hong Kong, India, Indonesia, Japan, Korea, Malaysia, the Philippines, Singapore, Taiwan, and Thailand, between October 2012 and December 2017. Geographic regions were grouped based on the United Nations Regional Groups: East Asia (Hong Kong, Japan, South Korea, Taiwan), South Asia (India), and Southeast Asia (Indonesia, Malaysia, Philippines, Singapore and Thailand). Inclusion and exclusion criteria for recruitment to the ASIAN-HF registry have been previously described (12,14,18).

Race-ethnicity was defined by participant-defined race at the time of enrollment into the registry. The broad ethnic groups in this study comprised Indian, Chinese, and Malay. Ethnic groups included individuals of differing nationalities (eg, Indians from India, Malaysia, and Singapore; Chinese from Taiwan, Hong Kong, Malaysia, Indonesia, and Singapore). Japanese and Korean patients were analyzed together due to limited numbers, regional proximity, and known similarities (19). Participants of Thai, Filipino, and other descents were analyzed as a combined group due to similarly limited numbers and regional proximity.

Ethics approvals were 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.

DEFINITION OF FRAILTY AND GENERATION OF A FI. We used the accumulation-of-deficits model to generate a FI to characterize frailty as a state (2,20). A 48-item FI was constructed using variables from the ASIAN-HF registry that encompassed demographic data, clinical signs, symptoms, laboratory values, chronic conditions, and disabilities (Supplemental Table 1). The FI was constructed using a similar methodology that has been previously described (5,6,20,21). Variables selected must meet certain

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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criteria: deficits should be associated with health status but not related to normal aging (eg, graying hair, presbyopia), cover a range of body systems, and be applied consistently throughout the study sample, and with accumulation of at least 30 to 40 total deficits (5,6,20). The assessment of health-related quality of life in patients with HF was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a 23-item self-administered HF-specific questionnaire validated in multiple HF-related disease states (22-24). This instrument has been widely used in recent international HF clinical trials and has been validated in several languages (19). The KCCQ is the most sensitive surrogate measure to capture such patients' health status. We utilized the 15 items in KCCQ that can quantify physical function, social function, and quality-of-life domains (Supplemental Table 1).

Binary variables were scored as 0 (absence of deficit) or 1 (presence of deficit) for comorbidities and clinical or laboratory measurements (Supplemental Table 1). For quality-of-life and symptom questions or domains, a graduated scale between 0 and 1 was allocated based on the degree of severity (Supplemental Table 1). The FI score was calculated as a ratio based on sum of deficits divided by total number of deficits assessed. A cutpoint of FI more than 0.21 is widely accepted to define frail individuals living in the community (25). In the absence of a definite cutoff for frailty in HF, the same cutoff for FI was applied, similar to other studies (5,6). We categorized the ASIAN-HF registry participants by FI class 1 (0.21 or less), class 2 (>0.21 to 0.31), or class 3 (>0.31), ranging from least to most frail.

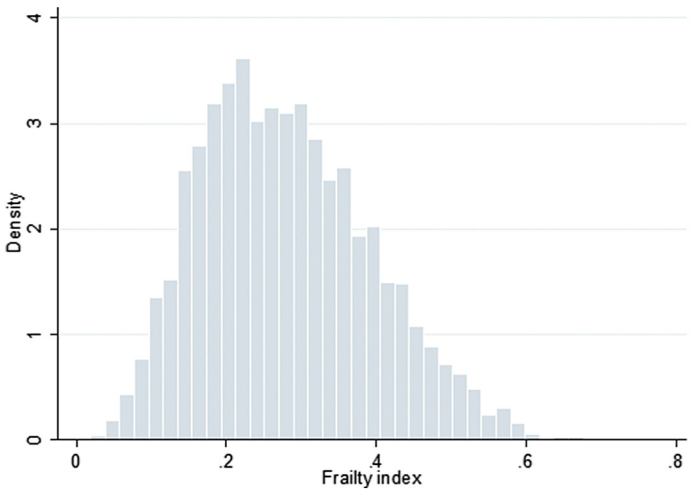
OUTCOMES. The primary outcome was the composite of all-cause death or hospitalization for HF within 1 year. The secondary outcome was all-cause death within 1 year. An independent event adjudication committee adjudicated all outcomes.

