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ORIGINAL ARTICLE

Patient profiles on outcomes in patients hospitalized for heart failure: a 10-year history of the Malaysian population

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Abstract

Aims Heart failure (HF) affects an estimated 38 million people worldwide and is the leading cause of hospitalization among adults and the elderly. Evidence suggests that there may be regional and ethnic differences in the prevalence, outcomes and management of HF. The aim of this study was to understand the disease burden and treatment patterns of patients hospitalized for HF in multi-ethnic Malaysia.

Methods and results A retrospective, non-interventional study was conducted utilizing 10 years of medical records from the National Heart Institute Malaysia (IJN) from 1 January 2009 to 31 December 2018. Of the 4739 patients in the IJN database, 3923 were eligible and were included in this analysis. The study recorded a high male prevalence (72.3%) with a mean age of 62.0 (±13.26) years. The 30-day and 1-year rehospitalization rate was 6.8% and 24.7%, respectively. In-hospital mortality was 7.2% with 27.0% due to cardiovascular causes and 14.2% non-cardiovascular causes. The 30-day and 1-year rehospitalization rates were significantly higher in patients with lower systolic blood pressure (SBP, $P < 0.001$ and $P = 0.002$), diastolic blood pressure (DBP, $P < 0.001$ and $P = 0.017$), sodium ($P < 0.001$ and $P = 0.029$) and estimated glomerular filtration rate (eGFR, $P < 0.001$ and $P = 0.002$) and higher urea ($P < 0.001$ for both), serum creatinine ($P < 0.001$ and $P = 0.003$), and uric acid ($P < 0.001$ for both), respectively. Risk of hospitalization within 1 year varied significantly by ethnicity and was relatively higher in Indian (28.3%), followed by Malay (24.4%) and Chinese (21.9%; $P = 0.008$). In-hospital mortality within 1-year post-index date was higher in patients with lower weight ($P = 0.002$), body mass index ($P = 0.009$), SBP ($P < 0.001$), DBP ($P < 0.001$), sodium ($P < 0.001$), eGFR ($P < 0.001$) and higher heart rate ($P = 0.039$), urea ($P < 0.001$), serum potassium ($P = 0.038$), serum creatinine ($P < 0.001$), and uric acid ($P < 0.001$). In-hospital mortality within 1-year post-index date was also higher in patients with severe or end-stage chronic kidney disease (CKD) compared with mild/moderate CKD ($P < 0.001$) and in patients with HF with reduced ejection fraction (HFrEF) compared with those with mid-range or preserved ejection fraction ($P < 0.001$). The most commonly prescribed HF medications at discharge were loop diuretics (89.2%), β-blockers (68.5%), mineralocorticoid receptor antagonists (56.2%), angiotensin-converting enzyme inhibitors (31.5%), and angiotensin receptor blockers (20.8%).

Conclusions This study provides a greater understanding of the characteristics, treatment patterns, and outcome of hospitalized HF patients in a leading referral centre in Malaysia and will aid the implementation of meaningful interventions to improve patient outcome for HF patients.

Keywords Heart failure; Malaysia; Patient profile; Treatment pattern

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Introduction

Heart failure (HF) is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and is corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.[1]

HF affects an estimated 38 million people, which accounts for 1–3% of the adult population worldwide.[2–7] HF is the leading cause of hospitalization among adults and the

elderly.[5] Globally, HF accounts for 1–2% of all hospital admissions, with numbers as high as one-fifth of total hospitalizations in some countries. In Malaysia, HF accounts for 6–10% of the total hospitalizations.[8,9] Among HF patients, those who are hospitalized have a worse prognosis. An estimated of 5–10% of patients die during hospitalization,[10] and the mortality rate rises to 15% within 30–60 days' post-discharge, with a readmission rate approaching 30%.[11]

Globally, HF imposes a substantial financial burden on healthcare systems, for example, ~US$100 billion in 2012, 60% of which was spent directly on medical costs.[12] These costs are expected to increase substantially due to an ageing worldwide population.[13,14] The substantial disease and healthcare burdens associated with hospitalized HF patients warrant a continuous focus on treatment improvement and highlight the need to implement meaningful interventions.[11]

Nonetheless, evidence indicates that there may be regional and ethnic differences in the prevalence, outcomes and management of HF. Some studies suggest that mortality in patients with HF in low-income or middle-income countries is greater than patients in high-income countries.[15–17] Moreover, the literature on the epidemiology, management and outcomes of HF is most often from studies conducted in North America and Europe. Application of these data to the global population is unreliable[18] as much less information has been collected from the rest of the world.[19–22]

Malaysia consists of a multi-ethnic population, and only a few registries report the epidemiological data of hospitalized HF patients specific to Malaysia. Therefore, the aim of this study was to utilize the vast number of medical records from the National Heart Institute Malaysia (IJN) to help understand disease burden and treatment patterns of patients hospitalized for HF in Malaysia.

Methods

Study design

This retrospective, non-interventional, single-centre study utilized anonymized medical records from hospitalized HF patients at IJN.

All necessary measures were taken to ensure the confidentiality and privacy of individuals. The study was approved by the IRB/IEC of IJN.

The study covered the period from 1 January 2009 to 31 December 2018 and consisted of an identification period (first recorded hospitalization from 1 January 2009 to 31 December 2017) and a 1-year follow-up period after the discharge index date. The index date indicates the date of the first recorded hospitalization (Day 0), whereas the discharge index date refers to the discharge date of the first recorded hospitalization.

