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ORIGINAL RESEARCH ARTICLE

Prevalence, clinical correlates, and outcomes of anaemia in multi-ethnic Asian patients with heart failure with reduced ejection fraction

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Abstract

Aims Recent international heart failure (HF) guidelines recognize anaemia as an important comorbidity contributing to poor outcomes in HF, based on data mainly from Western populations. We sought to determine the prevalence, clinical correlates, and prognostic impact of anaemia in patients with HF with reduced ejection fraction across Asia.

Methods and results We prospectively studied 3886 Asian patients (60 ± 13 years, 21% women) with HF (ejection fraction ≤40%) from 11 regions in the Asian Sudden Cardiac Death in Heart Failure study. Anaemia was defined as haemoglobin <13 g/dL (men) and <12 g/dL (women). Ethnic groups included Chinese (33.0%), Indian (26.2%), Malay (15.1%), Japanese/Korean (20.2%), and others (5.6%). Overall, anaemia was present in 41%, with a wide range across ethnicities (33–54%). Indian ethnicity, older age, diabetes, and chronic kidney disease were independently associated with higher odds of anaemia (all $P < 0.001$). Ethnicity modified the association of chronic kidney disease with anaemia ($P_{interaction} = 0.045$), with the highest adjusted odds among Japanese/Koreans [2.86; 95% confidence interval (CI) 1.96–4.20]. Anaemic patients had lower Kansas City Cardiomyopathy Questionnaire scores ($P < 0.001$) and higher risk of all-cause mortality and HF hospitalization at 1 year (hazard ratio = 1.28, 95% CI 1.08–1.50) compared with non-anaemic patients. The prognostic impact of anaemia was modified by ethnicity ($P_{interaction} = 0.02$), with the greatest hazard ratio in Japanese/Koreans (1.82; 95% CI 1.14–2.91).

Conclusions Anaemia is present in a third to more than half of Asian patients with HF and adversely impacts quality of life and survival. Ethnic differences exist wherein prevalence is highest among Indians, and survival is most severely impacted by anaemia in Japanese/Koreans.

Keywords Ethnicity; Heart failure; Anaemia; HFrEF
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All the authors above take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Introduction

Recent international heart failure (HF) guidelines recognize anaemia as an important comorbidity contributing to symptomatology and poor outcomes in HF.[1] The causes of anaemia in HF are multifactorial, and its impact on quality of life (QoL) and outcomes may vary by ethnic background. Prior reports are mainly from Western populations, where the

prevalence of anaemia in patients with heart failure with reduced ejection fraction has been reported to range between 16% and 34%, and anaemia has been shown to contribute independently to morbidity and mortality.[2–13] Prevalence of anaemia is higher in the general population of Asian compared with Western countries and varies widely across Asia.[14] Yet in contrast to the wealth of data in Western patients, data on anaemia in Asian patients with HF are scarce and limited to single country surveys.[15,16] We therefore aimed to determine the prevalence, clinical correlates, and impact of anaemia on the QoL and outcomes among Asian patients with HF in the multinational multi-ethnic Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry.[17,18]

Methods

The ASIAN-HF registry[17,18] is a prospective observational multinational registry of Asian patients >18 years of age with symptomatic HF (at least one episode of decompensated HF in the previous 6 months that resulted in a hospital admission or was treated in an outpatient clinic) and left ventricular ejection fraction (LVEF) ≤40% on baseline echocardiography, from 46 medical centres across 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand). Those with severe valve disease as the primary cause of HF, life-threatening comorbidity with life expectancy of <1 year, who were unable or unwilling to give consent, or have concurrent participation in a clinical therapeutic trial were excluded.[17,18] Comprehensive data collection at baseline included demographic characteristics, clinical attributes, laboratory investigations, and health-related QoL scores.

A total of 3886 out of 5276 patients enrolled in the study had serum haemoglobin (Hb) levels recorded at baseline and were included in the current analyses. Anaemia was defined according to World Health Organization (WHO) criteria of Hb <13 g/dL for men and <12 g/dL for women.[19] The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease formula. Chronic kidney disease (CKD) was defined as eGFR < 60 mL/min/1.73 m^2.[20]

Self-reported ethnicity was classified as Chinese, Indian, Malay, Japanese/Korean, and others. Other ethnicities included Thai, Filipino, and indigenous South-east Asian patients, which were grouped due to small numbers. Geographic regions were categorized according to the United Nations classification as North-east Asia (South Korea, Japan, Taiwan, Hong Kong, and China), South Asia (India), and South-east Asia (Thailand, Malaysia, Philippines, Indonesia, and Singapore). Regions were also classified according to WHO income level groups as lower income (Indonesia, Philippines, and India), middle income (China, Thailand, and Malaysia), and higher income (Singapore, Hong Kong, Taiwan, South Korea, and Japan) groups.

