SMJ Singapore Medical Journal

Ten-year survival and factors associated with increased mortality in patients admitted for acute decompensated heart failure in Thailand

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Singapore Med J 2019, 1–19
https://doi.org/10.11622/smedj.2019108
Published ahead of print: 6 September 2019

Online version can be found at
http://www.smj.org.sg/online-first

ABSTRACT

Introduction: Data on the long-term outcomes of Asian patients admitted for acute decompensated heart failure is scarce. The objectives of this study were to determine short-term, intermediate-term, and long-term survival among patients admitted for acute decompensated heart failure in Thailand, and to identify factors independently associated with increased mortality.

Methods: Patients who were admitted with a primary diagnosis of heart failure were enrolled in the Thai Acute Decompensated Heart Failure Registry (ADHERE) from 18 hospitals located across Thailand during 2006. Medical record data was collected according to ADHERE protocol. Mortality data was collected from death certificates on file at the Thailand Bureau of Registration Administration.

Results: A total of 1,451 patients were included. The mean age of the patients was 63.7 ± 14.4 years, and 49.7% were male. One-year, five-year and ten-year mortality rates in Thai patients admitted for acute decompensated heart failure were 28.0%, 58.2% and 73.3%, respectively. Independent predictors of increased mortality were identified. There were more cardiovascular-related deaths than non-cardiovascular-related deaths (54.6% vs. 45.4%, respectively).

Conclusions: The ten-year mortality rate in Thai patients admitted for acute decompensated heart failure was 73.3%. Many factors were found to be independently associated with increased mortality, including left ventricular ejection fraction.

Keywords: acute decompensated heart failure, ADHERE registry, mortality, Thailand

INTRODUCTION

Heart failure (HF)[1] is a common condition with a prevalence of approximately 0.5%–2%.[2,3] Its prevalence has increased over the past decade, especially among the elderly.[4,5] HF accounts for 0.3%–3.0% of all primary diagnoses that require hospital admission.[3] Despite advances in the management of HF, the mortality rate remains high in both Western and Asian populations.[1,6] HF-related mortality during hospital admission was reported in many studies to range from 3.8% to 9% in Western populations, and from 2% to 6% in Asian populations.[7] There are regional differences in HF outcome, which may be related to healthcare infrastructure, quality of care, access to healthcare and other environmental factors.[8] Even within Asia, there are differences in the phenotypes of HF and comorbid conditions.[9] In Thailand, 6% of patients admitted with HF were reported to have died in hospital.[10] It was estimated that 17%–45% of patients who were admitted with HF died within one year, and more than 50% died within five years, regardless of aetiology or gender.[3]

Data from the Asia-Pacific Acute Decompensated Heart Failure Registry (ADHERE) showed that the average age of patients admitted for HF in this region was approximately ten years less than that of patients in the United States and European ADHERE.[11-13] Additionally, their clinical presentation appeared to be more severe than in Caucasian populations. A better understanding of clinical presentation, survival/mortality, and comparisons with other countries and ethnicities is needed to improve the standard of care for HF patients in the Asia-Pacific region.

Accordingly, the aim of this study was to determine short-, intermediate- and long-term survival among patients admitted for acute decompensated HF in Thailand, and to identify factors independently associated with increased mortality in this patient population.

METHODS

The 2006 Thai ADHERE study included 18 medical centres from across Thailand and was conducted using a protocol similar to that in the ADHERE study conducted in the United States. Ten of the medical centres were university hospitals, three were government hospitals, and five were private hospitals. Patients aged ≥ 18 years who were admitted with a primary diagnosis of HF were enrolled. Patients with cardiogenic shock, preoperative HF or HF as a secondary diagnosis, or comorbid conditions were excluded. The principal investigator at each centre was instructed to enrol consecutive patients. Index cases could be newly diagnosed acute HF or chronic HF with decompensation. The diagnosis of HF was verified by a cardiologist in each included case. This study was approved by the institutional review board of each participating hospital. All patients gave written informed consent prior to participation.