Patients

The study included adult patients (aged ≥18 years) with a confirmed diagnosis of HF and first recorded hospitalization from 1 January 2009 to 31 December 2017. Non-Malaysian patients or patients currently enrolled in clinical studies with investigational drugs, devices or procedures were excluded.

Outcomes

The primary objective of this study was to evaluate the rehospitalization events of HF patients hospitalized in a tertiary care centre in Malaysia. The key secondary objectives were to assess the in-hospital mortality of HF patients, describe demographic and clinical characteristics of hospitalized HF patients and characterize the patterns of in-hospital management for HF patients during each hospitalized visit.

Data

Medical records of hospitalized adult HF patients in IJN were collected retrospectively for the period from 1 January 2009 to 31 December 2018. Data extracted from the medical records included patient demographics, medical history, smoking status, length of stay, aetiology, in-hospital treatment, investigations, co-morbidities, rehospitalization, and treatment at discharge.

Baseline chronic kidney disease (CKD) was categorized based on the estimated glomerular filtration rate (eGFR) into Stage 1 (normal CKD, eGFR ≥ 90 mL/min/1.73 m^2), Stage 2 (mild CKD, eGFR = 60–89 mL/min/1.73 m^2), Stage 3 (moderate CKD, eGFR = 30–59 mL/min/1.73 m^2), Stage 4 (severe CKD, eGFR = 15–29 mL/min/1.73 m^2), and Stage 5 (end-stage CKD, eGFR <15 mL/min/1.73 m^2). Patients were classified according to baseline left-ventricular ejection fraction (LVEF) into HF with reduced ejection fraction (HFrEF; LVEF <40%), HF with mid-range ejection fraction (HFmrEF; LVEF = 40–49%) and HF with preserved ejection fraction (HFpEF; LVEF ≥50%). The medications analysed in this study included angiotensin receptor-neprilysin inhibitors (ARNis), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers (BBs), loop diuretics, thiazide, ivabradine and digoxin. Medications not listed above were considered 'others'.

Statistical analysis

The estimated number of patients in IJN eligible for screening over the last 10 years was 4000. Assuming a loss to follow-up

rate of 50%, the expected number of remaining HF patients was 2000; this was sufficient to observe the rehospitalization probability of 32% and 45% at 30 days and 1 year, respectively.

For analysis of the primary endpoints, the count and proportion of HF patients who had a rehospitalization event within 30 days and 1 year after discharge index date were summarized descriptively.

For analysis of the secondary endpoints, the count and proportion of in-hospital mortality event and the primary cause of death at 1-year post-index, demographics and clinical characteristics of HF patients at index date stratified by rehospitalization event, in-hospital mortality and stages of CKD, the number of days of hospitalization for HF patients, in-hospital medical treatment and treatment at discharge for HF and in-hospital investigation at each hospitalization (first hospitalization and three consecutive rehospitalizations) within 1 year after the discharge index date and HF medication combinations at admission (chronic) and those prescribed at discharge were summarized descriptively. This analysis includes up to three rehospitalizations only.

For continuous variables, two-sample *t*-test/one-way analysis of variance was performed, and the *P* value is reported. Mann–Whitney *U* test/Kruskal–Wallis H was performed in case of skewed data. Chi-squared tests were performed, and *P* value was reported for categorical variables. Fisher's exact test was used in the case of sparse cell size. No imputation was performed on the missing data. A *P* value of ≤ 0.05 is statistically significant.

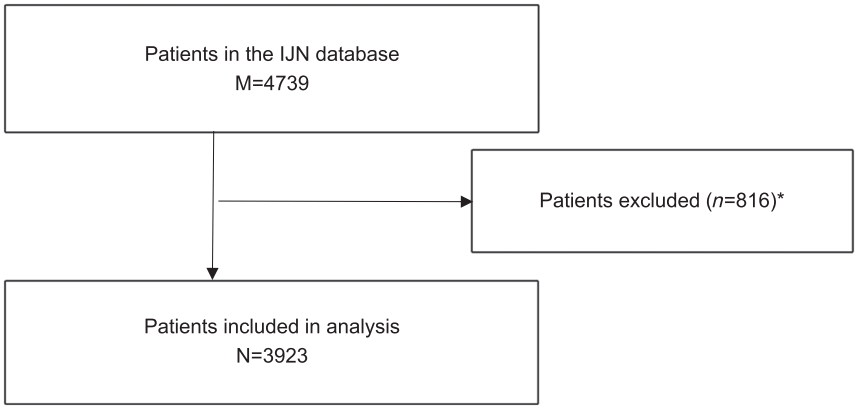
Results

Details of 4739 patients were included in the IJN database. Of these, 710 patients did not fulfil the inclusion criteria, and 106 patients met the exclusion criteria, making an overall total of 3923 patients included in the analysis (*Figure 1*).

Demographics and baseline characteristics

The study recorded a high male prevalence (72.3%) with a mean age ± standard deviation (SD) of 62.0 ± 13.26 years. Overall, 55.4% of patients were Malay, 24.1% Indian, 17.0% Chinese, and 3.4% were of other ethnicities. Over 40% of patients were obese (body mass index [BMI] $\geq$ 30) or overweight (BMI 25–<30). The most common aetiologies for HF in this study were ischaemic heart disease (66.0%), followed by valvular heart disease (29.9%) and cardiomyopathy (26.8%). The mean eGFR at baseline was 59.0 mL/min/1.73 m^2 with a majority of patients having mild-to-moderate CKD (Stage 2: 39.2% and Stage 3: 33.0%). A majority of patients had HFrEF (62.9%), followed by HFpEF (12.7%) and HFmrEF (12.4%). The most commonly reported co-morbidities at baseline were hypertension (72.4%), diabetes (63.2%), coronary artery disease (CAD; 56.5%) and hyperlipidaemia/dyslipidaemia (41.8%). Other baseline demographics and clinical characteristics are presented in *Table 1*.