All patients were followed for 1 year for the primary composite outcome of all-cause mortality and HF hospitalizations and the secondary outcome of all-cause mortality. An independent outcomes committee adjudicated all outcome events.

This study complied with the Declaration of Helsinki, and all patients provided written informed consent. Ethics approval was obtained from the relevant local human ethics committees at all sites. Quintiles Outcomes, the contract research organization appointed by the ASIAN-HF academic Executive Committee, handled all registry operations and data management.

Statistical analysis

Categorical variables are presented as numbers with percentages. Continuous variables are presented as medians with interquartile (IQR) ranges or as means ± standard deviation as appropriate. Baseline characteristics of anaemic vs. non-anaemic patients were compared using χ^2 tests, Student's *t*-tests, or Wilcoxon rank-sum tests depending on the type and distribution of variables.

Univariable logistic regression was first performed on all baseline variables for their association with anaemia. Variables that had $P < 0.10$ and clinically important variables were then included in the final multivariable model for anaemia. These included age, sex, ethnicity, income region, New York Heart Association class, LVEF, HF aetiology, alcohol history, presence of peripheral oedema or elevated jugular venous pressure (JVP), body mass index, diastolic blood pressure, use of diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs), or mineralocorticoid receptor antagonists (MRAs), presence of diabetes, or CKD. Interaction analysis was performed to assess if the relationship between anaemia and clinically important variables varied by ethnicity.

We depicted outcomes between anaemic and non-anaemic patients using Kaplan–Meier curves and tested differences in crude survival using the log-rank test. For multivariable analyses, we performed Cox regression analysis and validated the proportional hazards assumption using Schoenfeld residuals. The Cox regression model was adjusted for clinically meaningful covariates including age, sex, ethnicity, regional income, education level, HF aetiology, LVEF, alcohol, smoking history, use of MRAs, ACEi/ARBs, beta-blockers and diuretics, and presence of CKD, diabetes, atrial fibrillation/flutter, peripheral artery disease, liver disease, stroke, chronic obstructive pulmonary disease, and cancer. Interaction analysis was performed to assess if the relationship between anaemia and the composite outcome was modified by ethnicity or clinically

important variables such as diabetes and CKD. Similar analyses were performed to study the associations between Hb (modelled as quintiles) and the primary or secondary outcomes.

The Kansas City Cardiomyopathy Questionnaire (KCCQ), a 23-item self-administered HF-specific questionnaire, was used to examine patient-centred QoL. This instrument has been widely used in recent international HF clinical trials and has been validated in several languages.[21,22] Non-English speaking participants used certified versions of the KCCQ translated into their native languages. Computed KCCQ scores[23] range from 0 to 100, with higher scores representing better health-related QoL. KCCQ scores were adjusted for the same clinically meaningful covariates as described previously.

A value of $P \leq 0.05$ was considered statistically significant. STATA (version 13) software was used to perform all analyses (StataCorp LP, College station, Texas, USA).

Results

Baseline characteristics

Among 3886 Asian patients with HF (60 ± 13 years, 21% women) and available Hb values, anaemia was present in 40% men and 45% women. Compared with non-anaemic patients, anaemic patients were older, more often female, with worse New York Heart Association functional status, higher prevalence of hypertension, diabetes, CKD, and peripheral artery disease, and worse signs of congestion (peripheral oedema and raised JVP) (*Table 1*). Furthermore, anaemic patients were more often treated with diuretics but less often treated with evidence based therapy such as ACEi/ARBs, beta-blockers, and MRAs, than non-anaemic patients (all $P < 0.02$) (*Table 1*).

As shown in Supporting Information, *Table S1*, compared with patients without Hb values, those with Hb values were slightly older, more likely to be from high income regions, and had a greater burden of comorbidities.