A visual analog scale (VAS) and the New York Heart Association (NYHA) functional class were included as secondary outcomes for associations between patient-reported health status (26) and physician-reported functional status with frailty class, respectively. The VAS assesses the patients' current health perception and is scored 0 to 100, with 0 indicating worst possible health and 100 indicating perfect health.

STATISTICAL ANALYSIS. Participants were stratified into 3 groups based on their FI. Descriptive statistics, mean ± SD, median (interquartile range), or number and proportion, were used to describe patients in these groups. A test of trend across the FI classes was performed with linear regression and Wilcoxon rank sum test for continuous and categorical variables respectively. Patients with ≥20% missing data were excluded from the analyses. Imputation of missing data was performed using random forest regression models implemented in the MICE package (27).

Multivariable Cox regression models, adjusting for age, sex, inpatient enrollment, NYHA functional class, heart rate, left ventricular EF, duration of HF, and previous hospitalization for HF, were used to examine the association of FI and 1-year outcomes. Interactions between FI class and age, sex, HF phenotypes, ethnicity, and geographical location were checked in the Cox models. In the presence of significant interactions, further stratified analyses were undertaken. We tested the proportionality of hazards assumptions and they were valid. For all analyses, reported *P* values were 2-sided and found significant at the 5% level. All analyses were performed using Stata version 14 (StataCorp).

FIGURE 1 Distribution of FI Among Asian Patients With Heart Failure



Density plot showing the distribution of frailty index in ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry subjects. The frailty index (FI) was constructed using variables from ASIAN-HF registry, which included demographic data, clinical signs, symptoms, laboratory values, chronic conditions, and disabilities. An FI score of >0.21 deemed participants as frail.

RESULTS

PREVALENCE OF FRAILTY IN STUDY POPULATION AND SUBGROUPS. Among the 3,881 ASIAN-HF registry participants (mean age 61 ± 13 years, 27% female), the mean FI at baseline was 0.28 ± 0.11 (median 0.27 [interquartile range: 0.19-0.36]), and 69% of them were considered frail (defined as FI