Figure 1 Patient disposition.



*Patient excluded by inclusion/exclusion criteria

HF, heart failure; M, total number of patients in database; N, total number of patients included in analysis

Table 1 Patient demographic and disease characteristics at baseline

Demographic characteristics	Overall (N = 3923)
Age (years), mean (SD)	62.0 (13.26)
Age group (years)	
<50	654 (16.7)
50–59	931 (23.7)
60–69	1213 (30.9)
70–79	848 (21.6)
≥80	277 (7.1)
Gender	
Male	2836 (72.3)
Ethnicity	
Malay	2175 (55.4)
Chinese	668 (17.0)
Indian	946 (24.1)
Others	134 (3.4)
BMI (kg/m^2), mean (SD)	n = 2731
	27.3 (5.80)
Underweight (<18.5)	89 (2.3)
Normal (18.5–<25)	948 (24.2)
Overweight (25–<30)	981 (25.0)
Obese (≥30)	713 (18.2)
Missing	1192 (30.4)
Smoking history	
Former	1305 (33.3)
Current	395 (10.1)
Never	1713 (43.7)
Unknown	510 (13.0)
Aetiology of HF	
Ischaemic heart disease	2590 (66.0)
Hypertension	129 (3.3)
Cardiomyopathy	1053 (26.8)
Congenital heart disease	37 (0.9)
Valvular heart disease	1172 (29.9)
Systolic BP (mmHg), mean (SD)	n = 3892
	129.7 (25.26)
Diastolic BP (mmHg), mean (SD)	n = 3885
	77.5 (14.91)
Heart rate (b.p.m.), mean (SD)	n = 3889
	86.3 (20.24)
Laboratory test, mean (SD)	
Urea (mmol/L)	n = 3922
	8.9 (5.25)
Sodium (mmol/L)	n = 3922
	137.2 (4.64)
Serum potassium (mmol/L)	n = 3909
	4.5 (0.65)
Serum creatinine (μmol/L)	n = 3920
	141.0 (104.41)
Uric acid (μmol/L)	n = 3922
	519.7 (169.97)
RBS (mmol/L)	n = 3545
	9.2 (5.06)
eGFR (mL/min/1.73 m^2)	n = 3920
	59.0 (27.74)
Stage of CKD	
Stage 1 with normal or high GFR	517 (13.2)
Stage 2 mild CKD	1294 (33.0)
Stage 3 moderate CKD	1536 (39.2)
Stage 4 severe CKD	426 (10.9)
Stage 5 end stage CKD	147 (3.7)
Missing	3 (0.1)
HF ejection fraction	
HFrEF	2469 (62.9)
HFmrEF	486 (12.4)
HFpEF	500 (12.7)
Missing	468 (11.9)
Co-morbidities	
Coronary artery disease	2217 (56.5)
PCI	978 (24.9)
CABG	910 (23.2)
Previous MI	1008 (25.7)
Renal insufficiency	959 (24.4)
Atrial fibrillation	849 (21.6)
Diabetes	2481 (63.2)
Hypertension	2840 (72.4)
Hyperlipidaemia/dyslipidaemia	1641 (41.8)
Stroke/TIA	228 (5.8)
COPD/Asthma	395 (10.1)

BMI, body mass index; BP, blood pressure; b.p.m., beat per minute; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; MI, myocardial infarction; n, number of patients; N, total number of patients; PAH, pulmonary arterial hypertension; PCI, percutaneous coronary intervention; PHT, pulmonary hypertension; RBS, random blood sugar; SD, standard deviation; TIA, transient ischaemic attack.
Data presented in n (%) unless otherwise stated; eGFR was calculated based on MDRD equation.

30-day and 1-year rehospitalization

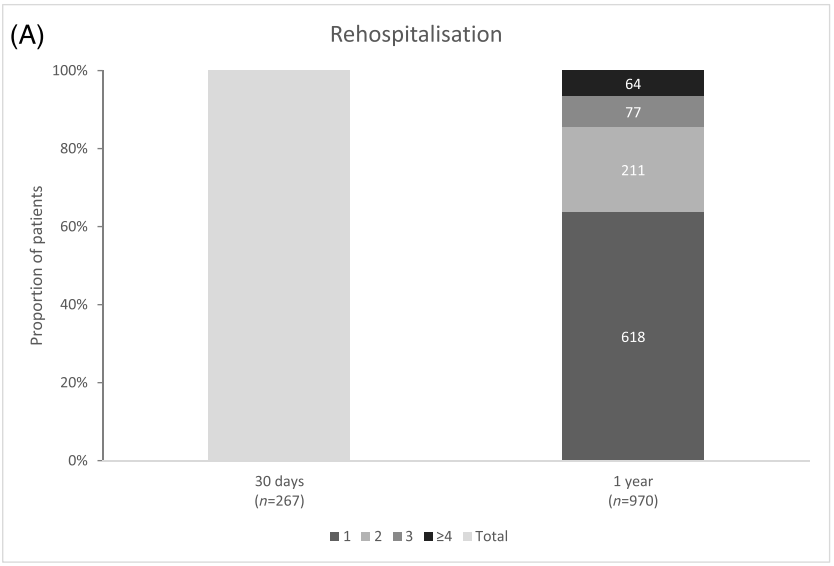
Thirty-day rehospitalization was recorded for a total of 267 (6.8%) patients. Patients hospitalized within 30 days tended to have lower systolic blood pressure (SBP; $P < 0.001$) and diastolic blood pressure (DBP; $P < 0.001$); higher baseline laboratory measurement of urea ($P < 0.001$), serum creatinine ($P < 0.001$) and uric acid ($P < 0.001$); and lower baseline laboratory measurement of sodium ($P < 0.001$) and eGFR ($P < 0.001$) (Supporting Information, *Table S1*). Patients hospitalized within 30 days tended to be older (by year $P = 0.003$, by group $P = 0.024$) and have more severe CKD stage ($P = 0.007$).