Association between anaemia and clinical variables

The prevalence of anaemia varied among ethnicities and was highest in Indians (54.4%), followed by Malays, Japanese/Koreans, Chinese, and other ethnicities (*Figure 1A–B*). Independent predictors of anaemia were older age [odds ratio (OR) = 1.03, 95% confidence interval (CI) 1.02–1.03], Indian ethnicity (OR = 3.00, 95% CI 2.17–4.17), LVEF (OR = 1.04, 95% CI 1.02–1.05), diuretic use (OR = 1.26, 95% CI 1.01–1.56), diabetes (OR = 1.75, 95% CI 1.47–2.08), and CKD (OR = 1.71, 95% CI 1.44–2.03). In contrast, patients with a history of alcohol use (OR = 0.75, 95% CI 0.62–0.90), higher body mass index (OR = 0.96, 95% CI 0.94–0.98), higher diastolic blood pressure (OR = 0.98, 95% CI 0.97–0.98), and receiving ACEi/ARBs (OR = 0.67, 95% CI 0.55–0.81) were less likely to be anaemic. Ethnicity modified the association between anaemia and CKD ($P_{interaction} = 0.045$), where the strongest independent associations between anaemia and CKD were observed in Japanese/Korean (OR = 2.86, 95% CI 1.96–4.20) and other ethnicities (OR = 4.40, 95% CI 1.85–10.48); however, the CIs for the latter were wide.

Quality of life of ASIAN-HF patients with anaemia

Importantly, anaemia adversely affected patients' health-related QoL (using the KCCQ), with adjusted KCCQ scores being significantly lower in anaemic vs. non-anaemic patients across most KCCQ domains (*Table 1*). In particular, physical limitation, social limitation, and symptom frequency domains were affected. Ethnicity did not modify the effect of anaemia on KCCQ scores in this cohort.

Outcomes of ASIAN-HF patients with anaemia

A total of 767 (22.1%) patients experienced the primary composite outcome of death or HF hospitalization at 1 year. Crude 1 year mortality was higher in anaemic vs. non-anaemic patients [201 (14.1%) vs. 194 (9.6%), $P < 0.001$]. Anaemia was associated with higher hazards of the primary composite outcome [hazard ratio (HR) = 1.28, 95% CI 1.08–1.50] (*Table 2*) and 1 year all-cause mortality (HR = 1.39, 95% CI 1.10–1.75). A significant interaction was found between ethnicity and anaemia on the primary composite outcome ($P_{interaction} = 0.023$). Here, we found that anaemia was associated with worse outcomes in Japanese/Koreans patients (adjusted HR 1.82; 95% CI 1.14–2.91, $P = 0.012$) (*Table 2*). Despite the higher prevalence of anaemia in Indians, the absence of significant association between anaemia and outcomes in Indians was observed. Outcomes among Indian patients were better compared with other ethnic groups (*Table 2*, *Figure 1C*). Intriguingly, Indians with anaemia were found to have the highest eGFR (63 [IQR 40, 86] mL/min/1.73 m^2) when compared with the other ethnicities with anaemia (range: 43 [IQR 25, 58] to 53 [IQR 35, 74] mL/min/1.73 m^2). Anaemic Indians were also significantly younger (61.1 ± 12.4 years) when compared with anaemic Chinese (66.8 ± 11.9 years), Japanese/Koreans (69.6 ± 12.8 years), and other ethnicities (62.4 ± 12.5 years), respectively.

When Hb was modelled as quintiles (*Table 3*), the lowest Hb quintile 5.0–11.3 g/dL was significantly associated with

Table 1 Baseline characteristics of the overall cohort and anaemic/non-anaemic subgroups in Asians with heart failure and reduced ejection fraction