The data for this study was derived from the 2006 ADHERE Thailand, with the aim of evaluating short-term (one-year), intermediate-term (five-year) and long-term (ten-year) mortality/survival. Medical record data was collected from first contact at the emergency department to the time of hospital discharge, transfer to another hospital or in-hospital death. The following data was collected and recorded: demographic data; medical history; causes and precipitating causes of HF; clinical presentation; investigations including left ventricular ejection fraction (LVEF); hospital course; medication (oral and intravenous) given prior to, during and at hospital discharge; procedures; and death. An electronic data capture system was used to collect data from the participating medical centres. Data from each site was entered into an electronic case record form in the Web-based system. All data was verified to ensure accuracy and completeness. Longitudinal unique identifier (LUID) software was used to anonymise included patients. Each patient's LUID was stored in the database and used to track patients' hospital re-admission and

clinical outcomes. In-hospital death and cause of death were recorded from the hospital discharge summary. Out-of-hospital mortality data, including date and cause of death, were collected from death certificates on file at the Thailand Bureau of Registration Administration.

Demographic and clinical data were summarised using descriptive statistics. Continuous data was presented as mean ± standard deviation, while categorical data was presented as number and percentage. Student's *t*-test was used to compare continuous unpaired data, and chi-square test was used to compare categorical data. Univariate and multivariate Cox proportional hazard ratio analysis was performed to identify factors independently associated with increased risk of mortality. Variables with a p-value < 0.2 in univariate analysis were included in multivariate analysis. A p-value < 0.05 in multivariate analysis was considered statistically significant. All data analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY, USA).

RESULTS

A total of 1,451 patients were included. Their mean age was 63.7 ± 14.4 years, and 49.7% were male. Baseline characteristics were compared between patients who survived and those who died during the ten-year follow-up period (Table I). There were a total of 1,064 deaths at ten years, an overall mortality rate of 73.3%. Many parameters from the medical history, physical examination and laboratory data subsections were found to be associated with increased risk of mortality. These included diabetes mellitus (survived 31.0% vs. deceased 50.3%; p < 0.001), hypertension (survived 48.1%, deceased 67.1%; p < 0.001), rales (survived 79.1%, deceased 85.2%; p = 0.006), LVEF (survived 48.3%, deceased 45.4%; p = 0.011) and serum creatinine (survived 1.47 ± 1.54 mg/dL, deceased 1.95 ± 1.75 mg/dL; p < 0.001). Certain medications were found to be associated with decreased risk of death, such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin

receptor blockers (ARBs) (survived 59.2%, deceased 42.6%; p < 0.001) and beta blockers (survived 30.2%, deceased 23.0%; p = 0.005).

In our registry, very few patients (1.9%, n = 28) received cardiac implantable electronic devices (CIEDs). Among them, three had a cardiac resynchronisation therapy defibrillator, three had an implantable cardioverter defibrillator, seven had a cardiac resynchronisation therapy device, and 15 had pacemakers.

Table I. Comparison of the baseline characteristics of patients who survived and those who died during the ten-year follow-up period.

Variable	**No. (%)/mean ± standard deviation**			**p-value**
	All patients (n = 1,451)	**Survived (n = 387)**	**Deceased (n = 1,064)**	
Age (yr)	63.7 ± 14.4	57.3 ± 14.4	66.0 ± 13.6	< 0.001
Male gender	721 (49.7)	195 (50.4)	526 (49.4)	0.749
Body weight (kg)	60.4 ± 14.1	63.1 ± 15.5	59.2 ± 13.6	0.001
Medical history				
History of heart failure	893 (61.5)	189 (48.8)	704 (66.2)	< 0.001
CAD	606 (41.8)	116 (30.0)	490 (46.1)	< 0.001
History of MI	345 (23.8)	62 (16.0)	283 (26.6)	< 0.001
Hypertension	900 (62.0)	186 (48.1)	714 (67.1)	< 0.001
Diabetes mellitus	655 (45.1)	120 (31.0)	535 (50.3)	< 0.001
Dyslipidaemia	667 (46.0)	138 (35.7)	529 (49.7)	< 0.001
Stroke/TIA	156 (10.8)	21 (5.4)	135 (12.7)	< 0.001
Pacemaker/ICD	28 (1.9)	1 (0.3)	27 (2.5)	0.004
PAD	43 (3.0)	4 (1.0)	39 (3.7)	0.008
CKD	246 (17.0)	20 (5.2)	226 (21.2)	< 0.001
COPD/asthma	100 (6.9)	16 (4.1)	84 (7.9)	0.012
Smoking	98 (6.8)	32 (8.3)	66 (6.2)	0.166
Presentation/evaluation				
NYHA class IV	929 (64.0)	230 (59.4)	699 (65.7)	0.028
Rales	1,212 (83.5)	306 (79.1)	906 (85.2)	0.006
Oedema	863 (59.5)	211 (54.5)	652 (61.3)	0.020
SBP (mmHg)	136.3 ± 32.1	136.7 ± 32.0	136.1 ± 32.1	0.747
DBP (mmHg)	78.6 ± 20.2	80.0 ± 22.6	78.1 ± 19.3	0.142
Heart rate (beats/min)	93.6 ± 22.9	97.2 ± 22.9	92.3 ± 22.8	< 0.001
Pulmonary congestion	1,283 (88.4)	341 (88.1)	942 (88.5)	0.825
LVEF (%)	46.2 ± 18.2	48.3 ± 17.9	45.4 ± 18.3	0.011
AF on ECG	333 (22.9)	88 (22.7)	245 (23.0)	0.908