One-year rehospitalization was recorded for a total of 970 (24.7%) patients (*Figure 2A*). Among patients with a 1-year rehospitalization record, the majority (n = 618, 63.7%) were rehospitalized once, whereas 211 (21.8%), 77 (7.9%) and 64 (6.6%) of patients were rehospitalized 2, 3 and ≥4 times, respectively.

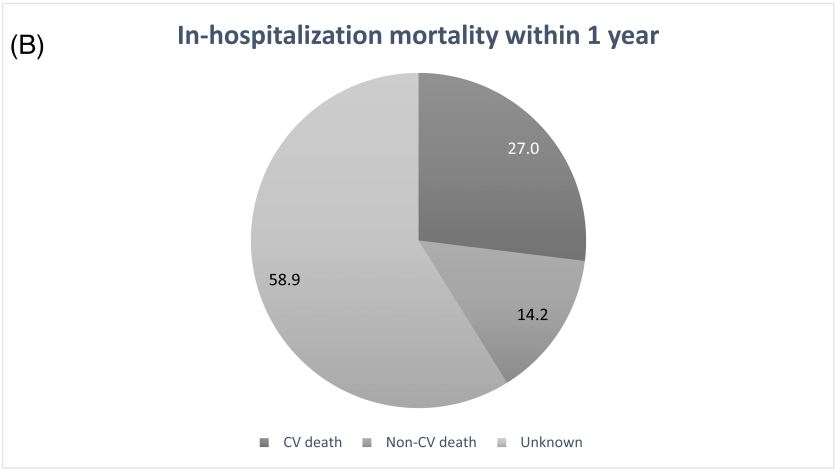
Similar to patients with a 30-day rehospitalization, those hospitalized within 1 year tended to have lower SBP ($P = 0.002$) and DBP ($P = 0.017$); higher baseline laboratory measurement of urea ($P < 0.001$), serum creatinine ($P = 0.003$) and uric acid ($P < 0.001$); and lower baseline laboratory measurement of sodium ($P = 0.029$) and eGFR ($P = 0.002$) (Supporting Information, *Table S1*).

Risk of hospitalization within 1 year varied significantly by ethnicity, being relatively higher in Indian (28.3%), followed by Malay (24.4%) and Chinese (21.9%; $P = 0.008$). Patients with HFrEF had higher risk of hospitalization within a year

Figure 2 From the first hospitalization (index date), proportion of patients (A) rehospitalization within 30 days or 1 year and (B) reported in-hospital mortality within 1 year.



n, number of patients



CV, cardiovascular

(25.4%), followed by HFmrEF (20.4%) and HfpEF (20.2%; $P = 0.007$) (Supporting Information, *Table S1*).

In-hospital mortality within 1-year post-index date

We reported the in-hospital mortality rate within 1-year post-index date as 7.2% ($n = 282$), 27.0% of which was due to cardiovascular (CV) events and 14.2% due to non-CV events. Causes of 58.9% in-hospital deaths were not reported/unknown (*Figure 2B*).

A higher rate of 1-year in-hospital mortality was observed in patients with lower weight ($P = 0.002$), BMI ($P = 0.009$), SBP ($P < 0.001$) and DBP ($P < 0.001$) and in those with a higher heart rate ($P = 0.039$) (Supporting Information, *Table S2*). Higher in-hospital mortality within 1-year post-index date was also observed in patients with higher baseline urea ($P < 0.001$), serum potassium ($P = 0.038$), serum creatinine ($P < 0.001$), uric acid ($P < 0.001$), lower baseline sodium ($P < 0.001$) and eGFR ($P < 0.001$). Chronic kidney disease stages were significantly associated with in-hospital mortality within 1-year post-index date ($P < 0.001$). Severe or end-stage CKD was associated with higher in-hospital mortality compared with mild/moderate CKD. A statistically significant asso-

ciation ($P < 0.001$) was found between HF ejection fraction and in-hospital mortality events within the 1-year post-index date. HFrEF was associated with higher in-hospital mortality events within the 1-year post-index date compared with HFmrEF and HFpEF (Supporting Information, *Table S2*).