Variable	Overall	Non-anaemic	Anaemic	*P*-value
N (%)	3884	2278 (59)	1606 (41)	
Demographics				
Age in years ± SD	60 ± 13	58 ± 13	64 ± 13	<0.001
Female, *n* (%)	827 (21)	456 (20)	371 (23)	0.020
Geographical region, *n* (%)				<0.001
North-east Asia	1456 (37)	952 (42)	504 (31)	
South Asia	876 (23)	401 (18)	475 (30)	
South-east Asia	1554 (40)	927 (41)	627 (39)	
Ethnicity, *n* (%)				<0.001
Chinese	1280 (33)	819 (36)	461 (29)	
Indian	1019 (26)	465 (20)	554 (35)	
Malay	585 (15)	353 (16)	232 (14)	
Japanese or Korean	785 (20)	496 (22)	289 (18)	
Other	215 (6)	145 (6)	70 (4)	
Income region, *n* (%)				<0.001
Low	1168 (30)	604 (26)	564 (35)	
Middle	755 (19)	545 (24)	210 (13)	
High	1963 (51)	1131 (50)	832 (52)	
Medical history, *n* (%)				
Ischaemic aetiology of HF	1867 (51)	964 (45)	903 (60)	<0.001
NYHA Class III/IV	1353 (39)	785 (37)	568 (41)	0.033
Hypertension	2102 (54)	1164 (51)	938 (59)	<0.001
Atrial fibrillation/flutter	770 (20)	473 (21)	297 (19)	0.085
Diabetes	1627 (42)	776 (34)	851 (53)	<0.001
CKD	1710 (45)	801 (36)	909 (58)	<0.001
Cancer	136 (4)	69 (3)	67 (4)	0.057
Previous stroke	276 (7)	154 (7)	122 (8)	0.308
COPD	365 (9)	224 (10)	141 (9)	0.276
PAVD	160 (4)	68 (3)	92 (6)	<0.001
Peptic ulcer disease	127 (3)	75 (3)	52 (3)	0.936
Liver disease	149 (4)	85 (4)	64 (4)	0.674
Smoking history	1882 (49)	1183 (52)	699 (44)	<0.001
Alcohol history	1210 (31)	800 (35)	410 (26)	<0.001
Physical exam				
SBP mmHg, mean ± SD	118 ± 20	118 ± 20	119 ± 20	0.662
DBP mmHg, mean ± SD	72 ± 13	74 ± 13	70 ± 12	<0.001
Peripheral oedema, *n* (%)	1022 (26)	558 (24)	464 (29)	0.002
Elevated JVP, *n* (%)	709 (18)	369 (16)	340 (21)	<0.001
BMI kg/m^2	24.7 ± 5.0	25.1 ± 5.3	24.1 ± 4.7	<0.001
Current medications, *n* (%)				
ACEi/ARB	2746 (73)	1741 (79)	1005 (65)	<0.001
Beta-blocker	2972 (79)	1801 (81)	1171 (76)	<0.001
MRA	2146 (57)	1365 (62)	781 (51)	<0.001
Diuretics	3059 (81)	1774 (80)	1285 (83)	0.019
Laboratory data				
Hb (g/dL), mean ± SD	13.1 ± 2.1	14.5 ± 1.3	11.1 ± 1.2	<0.001
LVEF (%), median (IQR)	28.0 [21.5, 33.0]	27.0 [20.6, 33.0]	29.0 [23.0, 34.2]	<0.001
eGFR mL/min/1.73 m^2, median (IQR)	63.4 [45.1, 82.8]	68.5 [52.9, 85.8]	53.7 [34.7, 74.7]	<0.001
Creatinine (mg/dL), median (IQR)	1.10 [0.90, 1.50]	1.04 [0.90, 1.30]	1.30 [0.92, 1.80]	<0.001
Health-related QoL domain[a]				
KCCQ clinical summary score		67.8 ± 0.5	63.1 ± 0.7	<0.001
KCCQ overall summary score		62.0 ± 0.5	58.1 ± 0.7	<0.001
KCCQ physical limitation score		67.1 ± 0.6	61.7 ± 0.8	<0.001
KCCQ quality of life score		53.3 ± 0.6	52.1 ± 0.7	0.243
KCCQ social limitation score		58.4 ± 0.8	53.0 ± 1.0	<0.001
KCCQ self-efficacy score		63.8 ± 0.7	64.2 ± 0.8	0.694
KCCQ symptom burden score		69.5 ± 0.6	66.4 ± 0.8	0.003
KCCQ symptom frequency score		67.3 ± 0.7	62.2 ± 0.8	<0.001
KCCQ symptom stability score		64.1 ± 0.7	63.4 ± 0.9	0.540
KCCQ total symptom score		68.4 ± 0.6	64.3 ± 0.8	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; IQR, interquartile range; JVP, jugular venous pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PAVD, peripheral arterial vascular disease; QoL, quality of life; SBP, systolic blood pressure; SD, standard error.