TABLE 1 Baseline Characteristics of ASIAN-HF Registry Participants, by FI Class

	FI Class 1	FI Class 2	FI Class 3		
	FI ≤0.210 (n = 1,193)	0.210 < FI ≤ 0.310 (n = 1,240)	FI >0.310 (n = 1,448)	*P* Value	*P* Trend
Demographics					
Age, y	59.4 ± 13.0	62.1 ± 13.3	62.6 ± 13.2	<0.0001	<0.0001
Female	335 (28.1)	344 (27.7)	354 (24.4)	0.061	0.031
Enrolled as inpatient	100 (8.4)	284 (22.9)	781 (53.9)	<0.0001	<0.0001
Ethnicity				<0.0001	0.415
Chinese	286 (24.0)	290 (23.4)	327 (22.6)		
Indian	462 (38.7)	455 (36.7)	464 (32.0)		
Malay	85 (7.1)	128 (10.3)	312 (21.5)		
Japanese/Korean	255 (21.4)	261 (21.0)	262 (18.1)		
Thai/Filipino/others	105 (8.8)	106 (8.5)	83 (5.7)		
Geographical region				<0.0001	0.129
Northeast Asia	437 (36.6)	421 (34.0)	414 (28.6)		
South Asia	446 (37.4)	421 (34.0)	391 (27.0)		
Southeast Asia	310 (26.0)	398 (32.1)	643 (44.4)		
Smoking	328 (27.5)	490 (39.5)	734 (50.7)	<0.0001	<0.0001
Medical history					
Duration of HF				0.067	0.002
<1 y	588 (49.3)	579 (46.7)	632 (43.6)		
1-5 y	376 (31.5)	391 (31.5)	479 (33.1)		
5-10 y	143 (12.0)	159 (12.8)	214 (14.8)		
>10 y	86 (7.2)	111 (9.0)	123 (8.5)		
Previous hospitalization for HF	619 (51.9)	756 (61.0)	991 (68.4)	<0.0001	<0.0001
Ischemic etiology of HF	354 (29.7)	519 (41.9)	845 (58.4)	<0.0001	<0.0001
Myocardial infarction	201 (16.8)	341 (27.5)	558 (38.5)	<0.0001	<0.0001
Hypertension	434 (36.4)	703 (56.7)	944 (65.2)	<0.0001	<0.0001
Diabetes	300 (25.1)	519 (41.9)	803 (55.5)	<0.0001	<0.0001
Coronary artery disease	364 (30.5)	620 (50.0)	911 (62.9)	<0.0001	<0.0001
Atrial fibrillation	182 (15.3)	238 (19.2)	319 (22.0)	<0.0001	<0.0001
Chronic kidney disease	215 (27.2)	428 (45.9)	726 (56.3)	<0.0001	<0.0001
Peripheral arterial disease	15 (1.3)	21 (1.7)	68 (4.7)	<0.0001	<0.0001
Anemia	181 (28.2)	333 (42.2)	640 (54.3)	<0.0001	<0.0001
COPD	44 (3.7)	109 (8.8)	153 (10.6)	<0.0001	<0.0001
Prior stroke	31 (2.6)	79 (6.4)	143 (9.9)	<0.0001	<0.0001
Clinical characteristics					
Ejection fraction, %	33.8 ± 15.0	32.1 ± 13.3	30.5 ± 13.0	<0.0001	<0.0001
Systolic BP, mm Hg	118.2 ± 17.7	119.6 ± 20.6	121.9 ± 22.8	<0.0001	<0.0001
Diastolic BP, mm Hg	72.5 ± 11.1	71.9 ± 12.6	72.6 ± 13.7	0.11	0.77
Pulse pressure, mm Hg	45.7 ± 14.0	47.8 ± 16.3	49.3 ± 17.7	<0.0001	<0.0001
Heart rate, beats/min	77.0 ± 13.8	77.8 ± 15.1	81.3 ± 17.1	<0.0001	<0.0001
BMI, kg/m^2	25.2 ± 5.7	25.2 ± 5.1	25.5 ± 5.9	0.190	0.129
Laboratory					
Serum potassium	4.3 (4.0-4.6)	4.3 (3.9-4.6)	4.2 (3.8-4.6)	<0.0001	<0.0001
Serum creatinine	1.0 (0.8-1.2)	1.1 (0.9-1.4)	1.2 (1.0-1.8)	<0.0001	<0.0001
Albumin	4.4 (4.0-27.0)	4.3 (3.8-31.0)	4.7 (3.7-35.0)	<0.0001	<0.0001
eGFR, mL/min/1.73 m^2	73.4 (58.5-89.0)	62.4 (45.4-83.0)	56.1 (37.0-74.5)	<0.0001	<0.0001
Hemoglobin, g/dL	13.6 ± 1.9	13.0 ± 2.0	12.5 ± 2.2	<0.0001	<0.0001
Medications					
ACE inhibitor/ARB	1000 (83.8)	977 (78.8)	1021 (70.5)	<0.0001	<0.0001
Beta-blocker	989 (82.9)	1003 (80.9)	1067 (73.7)	<0.0001	<0.0001
Diuretics	895 (75.0)	1041 (84.0)	1258 (86.9)	<0.0001	<0.0001
MRA	681 (57.1)	712 (57.4)	784 (54.1)	0.166	0.115

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TABLE 1 Continued

	FI Class 1	FI Class 2	FI Class 3		
	FI ≤0.210 (n = 1,193)	**0.210 < FI ≤ 0.310 (n = 1,240)**	**FI >0.310 (n = 1,448)**	***P* Value**	***P* Trend**
Outcomes					
NYHA functional class				<0.0001	<0.0001
I	232 (21.0)	162 (13.9)	84 (6.3)		
II	734 (66.3)	706 (60.8)	593 (44.6)		
III	126 (11.4)	269 (23.1)	546 (41.1)		
IV	15 (1.4)	25 (2.2)	107 (8.0)		
Visual analog scale	68.8 ± 16.0	61.3 ± 17.1	53.9 ± 18.4	<0.0001	<0.0001
1-y death	52 (4.4)	91 (7.3)	231 (16.0)	<0.0001	<0.0001
1-y death or HF hospitalization	89 (7.5)	164 (13.2)	418 (28.9)	<0.0001	<0.0001

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASIAN-HF = Asian Sudden Cardiac Death in Heart Failure; BMI = body mass index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; FI = frailty index; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

>0.21) (Figure 1). Across frailty classes (Table 1), frailer patients were older, and frailty was equally common in men and women. More patients with HFrEF were frail compared with patients with HFpEF (71% vs 60%; $P < 0.001$) (Figure 2), and patients who were enrolled as inpatients were frail compared with those enrolled as outpatients (91% vs 60%; $P < 0.001$). Malay patients had the highest prevalence of frailty (83.8%), followed by Chinese (68.3%) and Japanese or Korean patients (67.2%) (Table 1).