Other clinical features

The most common presenting clinical features during the first hospitalization were dyspnoea (97.1%), lung crepitation (79.3%) and peripheral oedema (67.7%). A similar pattern was seen for subsequent rehospitalizations. Patients in this study had a mean (± SD) duration of hospital stay of 9.2 ± 8.07 days, and a total stay in the intensive care and critical care units of 7.0 ± 7.58 and 6.2 ± 7.40 days, respectively. The length of hospital stay tended to increase (first rehospitalization: 9.7 ± 8.45 days; second rehospitalization: 10.6 ± 8.02 days; third rehospitalization: 9.5 ± 7.04 days), whereas the time to rehospitalization decreased with each subsequent rehospitalization (first rehospitalization: 109.9 ± 99.12 days; second rehospitalization: 73.0 ± 67.47 days; third rehospitalization: 56.4 ± 56.56 days, *Table 2*).

Management during hospitalization and rehospitalization

At first hospitalization, most patients were prescribed at least one HF medication (admission: 97.6%; discharge: 94.0%). The most commonly prescribed HF medication at admission and discharge was loop diuretics (81.1% and 89.0%, respectively), BBs (73.3% and 69.3%, respectively), mineralocorticoid receptor antagonist (MRA) (59.1% and 54.0%, respectively), ACEI (36.3% and 31.5%, respectively), and ARB (23.0% and 20.8%, respectively; *Table 3*).

There were 1473 events of rehospitalization recorded from the total patient population. During rehospitalization, most patients were prescribed at least one HF medication (admission: 97.2%; discharge: 92.4%). Of the total rehospitalization events, in 78.3% of cases, patients were given loop diuretics at admission, increasing to 89.8% of patients at discharge. For other drugs, a reduction from admission to discharge was observed: MRA (at admission: 69.7% vs. at discharge: 62.1%), BB (at admission: 70.9% vs. at discharge: 66.3%), ACEI (at admission: 32.3% vs. at discharge: 28.6%) and ARB (at admission: 22.0% vs. at discharge: 19.6%) (*Table 3*). The most commonly prescribed intravenous (IV) medications were diuretics (91.4%), dopamine (13.2%) and dobutamine (9.6%) for all hospitalization/rehospitalization visits. The use of other IV medications was low compared with diuretics and dopamine.

Several combinations of HF medications were examined per guideline-directed medical therapy (GDMT). During the index hospitalization, 30.9% of patients received ACEI/ARB + BB + MRA at admission, and 80.5% of those maintained the prescribed drugs at discharge. However, 4.8% had withdrawn MRA, 12.5% switched to other treatment combinations, and 2.1% received no HF medication at discharge. A similar treatment pattern was observed during rehospitalization. Overall, 15.3% and 9.1% of patients received ACEI/ARB + BB at admission during index hospitalization and

Table 2 Clinical features of hospitalization/rehospitalization

Description	First hospitalization	First rehospitalization	Second rehospitalization	Third rehospitalization
Total hospital stays (days), mean (SD)	*n* = 3923 9.2 (8.07)	*n* = 970 9.7 (8.45)	*n* = 352 10.6 (8.02)	*n* = 141 9.5 (7.04)
Time to rehospitalization, mean (SD)	NA	*n* = 970 109.9 (99.12)	*n* = 352 73.0 (67.47)	*n* = 141 56.4 (56.56)
Total stay in ICU (days), mean (SD)	*n* = 21 7.0 (7.58)	*n* = 2 14.5 (19.09)	*n* = 2 8.0 (8.49)	*n* = 0 NA
Total stay in CCU/HDU (days), mean (SD)	*n* = 667 6.2 (7.40)	*n* = 148 6.6 (8.54)	*n* = 61 7.5 (6.66)	*n* = 23 5.2 (2.94)
Clinical features				
Dyspnoea	3810 (97.1)	949 (97.8)	343 (97.4)	138 (97.9)
Peripheral oedema	2657 (67.7)	718 (74.0)	272 (77.3)	105 (74.5)
Ascites	664 (16.9)	214 (22.1)	87 (24.7)	44 (31.2)
Lung crepitation	3112 (79.3)	824 (84.9)	295 (83.8)	113 (80.1)
Elevated JVP	1687 (43.0)	440 (45.4)	172 (48.9)	76 (53.9)
Hepatomegaly	181 (4.6)	42 (4.3)	19 (5.4)	8 (5.7)
Hypotension	26 (0.7)	17 (1.8)	3 (0.9)	2 (1.4)
Poor peripheral perfusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	18 (0.5)	4 (0.4)	2 (0.6)	1 (0.7)

CCU, coronary care unit; HDU, high dependency unit; ICU, intensive care unit; JVP, jugular venous pressure; NA, not applicable; SD, standard deviation.
Data presented are *n* (%) unless otherwise stated. Total hospital stays (days), which was calculated by (date of discharge at visit k − date of admission at visit k) + 1. Time to rehospitalization = date of admission (visit k) − date of discharge (visit k − 1) + 1.