[a]Health-related QoL domain scores adjusted for age, sex, ethnicity, income region, HF aetiology, LVEF, alcohol and smoking history, ACEi/ARBs, MRAs, beta-blockers, diuretics, CKD, diabetes mellitus, atrial fibrillation/flutter, PAVD, liver disease, previous stroke, COPD, and cancer. Data presented as (adjusted) mean ± standard error of mean.

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Figure 1 Prevalence of anaemia in ASIAN-HF patients by (A) geographical region and by (B) ethnicity. (C) Kaplan–Meier curves of the primary composite outcome by ethnicity in anaemic and non-anaemic patients.

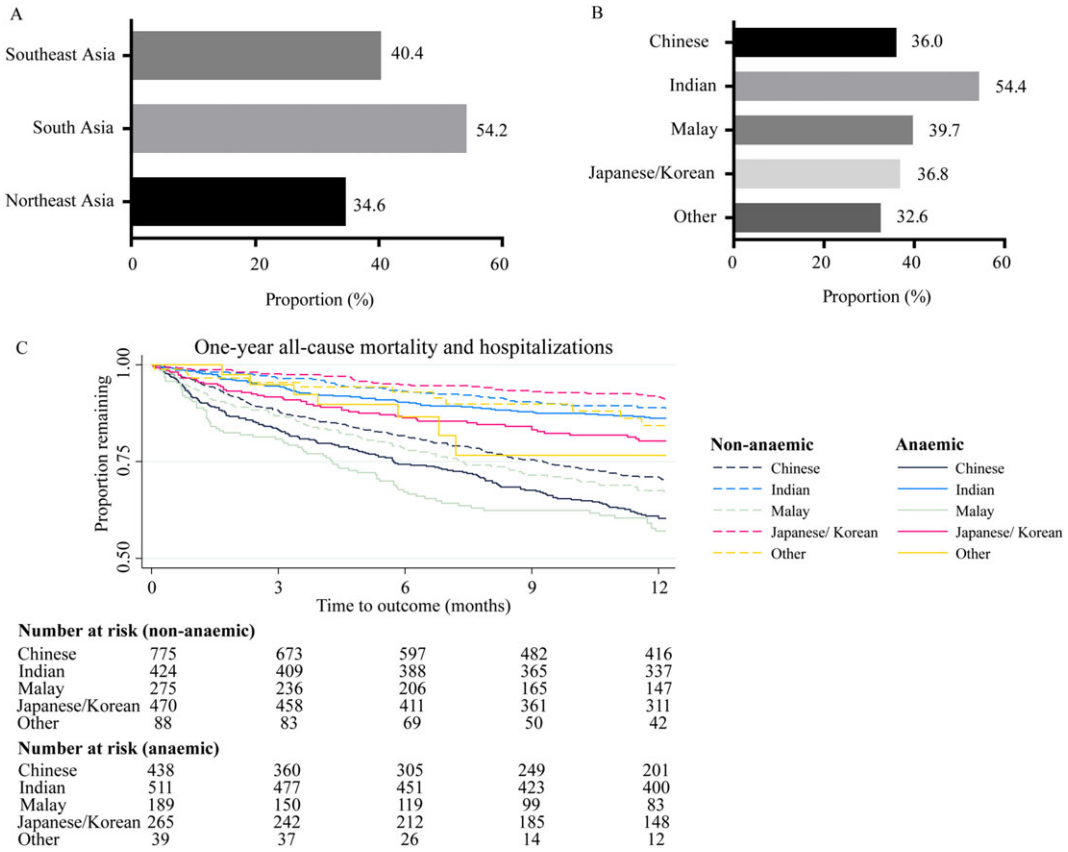

Table 2 Anaemia as a predictor of the primary composite endpoint of 1 year mortality and heart failure hospitalizations