Q wave on ECG	302 (20.8)	67 (17.3)	235 (22.1)	0.048
QRS width	101.4 ± 24.6	95.5 ± 16.9	103.4 ± 26.4	< 0.001
Serum sodium (mEq/L)	136.9 ± 5.6	137.5 ± 5.2	136.7 ± 5.7	0.014
BUN (mg/dL)	28.2 ± 20.5	22.3 ± 14.8	30.2 ± 21.9	< 0.001
Creatinine (mg/dL)	1.82 ± 1.71	1.47 ± 1.54	1.95 ± 1.75	< 0.001
Haemoglobin (g/dL)	11.8 ± 2.4	12.4 ± 2.1	11.6 ± 2.4	< 0.001
Serum albumin (mg/dL)	3.63 ± 1.38	3.78 ± 1.46	3.57 ± 1.35	0.029
Medication				
Loop diuretic	1,026 (70.7)	276 (71.3)	750 (70.5)	0.759
MRA	216 (14.9)	57 (14.7)	159 (14.9)	0.919
ACEI/ARB	682 (47.0)	229 (59.2)	453 (42.6)	< 0.001
Beta blocker	362 (24.9)	117 (30.2)	245 (23.0)	0.005
Nitrate	631 (43.5)	146 (37.7)	485 (45.6)	0.008
Digoxin	364 (25.1)	106 (27.4)	258 (24.2)	0.222
Warfarin	268 (18.5)	90 (23.3)	178 (16.7)	0.005
Antiplatelet	840 (57.9)	208 (53.7)	632 (59.4)	0.054
Lipid lowering	764 (52.7)	199 (51.4)	565 (53.1)	0.571

ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF: atrial fibrillation; BUN: blood urea nitrogen; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; ECG: electrocardiogram; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; PAD: peripheral arterial disease; SBP: systolic blood pressure; TIA: transient ischaemic attack

The causes of death are shown in Table II. The most common cause of cardiovascular death was HF, followed by myocardial infarction and stroke (28.9%, 14.5% and 5.0%, respectively, of those who died). The most common causes of non-cardiovascular death were sepsis, senility, renal failure and pneumonia (14.3%, 8.4%, 6.2% and 5.1%, respectively, of those who died). LVEF data was available in 1,313 (90.5%) patients. Of those, 505 (38.5%) patients had LVEF < 40% (HF with reduced ejection fraction [HFrEF] group), and 808 (61.5%) had LVEF ≥ 40% (HF with preserved ejection fraction [HFpEF] group).

Table II. Causes of death in the Thai Acute Decompensated Heart Failure National Registry (n = 1,451).

Cause of death	No.	% of total	% of deaths
CV death	581	40.0	54.6
Heart failure	307	21.2	28.9
Myocardial infarction	154	10.6	14.5
Valvular heart disease	38	2.6	3.6
Arrhythmia	23	1.6	2.2
Stroke	53	3.7	5.0
Pulmonary embolism	3	0.2	0.3
Systemic embolism	3	0.2	0.3
Non-CV death	483	33.3	45.4
Sepsis	152	10.5	14.3
Pneumonia	54	3.7	5.1
Renal failure	66	4.5	6.2
Cancer	41	2.8	3.9
Respiratory failure	22	1.5	2.1
Bleeding	9	0.6	0.8
Accident	7	0.5	0.7
Diabetic complication	7	0.5	0.7
Cirrhosis	7	0.5	0.7
COPD/asthma	8	0.6	0.8
Senility/unknown	89	6.1	8.4
Others	17	1.2	1.6

