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RESEARCH LETTER

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Potassium abnormalities in patients with heart failure from 11 Asian regions: insights from the ASIAN-HF registry

Abnormalities in serum potassium concentrations (hypo- and hyperkalaemia) are common in patients with heart failure (HF) and associated with discontinuation or down-titration of guideline-recommended medical therapies and adverse outcomes.¹⁻³ Therefore, current HF guidelines recommend frequent monitoring of serum potassium concentrations.⁴ Although over 60% of the world's population resides in Asia, data on potassium abnormalities in Asian patients with HF are scant and most previous studies on the prevalence and clinical consequences of potassium abnormalities in patients with HF were from Western populations.² The particularly high

prevalence of risk factors for potassium abnormalities such as diabetes and chronic kidney disease among Asian patients with HF and the substantial underuse of evidence-based HF pharmacotherapy makes them more vulnerable to potassium abnormalities. Furthermore, the striking regional differences in both patient characteristics and treatment patterns across Asia warrant an examination of potential regional variation in potassium levels and their correlates.^{5,6} Therefore, we investigated the frequency, predictors and clinical outcome associated with potassium abnormalities in Asian patients with HF.

A total of 6480 patients with HF from 46 centres and 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, and Thailand) were prospectively enrolled in the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry.⁷ Patients with symptomatic HF (at least one episode of decompensated HF in the previous 6 months resulting in hospital admission or treatment in outpatient clinic) and reduced or preserved ejection fraction, aged >18 years

could be enrolled in ASIAN-HF. Patients were excluded if their HF was caused by valvular disease, if they had a life expectancy <1 year, and/or were unable/unwilling to give consent.⁷ Although blood sampling was not required by study protocol, clinically available measurements were routinely recorded in the case report forms and for potassium measurements, serum concentrations were recorded in all participating sites. All patients included provided written informed consent and the study adhered to the medical research principles as recorded in the Declaration of Helsinki.

A total of 5054 (78%) patients had potassium measurements recorded at enrolment. Compared to patients without potassium measurements ($n=1426$), patients with potassium measurements were older with more co-morbidities but similar mean estimated glomerular filtration rate (eGFR) and were less often treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs) and mineralocorticoid receptor antagonists (MRAs) but more often treated with beta-blockers

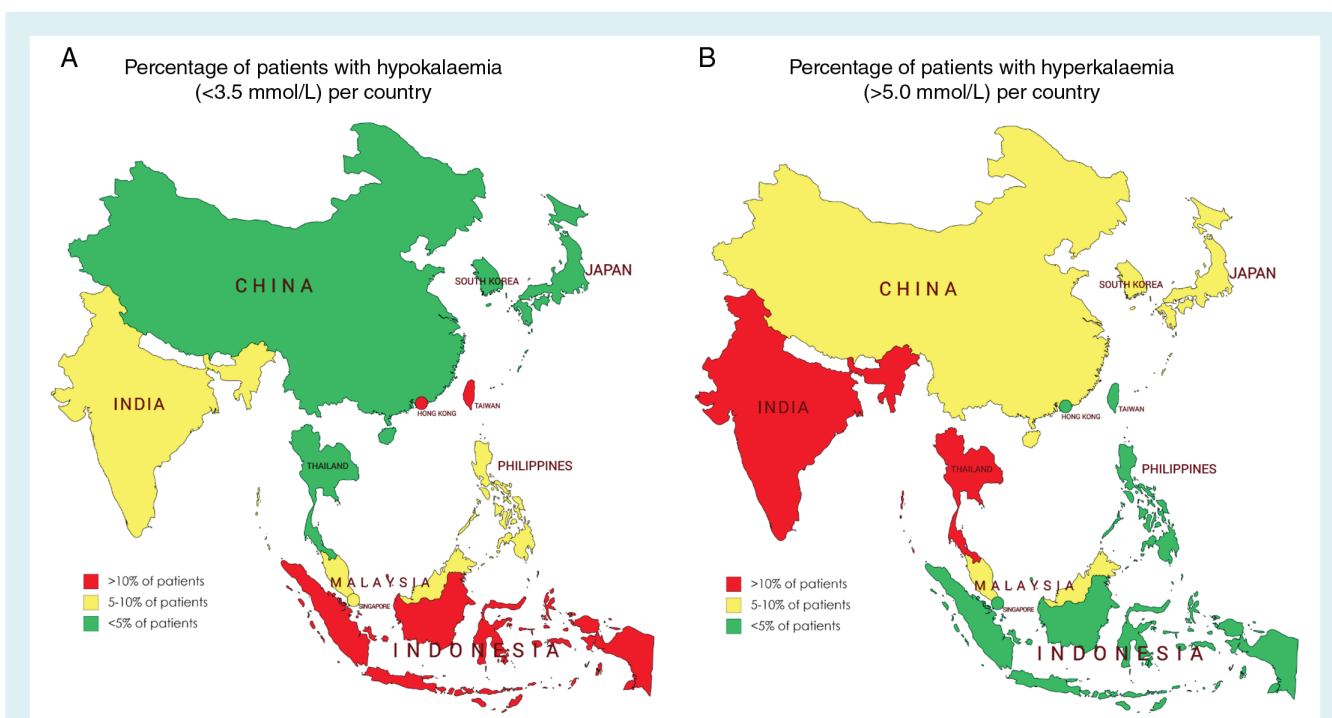


Figure 1 Percentages of Asian heart failure patients with potassium abnormalities at baseline per country. (A) Percentage of patients with hypokalaemia (<3.5 mmol/L) per country. (B) Percentage of patients with hyperkalaemia (>5.0 mmol/L) per country.