Table 3 Medication prescribed at admission and at discharge during index hospitalization and rehospitalization

	Index hospitalization		Rehospitalization	
HF medication	Admission	Discharge	Admission	Discharge
Any HF medication	3834 (97.7)	3713 (94.6)	1422 (97.2)	1352 (92.4)
ARNi	3 (0.1)	3 (0.1)	9 (0.6)	11 (0.8)
ACEI	1485 (37.9)	1276 (32.5)	472 (32.3)	418 (28.6)
ARB	917 (23.4)	834 (21.3)	322 (22.0)	286 (19.6)
MRA	2318 (59.1)	2117 (54.0)	1020 (69.7)	909 (62.1)
BB	2876 (73.3)	2719 (69.3)	1037 (70.9)	970 (66.3)
Loop diuretic	3182 (81.1)	3491 (89.0)	1145 (78.3)	1314 (89.8)
Thiazide	160 (4.1)	165 (4.2)	63 (4.3)	62 (4.2)
Ivabradine	383 (9.8)	271 (6.9)	212 (14.5)	166 (11.4)
Digoxin	1338 (34.1)	1176 (30.0)	568 (38.8)	525 (35.9)
No	89 (2.3)	210 (5.4)	41 (2.8)	111 (7.6)

		Discharge					
	Admission	ACEI/ARB + BB + MRA	ARNi + BB + MRA	ACEI/ARB + BB	ARNi + BB	Other	No treatment
Index hospitalization							
ACEI/ARB + BB + MRA	1212 (30.9)	976 (80.5)	0 (0)	58 (4.8)	0 (0)	152 (12.5)	26 (2.1)
ARNi + BB + MRA	2 (0.1)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0.0)
ACEI/ARB + BB	601 (15.3)	34 (5.7)	0 (0)	464 (77.2)	0 (0)	90 (15.0)	13 (2.2)
ARNi + BB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)
Other	2019 (51.5)	44 (2.2)	1 (0)	27 (1.3)	0 (0)	1811 (89.7)	136 (6.7)
No treatment	89 (2.3)	5 (5.6)	0 (0)	4 (4.5)	0 (0)	45 (50.6)	35 (39.3)
Rehospitalization							
ACEI/ARB + BB + MRA	458 (31.3)	345 (75.3)	2 (0.4)	24 (5.2)	0 (0)	68 (14.8)	19 (4.1)
ARNi + BB + MRA	3 (0.2)	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)
ACEI/ARB + BB	133 (9.1)	13 (9.8)	0 (0)	95 (71.4)	0 (0)	21 (15.8)	4 (3.0)
ARNi + BB	0 (0)	NA	NA	NA	NA	NA	NA
Other	828 (56.6)	26 (3.1)	3 (0.4)	7 (0.8)	0 (0)	726 (87.7)	66 (8.0)
No treatment	41 (2.8)	1 (2.4)	0 (0)	3 (7.3)	0 (0)	15 (36.6)	22 (53.7)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitors; BB, β blocker; CCB, calcium-channel-blocker; DC, discharge; HF, heart failure; MRA, mineralocorticoid receptor antagonist; n, number of patients; PDE5, phosphodiestrase-5; sGC, soluble guanylate cyclase; SGLT2, sodium-glucose co-transporter 2.
Data presented as *n* (%).

rehospitalization, respectively. Of these, 77.2% and 71.4% of patients maintained the same treatment combination, 5.7% and 9.8% had to add an MRA, 15.0% and 15.8% switched to another treatment combination, and 2.2% and 3.0% received no HF medication at discharge during index hospitalization and rehospitalization, respectively. A total of 5 patients received ARNis + BB + MRA at admission during index hospitalization and rehospitalization (*Table 3*).

Biomarker assessment

The median *N*-terminal pro-brain natriuretic peptide (NT-proBNP) was 5755.0 (interquartile range: 2636.8, 12674.5) pg/mL at first hospitalization. Increasing trends were observed in subsequent rehospitalizations (first rehospitalization 6971.0 [3416.8, 16881.5] pg/mL; second rehospitalization: 8018.5 [3779.2, 19349.8] pg/mL; third rehospitalization: 9777.0 [3979.0, 19840.0] pg/mL) (*Table 4*).

Chronic kidney disease

We present the analysis of HF patients stratified by CKD at baseline.

In total, 13.2% of patients had Stage 1 (normal or high eGFR) CKD, 39.2% Stage 2 (mild) CKD, 33.0% Stage 3 (moderate) CKD, 10.9% Stage 4 (severe) CKD and 3.7% Stage 5 (end-stage) CKD at baseline (*Table 1*).

Demographic characteristics were consistent among the overall population. The most common aetiology for HF was similar to the overall study population regardless of the CKD stage. The SBP and DBP were consistent among patients at different CKD stages. Laboratory indices were balanced across different CKD stages at baseline except for urea, serum creatinine, uric acid (increased with CKD stage) and eGFR (decreased with CKD stage). There was a numerically lower proportion of patients with HFrEF but a numerically higher proportion of patients with HFmrEF with increasing CKD severity.

Thirty-day rehospitalization was higher in patients with a more severe CKD stage ($P = 0.007$). The 30-day rehospitalization rate was 4.4% in patients with Stage 1 CKD, 5.6% in Stage 2 CKD, 7.7% in Stage 3 CKD, 8.9% in Stage 4 CKD and 9.5% in Stage 5 CKD (Supporting Information, *Table S1*). Chronic kidney disease severity was a significant factor associated with higher in-hospital mortality ($P < 0.001$). The 1-year in-hospital mortality rate was 4.8% in patients with Stage 1 CKD, 5.6% in Stage 2 CKD, 8.2% in Stage 3 CKD, 10.6% in Stage 4 CKD and 9.5% in Stage 5 CKD (Supporting Information, *Table S2*).

Discussion

To the best of our knowledge, this is the first registry in Malaysia describing the demographics, clinical characteristics and outcomes in hospitalized HF patients using 10-year Malaysian population data. IJN has treated over 3.7 million patients and is recognized as one of the leading cardiovascular and thoracic centres in the region. This study would be a valuable contribution to the epidemiology data of hospitalized HF patients specific to Malaysia.