COPD: chronic obstructive pulmonary disease; CV: cardiovascular

Fig. 1 shows a forest plot for the unadjusted hazard ratios of factors that might be associated with an increase in ten-year mortality. Multivariate analysis was performed for factors that predict ten-year mortality based on three levels of information: (a) Model 1, clinical information only; (b) Model 2, clinical information and investigation data; and (c) Model 3, clinical information, investigation data and medication data (Table III). When all three types of data were analysed together, elderly status, history of HF, stroke/TIA, use of cardiac devices, oedema, reduced ejection fraction and anaemia (haemoglobin < 12 g/dL) were found to be independent factors associated with increased risk of death. In contrast, taking either ACEIs or ARBs was found to be an independent predictor of decreased mortality.

Survival graphs of patients in the Thai ADHERE relative to total death, cardiovascular death and non-cardiovascular death are shown in Fig. 2. More patients died of cardiovascular-related causes than non-cardiovascular-related causes (581 vs. 483, respectively) (Table IV). Overall mortality at one month, six months, one year, five years and ten years was 8.1%, 21.1%, 28.0%, 58.2% and 73.3%, respectively (Table IV). Survival curves comparing patients with HFrEF and those with HFpEF are shown in Fig. 3. Patients with HFrEF had higher mortality than patients with HFpEF, and the increased risk of death in patients with HFrEF was mainly related to cardiovascular causes.

Table III. Multivariate analysis for independent factors predicting mortality based on three models* with different levels of information.

Variable	Model 1		Model 2		Model 3	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age ≥ 65 yr	1.58 (1.27–1.97)	< 0.001	1.74 (1.35–2.24)	< 0.001	1.73 (1.34–2.22)	< 0.001
History of heart failure	1.69 (1.39–2.05)	< 0.001	1.61 (1.28–2.04)	< 0.001	1.57 (1.24–1.99)	< 0.001
Diabetes mellitus	1.23 (1.01–1.49)	0.039				
Pacemaker/ICD	2.12 (1.27–3.55)	0.004			2.12 (1.14–3.94)	0.017
PAD	1.57 (1.06–2.34)	0.025				
CKD	1.72 (1.35–2.19)	< 0.001	1.44 (1.07–1.94)	0.017		
Stroke/TIA			1.45 (1.02–2.06)	0.038	1.47 (1.03–2.09)	0.032
Oedema			1.35 (1.07–1.70)	0.012	1.40 (1.12–1.76)	0.004
LVEF < 40%			1.33 (1.06–1.66)	0.013	1.47 (1.17–1.84)	0.001
Haemoglobin < 12 g/dL			1.39 (1.09–1.75)	0.007	1.44 (1.15–1.79)	0.001
ACEI/ARB					0.63 (0.50–0.79)	< 0.001

**Model 1: demographics and history, Model 2: Model 1 + physical exam and investigation, Model 3: Model 2 + medication. ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CI: confidence interval; CKD: chronic kidney disease; HR: hazard ratio; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; PAD: peripheral arterial disease; TIA: transient ischaemic attack*

Table IV. Total, CV-related and non-CV-related mortality compared between HFrEF and HFpEF mortality at various time points.

Type	No. (%)				
	1 mth	**6 mth**	**1 yr**	**5 yr**	**10 yr**
Total mortality					
All (n = 1,451)	118 (8.1)	306 (21.1)	407 (28.0)	845 (58.2)	1,064 (73.3)
HFrEF (n = 505)	46 (9.1)	121 (24.0)	161 (31.9)	320 (63.4)	387 (76.6)
HFpEF (n = 808)	57 (7.1)	151 (18.7)	205 (25.4)	442 (54.7)	574 (71.0)
CV death					
All (n = 1,451)	81 (5.6)	193 (13.3)	247 (17.0)	474 (32.7)	581 (40.0)
HFrEF (n = 505)	35 (6.9)	85 (16.8)	111 (22.0)	205 (40.6)	245 (48.5)
HFpEF (n = 808)	39 (4.8)	96 (11.9)	122 (15.1)	235 (29.1)	293 (36.3)
Non-CV death					
All (n = 1,451)	37 (2.5)	113 (7.8)	160 (11.0)	371 (25.6)	483 (33.3)
HFrEF (n = 505)	11 (2.2)	36 (7.1)	50 (9.9)	115 (22.8)	142 (28.1)
HFpEF (n = 808)	18 (2.2)	55 (6.8)	83 (10.3)	207 (25.6)	281 (34.8)