BASELINE CHARACTERISTICS, MEDICAL THERAPY, SEVERITY OF HF, AND PATIENT-REPORTED WELL-BEING. As expected from the components of the FI, frailer patients had more comorbidities, in particular, hypertension, coronary artery disease, chronic kidney disease, and diabetes (all $P < 0.0001$), than did less or nonfrail patients (Table 1). Frailer patients were more likely to have an ischemic etiology of HF (Table 1). They also tended to have lower estimated glomerular filtration rate and hemoglobin values, higher systolic blood pressure and pulse pressure, and lower ejection fraction. There was no difference in baseline body mass index among the different frailty classes (Table 1).

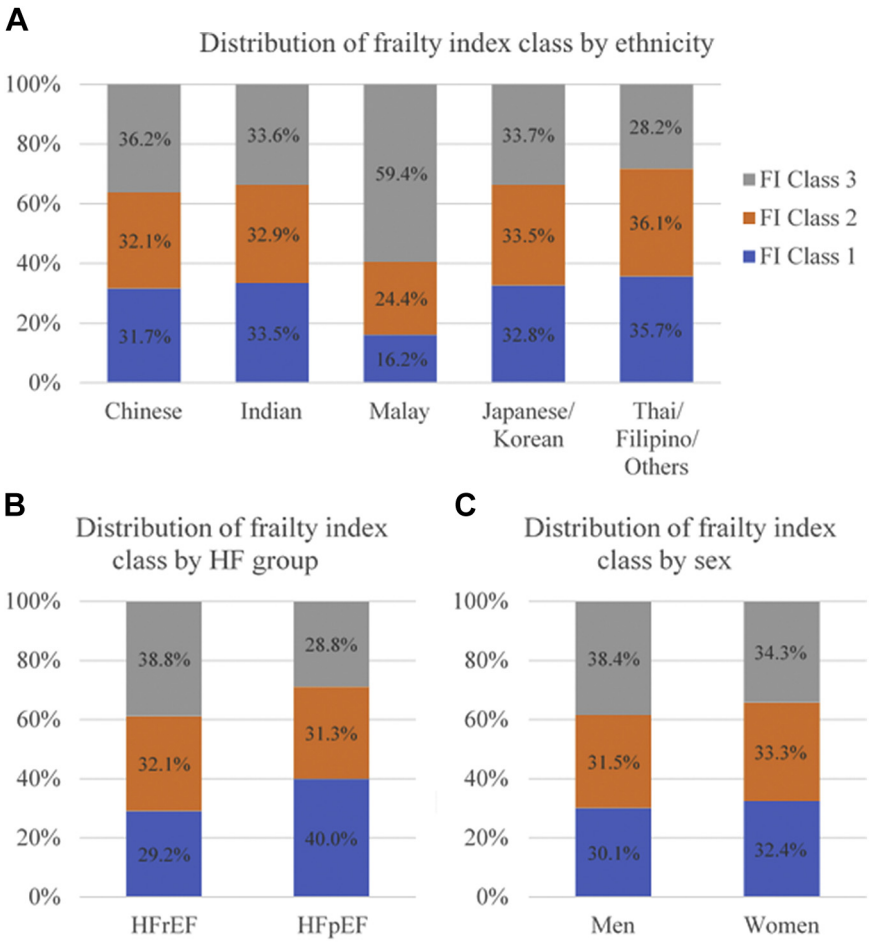
Guideline-indicated medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers) were prescribed in about 77% of the total cohort, with 81% of patients with HFrEF being prescribed beta-blockers. Among those with HFrEF, patients who were in higher FI classes (2 and 3) were less likely to be on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers and were more likely to have diuretics prescribed compared with the nonfrail (FI class 1).