We specifically compared and discussed the key findings of this study with HF registries within the region, and Malaysian data enrolling patients with acute decompensated HF, for example, Acute Decompensated Heart Failure National Registry International – Asia Pacific (ADHERE-AP), single-centre studies from Sarawak General Hospital (SGH-HF) and Universiti Teknologi MARA (UiTM Sungai Buloh).[23–26] Further comparison was also made with ASIAN-HF registry, which enrolled patients with a current diagnosis of symptomatic HF within 6 months of an episode of decompensated HF, treated in hospital or at an outpatient clinic.[26]

Table 4 In-hospital investigation by each visit within 1 year

	First hospitalization	First rehospitalization	Second rehospitalization	Third rehospitalization
Overall, *N*	3923	970	352	141
NT-proBNP (pg/mL), median (range)	*n* = 3456 5755.0 (2636.8, 12674.5)	*n* = 878 6971.0 (3416.8, 16881.5)	*n* = 324 8018.5 (3779.2, 19349.8)	*n* = 131 9777.0 (3979.0, 19840.0)
LVEF (%), median (range)	*n* = 3455 30.0 (23.0, 41.0)	*n* = 651 28.0 (21.0, 39.0)	*n* = 212 25.0 (20.0, 35.0)	*n* = 70 27.0 (20.0, 34.8)
HF ejection fraction, *n* (%)				
HFrEF	2492 (63.5)	503 (51.9)	175 (49.7)	60 (42.6)
HFmrEF	486 (12.4)	91 (9.4)	24 (6.8)	8 (5.7)
HFpEF	500 (12.7)	67 (6.9)	19 (5.4)	3 (2.1)
Missing	445 (11.3)	309 (31.9)	134 (38.1)	70 (49.6)

CK, creatine kinase; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left-ventricular ejection fraction; n, number of patients; NT-proBNP, N-terminal pro-brain natriuretic peptide.

In general, the mean age of patients at the time of hospital admission in our study was in line with previous findings in the region. Asian patients were generally younger (Southeast Asia: 58.9 years; Northeast Asia: 62.1 years; South Asia: 57.8 years)[26] than Caucasian patients (Europe: 70 years; USA: 72.2–74 years; Australia: 77 years).[23,27,28] The mean age (72.2 years) of patients in the GWTG-HF registry from the USA was higher by almost a decade than that observed in our study.[28] Comparable age was observed in all three local single-centre studies, including IJN ADHF registry, SGH-HF and UiTM Sungai Buloh (mean age of 62, 59 and 63, respectively).[24,25] These findings suggest that HF patients in Malaysia are relatively younger, which is not surprising. It has been reported that HF patients from low-income regions had the youngest mean age (Philippines: 54.3 years and Indonesia: 55.8 years), whereas those from high-income regions had the highest mean age (Hong Kong: 67.7 years, Japan: 64.9 years, South Korea: 63.3 years and Taiwan: 63.3 years).[23]

The current study recorded a high male prevalence (72.3%) in the Malaysian population, which was consistent with that reported in Singapore (64%), Indonesia (66%), Taiwan (72%) and the Asia-Pacific study in ADHERE (57%).[23,27] However, a much higher proportion of females (48.2%) was observed in the GWTG-HF registry from the USA than was seen in our analysis.[28]

Of the hospitalized HF patients in this study, 62.9% had reduced ejection fraction. A relatively lower proportion of HFrEF patients was reported in the SGH-HF (51%), UiTM Sungai Buloh (40.8%) and ADHERE-AP (53%) populations, indicating that half of the hospitalized HF patients had HFmrEF and HFpEF.[23–25] The proportion of patients with preserved ejection fraction in our analysis was much lower than that observed in the GWTG-HF registry (12.7% vs. 43%, respectively).[28]

The higher proportion of HF patients with ischaemic aetiology reported in this study (66%) compared with SGH-HF (41.1%) also explains the observation of a higher prevalence of patients with HFrEF.[24]

Results from the ASIAN-HF Registry showed that Southeast Asia had the highest prevalence of diabetes mellitus, stroke, hypertension, CKD and CAD, despite a relatively low mean age of patients.[26] Our study showed a similar incidence of CAD and atrial fibrillation (AF) but a higher incidence of hypertension, diabetes and stroke than the Southeast Asian population of the ASIAN-HF Registry, which indicates a higher burden of co-morbidities in Malaysia. The prevalence of AF, hypertension, hyperlipidaemia, chronic obstructive pulmonary disease and stroke was much higher in the US population, whereas diabetes and CAD were more prevalent in the current study.[28] Further comparison with data from hospitalized HF patients in the region and Malaysia consistently showed that hypertension is the most common co-morbidity in all four studies (72% in both IJN Registry and SGH-HF, 70.9% in UiTM Sungai Buloh and 64% in ADHERE-AP).[23–25] Diabetes and CAD were the second and third most common co-morbidities (45–63% for diabetes and 33–57.8% for coronary/ischaemic heart disease).[23–25] The finding that Malaysian hospitalized HF patients are generally younger with the highest burden of co-morbidities corroborated the findings from ASIAN-HF registry.[26] All these findings highlight the need for stricter medical intervention, as this group of patients has a longer lifespan with a higher burden of cardiovascular risk. Some striking differences in the burden of co-morbidities (e.g. CAD, diabetes and AF) observed between SGH-HF and IJN registry are likely due to the type of patients presented at each individual centre.[24] As IJN is the leading referral centre in Malaysia, patients with more severe clinical presentations may be more common, compared with a non-cardiology tertiary referral centre in Sarawak.