Table 1 Clinical variables associated with hypo- and hyperkalaemia at baseline in multivariable logistic regression models

Factor	Hypokalaemia			Hyperkalaemia		
	OR	Multivariable 95% CI (n = 3775)	P-value	OR	Multivariable 95% CI (n = 4039)	P-value
Age, per 10 years				1.06	0.95–1.19	0.271
Female sex	1.39	1.05–1.84	0.023			
Heart rate, per 10 bpm	1.15	1.07–1.24	<0.001	0.95	0.87–1.03	0.182
SBP, per 20 mmHg	1.08	0.97–1.22	0.172			
Estimated GFR, per doubling	0.99	0.75–1.32	0.964	0.52	0.40–0.69	<0.001
NYHA class III/IV, yes vs. no	0.96	0.73–1.28	0.802			
LVEF, per 10%	1.03	0.96–1.11	0.369	0.97	0.90–1.04	0.371
Orthopnoea, yes vs. no	1.12	0.83–1.53	0.464	0.56	0.40–0.79	0.001
Peripheral oedema, yes vs. no	1.38	1.05–1.81	0.023			
History of:						
Atrial fibrillation/flutter				0.77	0.56–1.07	0.122
Diabetes				1.32	1.01–1.71	0.040
Stroke				0.46	0.24–0.85	0.013
COPD				0.71	0.43–1.17	0.182
Cardiovascular therapy						
ACEi/ARB	0.89	0.67–1.19	0.420	1.09	0.82–1.45	0.551
MRA				0.84	0.64–1.09	0.191
Beta-blockers	0.75	0.56–1.00	0.051			
Loop diuretics	1.63	1.10–2.41	0.014	0.73	0.54–0.99	0.045
Laboratory data on baseline						
Haemoglobin, per 5 g/dL	0.97	0.70–1.34	0.866	1.30	0.94–1.81	0.114
Sodium, per 10 mmol/L				0.56	0.42–0.73	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; OR, odds ratio; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure.

All listed variables were tested univariate. All variables with a univariate association <0.1 were used in the multivariable models.

and loop diuretics (online supplementary Table S7).

For all sites, hypokalaemia and hyperkalaemia were defined as <3.5 mmol/L and >5.0 mmol/L, respectively. Hyperkalaemia was divided into mild (>5.0 to <5.5 mmol/L) and moderate/severe (≥ 5.5 mmol/L).^{8,9} The primary outcome was a composite of all-cause mortality and HF rehospitalization within 1 year and tested using Cox proportional hazards models. Tests for interaction between potassium concentrations and HF subtype were performed. All tests were two-sided and *P*-values <0.05 were considered statistically significant. Analyses were performed using Stata SE15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. StataCorp LLC, College Station, TX, USA).

Among the 5054 patients (mean age 62 years, 27% women, 81% HF with reduced ejection fraction) with available serum potassium concentrations, values ranged from 2.3 to 8.0 mmol/L, with a mean of 4.2 ± 0.56 mmol/L. Hypo- and hyperkalaemia

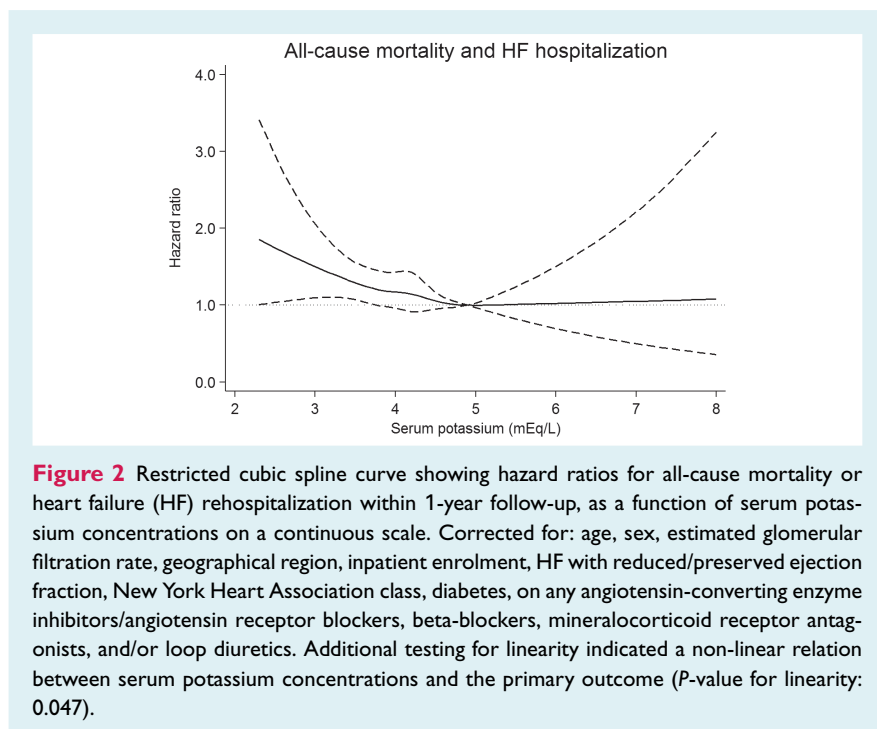
was present in 342 (6.8%) and 356 (7.0%) patients, respectively. A total of 98 patients (1.9%) had moderate/severe hyperkalaemia (≥ 5.5 mmol/L). Patients with hyper- or hypokalaemia had a similar New York Heart Association (NYHA) class compared to patients with normokalaemia (*P* = 0.14). Patients with hyperkalaemia were less frequently treated with MRAs, patients without potassium abnormalities were treated most frequently with ACEi/ARB, and patients with hypokalaemia were treated most often with loop diuretics (*P* < 0.05 for all). A total of 125 patients (2.5%) had moderate/severe hyperkalaemia (≥ 5.5 mmol/L). A slightly lower use of MRAs was seen in patients with moderate/severe hyperkalaemia compared to mild hyperkalaemia (35% vs. 46%, *P* = 0.048).