Extent of frailty was positively related to duration and severity of HF, with close to a quarter of the most frail (23.0% vs 19.0% nonfrail) patients who have had HF for more than 5 years and half of the most frail (vs 13.0% nonfrail) patients in NYHA functional class III or IV ($P < 0.01$) (Table 1). Consequently, VAS scores (patient-reported well-being) declined significantly (15 points difference) with increasing frailty class (P trend <0.0001) (Table 1).

CLINICAL OUTCOMES. Increasing degree of frailty was associated with a increase in risk of adverse outcomes (Table 1). Patients who were most frail (FI class 3) had almost 4-fold higher crude event rates for both the primary combined outcome of death or hospitalization for HF (28.9% vs 7.5%) and death alone (16.0% vs 4.4%) compared with FI class 1 (nonfrail) patients (Table 1). After adjustment, patients in FI class 2 and class 3 had a 1.5 and 2.7 times higher risk of death and HF hospitalization (adjusted hazard ratio [aHR]: 1.49; 95% confidence interval [CI]: 1.13-1.97; $P < 0.001$; and aHR: 2.69; 95% CI: 2.06-3.50; $P < 0.001$, respectively), than patients in FI class 1. Notably, the association between frailty (class) and a composite outcome was modified by ethnicity ($P_{\text{interaction}} = 0.0097$) (Central Illustration). The association between frailty and outcomes did not differ between men and women ($P_{\text{interaction}} = 0.186$) and HFrEF versus HFpEF ($P_{\text{interaction}} = 0.094$).

When stratified by ethnicity, the Malay patients had the highest crude composite event rates (32.8%), followed by the Chinese patients (21.8%) (Table 2). However, crude composite event rates among the most frail patients of Malay (in 41.7%) and Chinese (in 39.5%) descent did not differ significantly ($P = 0.283$). Of all ethnicities, among the nonfrail patients (as

FIGURE 2 Severity of FI Stratified by Ethnicity, HF Subtypes, and Sex



Distribution of ASIAN-HF registry participants with varying classes of FI stratified by, **(A)** various ethnic groups, **(B)** heart failure (HF) subtypes, and **(C)** men and women. FI = frailty index; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; other abbreviations as in Figure 1.

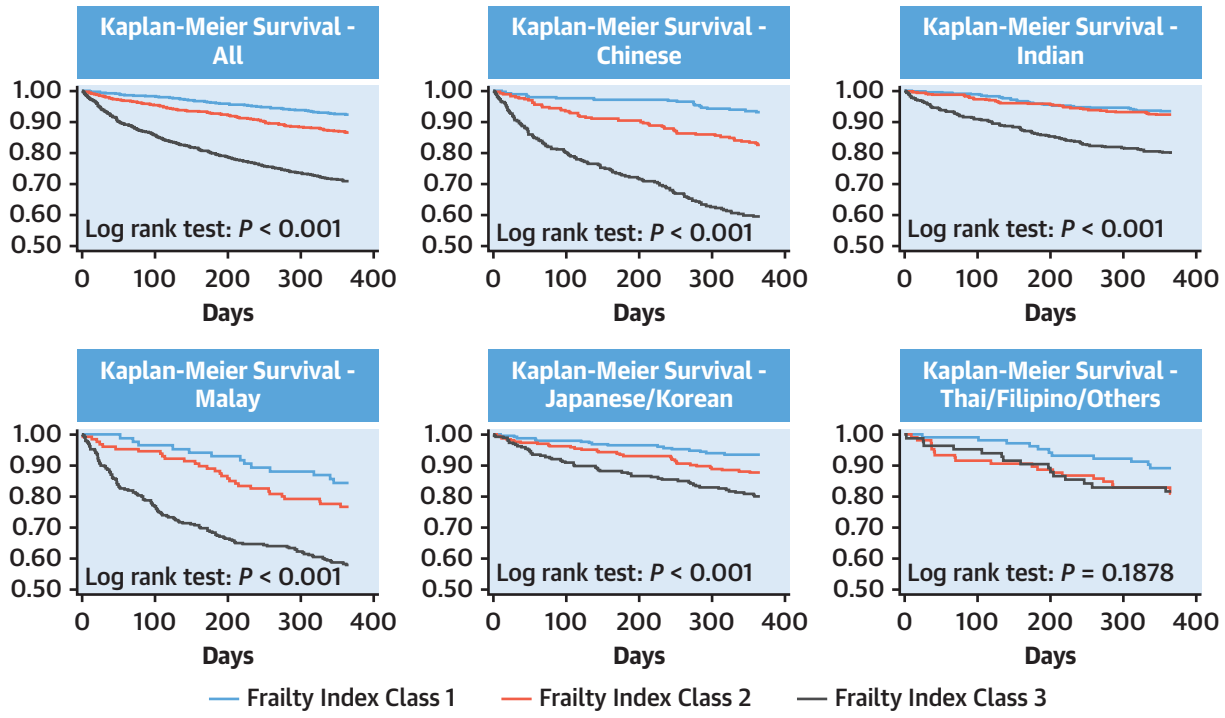
referent group), crude events were highest (15.3%) among the Malay patients versus other race-ethnicities (P = 0.035). Notably, the association of frailty with poor outcomes was strongest in Chinese patients (FI class aHR: 4.61; 95% CI: 2.54-8.39), followed by patients of Japanese or Korean descent (aHR: 2.68; 95% CI: 1.36-5.30), Malay (aHR: 2.26; 95% CI: 1.18-4.33), Indian, and other participants, compared with their nonfrail counterparts (Table 2).