Utilization of multiple HF therapies is known to individually extend lives of HF patients, and optimization of GDMT is crucial in the management of HF patients. This study revealed that the use of evidence-based therapies for HF, such as renin–angiotensin–aldosterone system inhibitors (21.3–54.0% vs. 94.5%) and BB (69.3% vs. 89.9%), was found to be lower compared with GWTG-HF registry.[28] On the contrary, the use of aldosterone antagonists was higher in this study (54.0% vs. 41.9%) compared with that reported in the GWTG-HF registry.[28] Although it has been well reported that hospitalization provides a great opportunity for optimization of HF therapies, it was observed that the proportion of HF medications at discharge in this study was generally lower than at admission. Meanwhile in SGH-HF, the number of prescriptions for HF medication was generally higher during hospitalization compared with pre-admission.[24] A similar trend was also observed in another major registry, EuroHeart Failure Survey II.[29] No comparisons of HF medication at admission versus discharge for ADHERE-AP can be made as admission data were not reported in the study. In this study, HF medications at discharge tended to be lower than at admission. The medication used at discharge is among the highest when compared with SGH-HF and ADHERE-AP, across different classes of GDMT.[23,24] The use of ARNis was low (0.2–0.3%) in the current study. These data components should be interpreted with care, as ARNis were only approved for use in HF in 2016 in Malaysia and were made available to the current institution by the end of 2017. Our study covered the period from 1 January 2009 to 31 December 2018; hence, the use of ARNis recorded in this study is expected to be low.

Lowering risks of readmission and mortality has always been the key treatment goal in the management of HF patients, and it is crucial to measure such outcomes in HF studies. The frequency of rehospitalization (6.8%) within 30 days was similar to that reported by other countries in the region (Indonesia and Vietnam: 7.0%) but lower than that reported in the USA (25%) and the GWTG-HF registry (13.7–17.1%).[27,28] The reason for such discrepancies between

Southeast Asia and the USA is currently unclear but could be due to variability in the source of data. Data for the current study and for Indonesia and Vietnam were collected from a single centre in each respective country. Among the four studies of IJN ADHF, SGH-HF, UiTM Sungai Buloh and ADHERE-AP, SGH-HF had the highest rehospitalization rate within 30 days (14%), with the lowest rehospitalization within 30 days reported in UiTM Sungai Buloh (4.1%).[23–25] Nonetheless, such indirect comparisons should be interpreted cautiously.

With regard to in-hospital mortality, Southeast Asia had a rate of 1.1–15%, China 7%, EU 6% and USA 4%.[27,28] Both IJN ADHF and SGH-HF showed similar rates (7.2% and 7.5%, respectively), followed by ADHERE-AP (4.8%) and the UiTM Sungai Buloh study (1.7%).[23–25]

When 1-year outcome in terms of hospitalization rate was compared between the studies, 76.1% of patients in the UiTM Sungai Buloh study were readmitted within 1 year; meanwhile, one of four (24.7%) was readmitted in the IJN study.[25] Similarly, an extraordinarily high 1-year mortality rate was observed in the UiTM Sungai Buloh study (49.7%), compared with 7.2% in the IJN study.[25] It should be noted that UiTM Sungai Buloh reported data on 1-year all-cause mortality, while the current study reported in-hospital mortality within a year.

Such indirect comparisons should always be interpreted cautiously. Reasons for discrepancies between these studies are currently unclear but could possibly be due to gaps and frequency of length of hospital stay, follow-up after discharge, optimization of life-saving medical and device therapies, severity of HF patients and many other factors.[25] Whenever possible, optimal care should be given to HF patients to *ensure* the *best possible patient outcomes*.

Evidence has also shown the prognostic significance of uric acid in patients hospitalized for HF.[30–33] In this study, uric acid was associated with higher in-hospital mortality within 1 year, which corroborated the earlier findings that high serum uric acid at discharge was an independent prognostic marker of an adverse outcome in HF patients.[34,35] While previous studies reported findings of patients who were enrolled according to strict criteria, IJN ADHF registry and the study by Ambrosio et al[35] utilized real-world data, making the interpretation more relevant in daily clinical practice.

Given the observational and retrospective nature of the data, this study was subject to the limitations inherent in all studies using secondary data. The authors are aware that the IJN registry was not specially designed for outcome research purposes. The secondary data used for this study were not specially designed to answer specific research questions such as rehospitalization events and mortality rates. The data from this single-institute, highly specialized heart centre may not be representative of the general HF population seen in other public/private clinical practice.

In conclusion, IJN ADHF registry provides a greater understanding of the characteristics, treatment patterns and outcomes of hospitalized HF patients in a leading referral centre in Malaysia. The 10-year population study shed light on what continues to impact morbidity and mortality of hospitalized HF patients, aiding the implementation of meaningful interventions to improve patient outcome for HF patients across the world.

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Conflict of interest

Mohd Ghazi and Teoh report no conflicts of interest. Abdul Rahim has been a member of advisory boards and has received speaker's honoraria from Novartis, Servier and Bayer.

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Supporting information

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

Table S1. Baseline demographics and clinical characteristics associated with rehospitalisation within 30 days and 1 year.
Table S2. Baseline demographics and clinical characteristics associated with in-hospital mortality within 1 year.

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