CV: cardiovascular; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction

DISCUSSION

The HF mortality rate was high in our study population at 8.1%, 21.1%, 28.0%, 58.2% and 73.3%, respectively, at one month, six months, one year, five years and ten years. Although many medications and CIEDs can significantly reduce mortality in patients with HF, mortality and readmission rates remain high.[2,14] In the Asia-Pacific region, patients with HF are reported to receive standard pharmacological treatment and device therapy at a suboptimal rate compared to patients in the West.[6,15]

HF registry data has been reported from many countries, including the United States, Europe and Asia, such as Japan, Korea and Taiwan. ADHERE is a worldwide registry of patients admitted due to HF. Data from the Asia-Pacific region was earlier reported.[11] Our data focused on patients enrolled in the ADHERE Thailand registry ten years ago, aiming to report long-term mortality in this group. Despite the trend towards decreased mortality due to HF,[16] in-hospital mortality is still approximately 2%–7% in both Asian and Western populations.[6,17] Specific to

ADHERE, in-hospital mortality was 4% for the global ADHERE,[12] 4.8% for the Asia-Pacific ADHERE[11] and 5.5% for the Thai ADHERE.[7] The age at presentation of HF was found to be approximately eight years younger in the Asia-Pacific region than in other regions. In addition, disease severity was greater and mortality was higher in the Asia-Pacific ADHERE than in other ADHEREs.[11] In the Thai ADHERE, in-hospital mortality was high compared to that of Western countries and other Asia-Pacific countries, a finding that may be partly related to disease severity and suboptimal treatment with standard medications.[6,7,11,12]

Poor outcomes were reported in both Western and Asian populations for patients with a diagnosis of HF. In the United States, HF mortality data at 30 days, one year and five years from the Atherosclerosis Risk in Communities study was 10%, 22% and 42%, respectively,[18] which is lower than our rates at the corresponding time points. However, data from their Medicare patients revealed a one-year mortality rate of 32.2%, slightly higher than our rate. A study from Australia reported 28% mortality at the one-year time point, which is similar to our finding.[19] Although national and regional mortality rates cannot be directly compared due to differences in study population and local management practice, they reflect the overall malignant nature of the condition or combination of conditions referred to as HF. Another study showed that half of HF patients were readmitted to the hospital within six months.[20] Generally, few studies have reported five- and ten-year mortality in HF. The five-year mortality rate of 58.2% in the present study is comparable to rates previously reported in the United States[16,21] and the United Kingdom.[22,23] Our ten-year mortality rate of 73.3% is comparable to a rate reported in Scotland.[23]

Factors predicting long-term mortality in our study included older age, history of HF, stroke, use of cardiac electronic devices, oedema, low LVEF, anaemia and not receiving ACEIs/ARBs. Previous data also showed that elderly status and comorbidities, such as diabetes

mellitus, renal dysfunction, anaemia and atrial fibrillation, were factors that predicted mortality and adverse outcomes in both Asian and Western populations.[24] Low blood pressure itself does not contribute to mortality in HF, but it is a surrogate marker for lower cardiac output state and intolerance to medications.[10,25] Adherence to guideline-recommended medications has been shown to be associated with better outcomes.[26] Data from the BIOSTAT-CHF (BIOlogy Study to TAilored Treatment in Chronic Heart Failure) study demonstrated that ACEIs/ARBs and beta-blockers were positively associated with clinical outcome.[27]

Studies showed that Asian HF patients received standard medication at a much lower proportion than Western populations.[7,11,24,25] Combined with the more severe clinical presentation observed among Asians during hospital admission, HF appears to be an emerging threat to Asia if a strategy is not developed to confront and overcome this problem. Although a recent clinical trial has shown the potential mortality benefit of new drugs that act on angiotensin receptor and neprilysin inhibition (e.g. sacubitril/valsartan),[28] data relating to the cost-effectiveness of these drugs in Asian populations is still lacking.[29]