DISCUSSION

Up to 69% of Asian patients with HF are frail, despite their relative youth. Patients of Malay ethnicity (vs Chinese and Indian), and those from Southeast Asia (vs East and South Asia) were particularly predisposed to frailty. Frail patients were less commonly prescribed life-saving guideline-directed HF medications. Importantly, frailty conferred up to 3-fold greater relative risk for death or hospitalization for HF compared with nonfrail individuals. Furthermore, higher frailty scores were related to poorer physician-reported functional status and patients' self-reported well-being. These results highlight the importance of frailty in determining outcomes of patients with HF and point to significant regional and ethnic differences in frailty in HF within Asia.

Previous studies suggest that prevalence of frailty varies widely among community-dwelling populations from various parts of the world (15,28). Among older community-dwelling individuals, a systematic review (21 international studies, 61,500

CENTRAL ILLUSTRATION **Kaplan-Meier Survival Curves of Composite Outcome by Severity of Frailty**



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Kaplan-Meier survival curves of composite outcomes, stratified by severity of frailty, among all Asians with heart failure, Chinese, Indian, Malay, Japanese/Korean, and others, including Thai and Filipino. FI = frailty index.

mainly Western participants) using the Fried frailty criteria showed that the overall weighted average prevalence of frailty was 10.7% (95% CI: 10.5%-10.9%), with a range of 4% to 59% in studies reviewed (28). Separately, another systematic review of 29 studies (43,083 individuals) restricted to Latin America and the Caribbean showed a pooled prevalence of 19.6% (95% CI: 15.4%-24.3%), with a range of 7.7% to 42.6% (29). Interestingly ethnic differences in the prevalence of frailty have been reported among older community-dwelling persons (30) and participants in the Cardiovascular Health Study (31). In Asia, epidemiological studies reported that the weighted prevalence of frailty using the Fried frailty criteria among older community-dwelling individuals varied from 5.2% to 15.2% (32-37). At country or region level in Asia, systematic reviews of individuals ≥65 years of age, pooled prevalence of frailty was 10% (95% CI: 8%-12%) in China (14 studies, 81,258 participants) (38) and 7.4% (95% CI: 6.1%-9.0%) in Japan (based on 5 studies, 11,940 Japanese participants) (39). A recent cross-sectional study from Indonesia reported a higher prevalence of 25.2% (40); however, the participants were enrolled from outpatient setting of hospitals rather than the general community.