	Event rate			Univariable analysis			Multivariable[a] analysis		
Variable	Overall	Non-anaemic	Anaemic	Hazard ratio	95% CI	*P*-value	Hazard Ratio	95% CI	*P*-value
Anaemia				1.35	1.17–1.56	<0.001	1.28	1.08–1.50	0.004
Stratified by ethnicity									
Chinese	31.08	27.65	37.13	1.43	1.17–1.75	0.001	1.17	0.91–1.49	0.222
Indian	12.49	11.29	13.48	1.25	0.87–1.82	0.231	1.49	0.98–2.27	0.059
Malay	35.50	31.50	41.27	1.44	1.06–1.97	0.02	1.27	0.89–1.81	0.186
Japanese or Korean	11.85	8.09	18.56	2.46	1.61–3.76	<0.001	1.82	1.14–2.91	0.012
Other	16.79	15.38	20.00	1.68	0.65–4.36	0.285	1.75	0.57–5.38	0.325
$P_{interaction}$						0.023			

CI, confidence interval.
The *P*-value for interaction is the interaction between ethnicity and anaemia for the association with the primary composite endpoint.
[a]Adjusted for age, sex, ethnicity, income region, heart failure aetiology, left ventricular ejection fraction, alcohol and smoking history, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, mineralocorticoid receptor antagonists, beta-blockers, diuretics, chronic kidney disease, diabetes mellitus, atrial fibrillation/flutter, peripheral artery vascular disease, liver disease, previous stroke, chronic obstructive pulmonary disease, and cancer.

higher hazard in the primary composite outcome, whereas the two lowest Hb quintiles 5.0–11.3 and 11.4–12.6 g/dL vs. the third Hb quintile 12.7–13.7 g/dL were associated with higher hazards of 1 year mortality. Sex did not modify the effect of Hb on both the primary composite and secondary outcomes tested.

Discussion

The results of this study show that anaemia is highly prevalent among Asian patients with HF, with significant variation among the different Asian ethnicities. Importantly, anaemia

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Table 3 Effect of haemoglobin quintiles on outcomes

	1 year all-cause mortality and HF hospitalizations					
	Univariable analysis			Multivariable[a] analysis		
Variable (g/dL)	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Q1 Hb 5.0–11.3	1.48	1.19–1.84	<0.001	1.43	1.13–1.82	0.003
Q2 Hb 11.4–12.6	1.21	0.96–1.52	0.105	1.24	0.97–1.58	0.086
Q3 Hb 12.7–13.7	1.00	Referent		1.00	Referent	
Q4 Hb 13.8–14.9	1.05	0.83–1.33	0.705	1.00	0.78–1.29	0.985
Q5 Hb 15.0–20.8	0.97	0.76–1.24	0.82	0.99	0.76–1.29	0.936
	1 year all-cause mortality					
	Univariable analysis			Multivariable[a] analysis		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Q1 Hb 5.0–11.3	1.81	1.33–2.47	<0.001	1.80	1.27–2.53	0.001
Q2 Hb 11.4–12.6	1.35	0.97–1.87	0.076	1.50	1.06–2.14	0.022
Q3 Hb 12.7–13.7	1.00	Referent		1.00	Referent	
Q4 Hb 13.8–14.9	1.04	0.73–1.48	0.829	1.11	0.76–1.63	0.578
Q5 Hb 15.0–20.8	1.13	0.80–1.59	0.498	1.38	0.94–2.03	0.096

CI, confidence interval; Hb, haemoglobin; HF, heart failure.
[a]Adjusted for age, sex, ethnicity, income region, HF aetiology, left ventricular ejection fraction, alcohol and smoking history, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, mineralocorticoid receptor antagonists, beta-blockers, diuretics, chronic kidney disease, diabetes mellitus, atrial fibrillation/flutter, peripheral artery vascular disease, liver disease, previous stroke, chronic obstructive pulmonary disease, and cancer.

severely impacts survival and QoL in Asian patients with HF. Indian patients are especially prone to anaemia, which is present in more than half of cases, whereas anaemia is related to the greatest risk of death or HF hospitalization in Japanese/Korean patients with HF. These findings may carry important implications for risk stratification and management of Asian patients with HF, especially given that iron deficiency is now recognized to be a key and treatable cause of anaemia in these patients.[4,16,24–27]

The prevalence of anaemia in HF has previously been reported in European studies to range between 16% and 53%.[3,5–8,12,13,28–36] Differences in characteristics of the study populations could account for this wide range in prevalence. For meaningful comparison with our results, we inspected previous reports using the WHO definition of anaemia and included patients with stable chronic heart failure with reduced ejection fraction. Studies of acute decompensated HF patients were excluded, as baseline Hb levels could be falsely lowered by the acute fluid overload status and haemodilution. The overall prevalence of anaemia in our Asian cohort (41%) was higher than that in similar studies of predominantly White ethnicities (16–34%), despite the younger age of our cohort (Supporting Information, *Table S2*).