Hypokalaemia was most prevalent among patients from Indonesia (19.7%), Hong Kong (17.5%), and Taiwan (10.2%) (Figure 1A), while hyperkalaemia was most prevalent in patients from India (12.7%) and Thailand

(10.6%) (Figure 1B) regardless of HF subtype (*P*_{interaction} > 0.5 for both). These geographic differences remained significant in multivariable analyses after correction for clinical confounders including age, sex, NYHA class, eGFR, history of diabetes, in- or outpatient enrolment, and use of ACEi/ARB, MRA, beta-blockers and loop diuretics.

Multivariable logistic regression showed that diabetes, impaired renal function, fewer signs and symptoms of HF, lower serum sodium concentrations, and no use of loop diuretics were associated with the presence of hyperkalaemia (Table 1). Patients with hypokalaemia were more often women, with higher heart rates and more signs and symptoms of HF; and were more often treated with loop diuretics (Table 1).

A total of 1001 (21.7%) patients died or were hospitalized for HF within 1 year. Hypokalaemia was associated with worse outcomes independent of HF subtype [hazard ratio (HR) 1.46; 95% confidence interval (CI) 1.17–1.81; *P* = 0.001; *P*_{interaction} > 0.5].



After correction for clinical confounders (Table 1), hypokalaemia remained significantly associated with worse outcomes (HR 1.28; 95% CI 1.02–1.61; $P=0.035$) but was no longer significant when adjusted for geographical region (HR 1.15; 95% CI 0.91–1.45; $P=0.237$).⁷ However, when analysed as a continuous variable in spline analysis (Figure 2), lower serum potassium concentrations were associated with the primary outcome, even after multivariable adjustment including region. The potassium concentration with the lowest HR for the primary outcome (4.9 mmol/L, risk nadir) was set as reference. In contrast, hyperkalaemia at baseline was not associated with worse outcomes (HR 0.86; 95% CI 0.66–1.12; $P=0.259$).

In this unique study on potassium abnormalities among Asian patients with HF, the overall frequency of hypokalaemia (6.8%) and hyperkalaemia (7.0%) were similar as reported in the Western populations.² Nevertheless, we observed geographical differences, independent of differences in co-morbidities, renal function and HF medication. We are unable to explain these findings but might reflect differences in healthcare systems or local practice.⁶ Clinical correlates of potassium abnormalities in Asian patients with HF were similar to those previously reported in Western and European populations and did not differ between geographical regions in Asia.² Based on spline analysis,

our results indicate that lower potassium concentrations were associated with more adverse outcomes, which is in line with earlier reports from the US,¹⁰ and in contrast to a previous study reporting U-shaped associations.¹ In the study of Aldahl *et al.*,¹ the association between hyperkalaemia and adverse outcomes became significant at relatively high (>5.5 mmol/L) concentrations of serum potassium, which was only present in 1.9% of the patients in our Asian cohort. This study is limited by the fact that serum values were based on the medical records of blood tests of patients performed at the respective medical centres closest to the date of the baseline visit; thus site-to-site differences in measurement technique and/or reporting errors are possible (although the latter was minimized by study monitoring). Unfortunately, no data on potassium supplementation were available.

In conclusion, potassium abnormalities are common among Asian HF patients, with striking regional differences. Hypokalaemia was more frequently observed among patients from Indonesia, Hong Kong, and Taiwan and hyperkalaemia in patients from India and Thailand. Compared to normal potassium concentrations, hypo- and hyperkalaemia did not affect outcomes in adjusted analyses. Yet, on a continuous scale, lower serum potassium concentrations at baseline were related to an increased risk for 1-year mortality or HF rehospitalization.

Conflict of interest: none declared.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Differences in characteristics of patients with and without available serum potassium concentrations at admission.

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