Among HF populations, prevalence of frailty also varies considerably depending on the HF populations (ambulatory vs hospitalized) and the frailty assessment tools used. Nevertheless, studies consistently report a much higher overall prevalence of frailty in patients with HF compared with community-based individuals. Based on a systematic review of 26 studies including 6,896 participants with HF, the prevalence of frailty was 44.5% (95% CI: 36.2%-52.8%) (4), escalating to 56% to 76% among hospitalized patients with HF (9). More recent studies (5-7) suggested a higher prevalence of 63% to 94%. Notably, in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial (6), 94% of these ambulatory HFpEF participants were frail, likely largely related to their older age (average 71.5 years, 49% female) as

TABLE 2 Association of FI Class With Outcomes, Overall and by Ethnicity

				FI Class 2		FI Class 3	
	At Risk	Events	FI Class 1	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value
Death or HF hospitalization at 1 y							
All	3,881	671 (17.3)	Reference	1.49 (1.13-1.97)	0.004	2.69 (2.06-3.50)	<0.0001
Chinese	903	197 (21.8)	Reference	2.38 (1.29-4.36)	0.005	4.61 (2.54-8.39)	<0.0001
Indian	1,381	158 (11.4)	Reference	0.89 (0.53-1.48)	0.647	1.82 (1.13-2.91)	0.013
Malay	525	172 (32.8)	Reference	1.45 (0.73-2.88)	0.289	2.26 (1.18-4.33)	0.014
Japanese/Korean	778	98 (12.6)	Reference	1.55 (0.77-3.09)	0.219	2.68 (1.36-5.30)	0.004
Thai/Filipino/others	294	46 (15.6)	Reference	1.79 (0.85-3.75)	0.125	1.44 (0.61-3.44)	0.406
Death at 1 y							
All	3881	374 (9.6)	Reference	1.42 (0.99-2.03)	0.055	2.50 (1.77-3.53)	<0.0001
Chinese	903	100 (11.1)	Reference	1.39 (0.63-3.11)	0.417	2.71 (1.24-5.92)	0.012
Indian	1381	116 (8.4)	Reference	1.03 (0.58-1.83)	0.924	2.10 (1.21-3.64)	0.008
Malay	525	94 (17.9)	Reference	1.59 (0.65-3.89)	0.314	2.09 (0.89-4.94)	0.092
Japanese/Korean	778	30 (3.9)	Reference	1.68 (0.42-6.71)	0.466	3.12 (0.83-11.72)	0.092
Thai/Filipino/others	294	34 (11.6)	Reference	2.25 (0.91-5.59)	0.081	1.55 (0.54-4.45)	0.413

Values are n or n (%), unless otherwise indicated. [a]Adjusted for age, sex, heart rate, NYHA functional class, left ventricular ejection fraction, duration of HF, previous hospitalization for HF and enrollment type.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

compared with those from the ASIAN-HF registry and the exclusively HFrEF cohort from the PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) (5) trials (**Table 3**). We used the cumulative deficits approach in computing the FI, similar to the approach used in the TOPCAT study (6) and the analysis from PARADIGM-HF and ATMOSPHERE trials (5). In all, higher FI scores were well correlated with adverse outcomes, worse health status (patient reported outcomes using VAS, EQ-5D or physician-assessed functional status with NYHA functional class), and lesser use of HF medications. Our study extends previous findings of frailty in HF (**Table 3**) (5,6), particularly as a unique study across vast geographical regions in Asia and interestingly for the differential relationship observed between frailty and outcomes in the different ethnicities.

In our study, Malay patients had the highest prevalence of frailty, whereas the adverse impacts of frailty on outcomes were strongest among Chinese patients. Reasons for these ethnic differences warrant further investigation, and may involve multiple factors including socioeconomic determinants (41). The concept of strong or positive social support as a buffer against stress is not new; in contrast, negative or the lack of social support exacerbates patients' outcomes, adding psychosocial distress and depression (42). Interestingly, in a cross-sectional convenience sample of persons caring for dementia patients undertaken in Malaysia (42), ethnic differences among the Chinese, Indian, and Malay caregivers were observed, with the former 2 ethnicities reporting being more burdened compared with their Malay counterparts. Cultural differences (43), religious beliefs, lower fertility rates (and related smaller family size), and nuclearization of families could partially explain the differences in social support and networks observed (42).