The prevalence of anaemia in the Indian subpopulation of our study was particularly high, affecting >50% of Indian patients with HF. A previous report on patients from Singapore showed that Indian patients with HF had high rates of iron deficiency.[16] This suggests that iron deficiency is a major contributing factor to the high prevalence of anaemia among Indian patients with HF and that Indian patients with HF may benefit from contemporary treatment for iron deficiency, including intravenous iron supplementation.[24] Vegetarianism, black tea drinking, and potential genetic factors have been explored as potential reasons for the high prevalence of iron deficiency among Indians;[11] however, this remains to be studied. Surprisingly, despite the high prevalence of anaemia in Indian patients, anaemia was not associated with outcomes in the Indian population. This could in part be due to the younger age and better renal function of anaemic Indians in ASIAN-HF, thus representing a lower risk ethnic group in general compared with the other Asian ethnic groups in ASIAN-HF. Accordingly, outcomes among Indian patients were better compared with other ethnic groups with anaemia (*Table 2*, *Figure 1C*).

Data from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD)[15] showed a 57% prevalence of anaemia, compared with 37.5% in the Japanese subpopulation of our ASIAN-HF cohort. We postulate that this may be related to the lower mean eGFR in JCARE-CARD (51.3 ± 25.3 mL/min/1.73 m^2) compared with that in the Japanese subpopulation of ASIAN-HF (65.2 ± 29.3 mL/min/1.73 m^2). This is further supported by the significant interaction we observed between CKD and anaemia. Here, Japanese/Korean patients in particular were at higher odds for having both CKD and anaemia, suggesting that CKD is a major driving factor for the occurrence of anaemia in Japanese/Korean patients with HF. This also holds true for Korean patients with HF. Previous studies from the Korean Heart Failure (KorHF) registry reported higher rates of anaemia of 41.7%,[37]

compared with 35.5% in the Korean subpopulation of the ASIAN-HF registry. In the KorHF registry, renal function was poorer compared with the Korean patients from the ASIAN-HF registry (creatinine level 1.5 ± 1.2 mg/dL vs. 1.3 ± 1.3 mg/dL). Taken together, these observations could explain why anaemia was associated with the worst adverse outcomes in Japanese/Korean patients, because the anaemic status is closely related to CKD, which in itself is associated with adverse outcomes.[38]

The clinical implications of this study are two-fold. The high prevalence and potent clinical impact of anaemia among Asian patients with HF suggest that screening for anaemia would be important for risk stratification in these patients. We further highlight particular subgroups of patients who may be targeted for screening (e.g. Indian ethnic group) and identify CKD as a key driver of anaemia in specific subgroups (Japanese/Koreans). Whether treatment of anaemia may improve outcomes among Asian patients with HF warrants further study in prospective clinical trials.

Study limitations

Iron indices were not available to enable determination of cause of anaemia. Potential selection bias is evident in our comparison of patients with and without Hb values and suggests that we have included more severe cases of HF in these analyses (Supporting Information, *Table S1*). While screening logs were encouraged but not available from all sites, every effort was made to ensure protocol adherence and standardization including language translations specific to each region, on-site investigator training, regular monitoring, and centralized database management. We further adjusted for peripheral oedema and raised JVP in an attempt to account for the hemodilutional effect of fluid overload.

Conclusions

This first multi-ethnic ASIAN-HF study shows that anaemia is highly prevalent in Asian patients with HF and adversely impacts QoL and survival, with remarkable differences among the different Asian ethnicities. The high prevalence and potent clinical impact of anaemia among Asian patients with HF suggest that anaemia may be an important therapeutic target in these patients.

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Conflict of interest

C.S.P.L. has received research support from Boston Scientific, Medtronic, and Vifor Pharma and has consulted for Bayer, Novartis, Takeda, Merck, Astra Zeneca, Janssen Research & Development, LLC, and Menarini. She has served on the Clinical Endpoint Committee for DC Devices.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Appendix S1. List of ASIAN-HF investigators.
Table S1. Baseline characteristics of patients with and without Hb values.
Table S2. Comparison with other similar studies on anaemia in heart failure.

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