In our study, 38.5% of patients were in the HFrEF group. The lower proportion of patients in this group may be related to the relatively high number of patients with comorbid diseases such as diabetes mellitus and high blood pressure. This finding is similar to that of the INTER-CHF (International Congestive Heart Failure) study, which showed that the proportion of HFrEF in Southeast Asian populations was 39%, and that there was a greater proportion of comorbid conditions in Southeast Asian patients.[8] Our study found that patients with HFrEF had a higher mortality rate than those with HFpEF. Data from Olmsted County, Minnesota, in the United States showed that long-term mortality over five years was similar between HFrEF and HRpEF, with more than half of all patients deceased after five years.[30] The higher mortality rate in patients with

HFrEF in our study was mainly due to increased cardiovascular mortality, although non-cardiovascular mortality also had a similar trend (Fig. 3). HFpEF has been reported as a contributing factor in approximately 40%–50% of HF cases.[30,31] A recent study indicated that the prevalence and proportion of HFpEF increased with age, so that there was a greater proportion of HFpEF than HFrEF among the elderly.[32] Long-term mortality rates in patients with HFrEF or HFpEF were found to be similar, although there was a trend towards higher mortality in patients with HFrEF.[31] This is similar to the results from our study; however, the five-year mortality rate in a previous report[31] was higher than our rate.

Our study has some limitations. First, it had a relatively small sample size, obtained by tracking the data of patients enrolled in the Thai ADHERE in 2006. However, that baseline data was selected for this study because we consider the quality of Thai ADHERE data to be high. Moreover, the 2006 data was collected from 18 medical centres located across Thailand and can, therefore, be regarded as representative of HF care and outcomes in Thailand in 2006. Second, as mortality data was collected from the Thailand Bureau of Registration Administration, the quality of the data on the death certificate depended on the judgment and skill of the physician who was in charge at the time of death.

In conclusion, the ten-year mortality rate in Thai patients admitted for acute decompensated HF was 73.3%. Many factors were found to be independently associated with increased mortality.

ACKNOWLEDGEMENTS

The Thai ADHERE was endorsed by the Heart Association of Thailand under the Royal Patronage of H.M. the King and the Heart Failure Council of Thailand. The Thai ADHERE is financially supported by the Clinical Research Collaboration Network of Thailand, Janssen-Cilag Limited (Thailand), and the Heart Association of Thailand under the Royal Patronage of H.M. the King.