STRENGTHS AND LIMITATIONS. The strengths of this study include the prospective, longitudinal, multinational design of the ASIAN-HF registry, allowing ethnic and regional comparisons in the same large cohort of real-world patients. We acknowledge that there is currently no perfect standard to define frailty in HF (9). Several assessment tools have been developed for use among the geriatric population; however, they are not convenient and not commonly used in routine management of patients with HF (9). Of the various frailty tools, the Fried criteria (1) is the most commonly used and well validated. In the absence of these criteria, we used the cumulative deficits approach (2,20), which captures health deficits across multiple domains (physical function, comorbidity, laboratory measurements, cognitive, social), has gained popularity due to its relative ease of use and has been reported to correlate well with outcomes (5,6,20). Numerous prior studies have

TABLE 3 Comparison With Other Heart Failure Trials

	ASIAN-HF Registry		PARADIGM-HF/ATMOSPHERE Trials	TOPCAT Trial
Study characteristics				
Study population	HFrEF	HFpEF	HFrEF	HFpEF
Participants	3,318	563	13,265	1,767
Type of study	Registry	Registry	Trial	Trial
Methods for defining FI	48-item FI	48-item FI	42-item FI	39-item FI
Definition of frailty	FI >0.21	FI >0.21	FI >0.21	FI >0.21
Prevalence of frailty, %	71	60	63	94
Frailty classes	Class 1, FI ≤0.21	Class 1, FI ≤0.21	Class 1, FI ≤0.21	Class 1, FI<0.3
	Class 2, FI 0.211-0.310	Class 2, FI 0.211-0.310	Class 2, FI 0.211-0.310	Class 2, FI 0.3-0.4
	Class 3, FI ≥0.311	Class 3, FI ≥0.311	Class 3, FI ≥0.311	Class 3, FI 0.4-0.5
				Class 4, FI ≥0.5
Demographics and characteristics				
Age, y	60.2 ± 13.0	68.7 ± 12.0	64.1 ± 11.0	71.5 ± 10.0
Women, %	23	50	21	49
NYHA functional class I/II/III/IV, %	13/56/27/4	14/59/24/3	3/69/27/1	6/59/35/1
Correlates of frailty	Older age, more comorbidities, lower usage of ACE inhibitor/ARB and beta-blockers but higher usage of diuretics		Older age, women, longer duration of HF, more symptoms and signs of HF, more comorbidities, higher BMI	Younger age, more comorbidities, higher usage of HF medications, higher BMI
Other QoL measure(s)	Visual analog scale; worse perceived health status in frailest patients		EQ-5D in the PARADIGM-HF trial; worse QoL in the frailest patients	None
Outcomes				
Primary outcome	Composite HF hospitalization or all-cause death at 1 y	Composite HF hospitalization or all-cause death at 1 y	Composite HF hospitalization or CV death	Composite HF hospitalization or CV death
Adjusted HR (frailest vs nonfrail) (95% CI)	2.67 (2.01-3.54)	3.43 (1.60-7.35)	1.71 (1.56-1.88)	3.51 (2.67-4.61)

ATMOSPHERE = Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure; CV = cardiovascular; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; PARADIGM-HF = Prospective Comparison of ARNI (Angiotensin Receptor–Neprilysin Inhibitor) with ACEI (Angiotensin-Converting-Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure; QoL = quality of life; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; other abbreviations as in Tables 1 and 2.

reported the association between gait speed and frailty; however, gait speed was not measured in our study. The lack of information from inflammatory markers also limits our mechanistic interpretability. There may be selective bias when considering frailty in the enrollment of patients from the inpatient versus outpatient settings. Finally, there might also be residual confounding of unmeasured factors in our analyses.

CONCLUSIONS

Most Asian patients with HF are frail. Our results reveal specific ethnic (Malay) and regional (Southeast Asia) predisposition to frailty and highlight its prognostic importance, especially among Chinese patients. Given emerging evidence that frailty is a dynamic reversible state, these results may provide guidance for the focusing of attention and resources to the prevention or treatment of frailty among Asian populations at particularly high risk of frailty and its adverse outcomes in HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HF and frailty are 2 major public health challenges; the presence of both portends poorer outcomes. Most Asian patients with HF are frail, despite being relatively younger than their Western counterparts. Our findings highlighted potential ethnic predisposition to frailty.

TRANSLATIONAL OUTLOOK: Given that frailty is a dynamic reversible state, prevention or treatment of frailty among Asian populations at particularly high risk of frailty and its adverse outcomes in HF is warranted.

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KEY WORDS Asia, frailty, heart failure, outcomes

APPENDIX For a list of the ASIAN-HF executive committee and the country/region and site investigators as well as a supplemental table, please see the online version of this paper.