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FIGURES

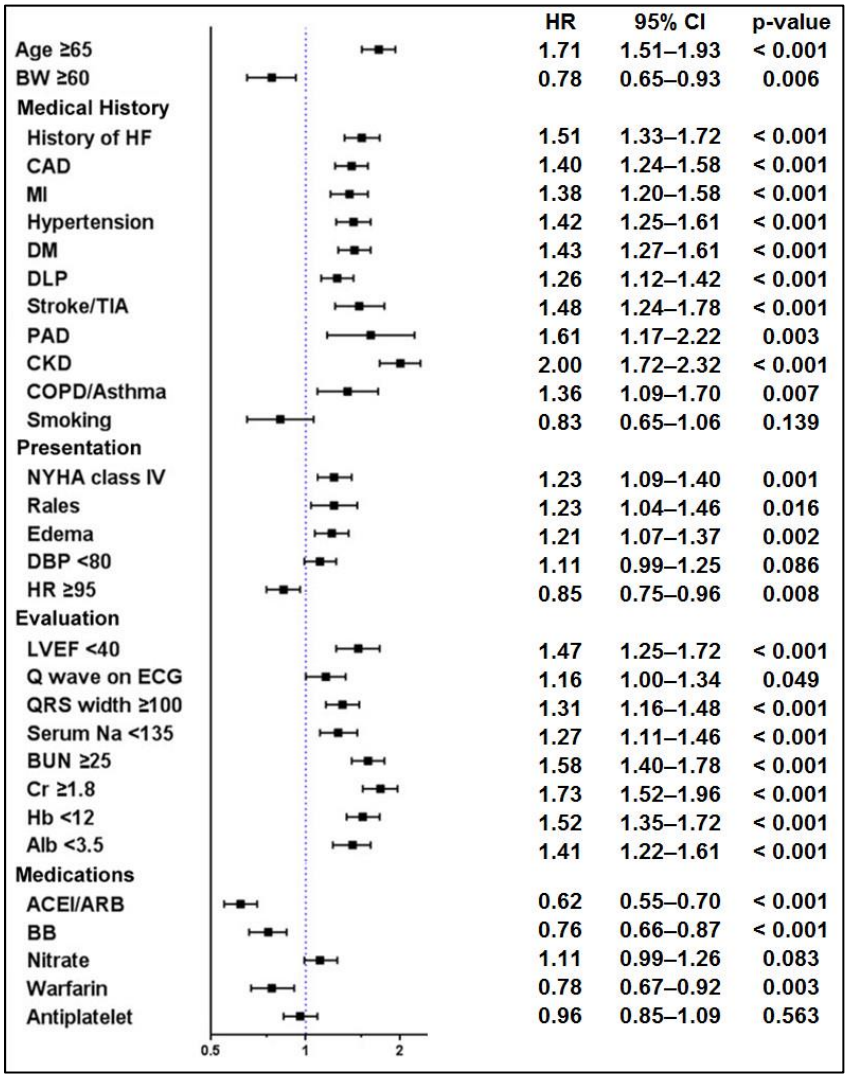

Fig. 1 Forest plot shows unadjusted hazard ratios of factors predicting mortality. ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; Alb: albumin; BB: beta blocker; BUN: blood urea nitrogen; BW: body weight; CAD: coronary artery disease; CI: confidence interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; Cr: creatinine; DBP: diastolic blood pressure; DLP: dyslipidaemia; DM: diabetes mellitus; ECG: electrocardiogram; Hb: haemoglobin; HF: heart failure; HR: heart rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PAD: peripheral arterial disease; Na: sodium; TIA: transient ischaemic attack

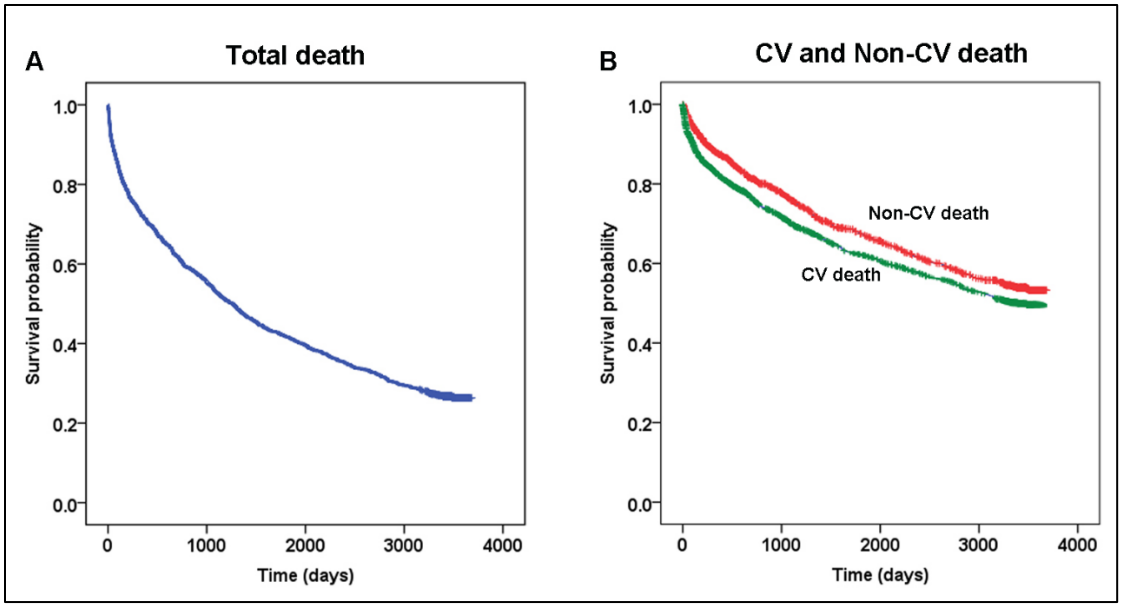

Fig. 2 Survival graphs show (a) all mortality; and (b) CV and non-CV mortality rates over time of patients in the Thai Acute Decompensated Heart Failure Registry. CV: cardiovascular

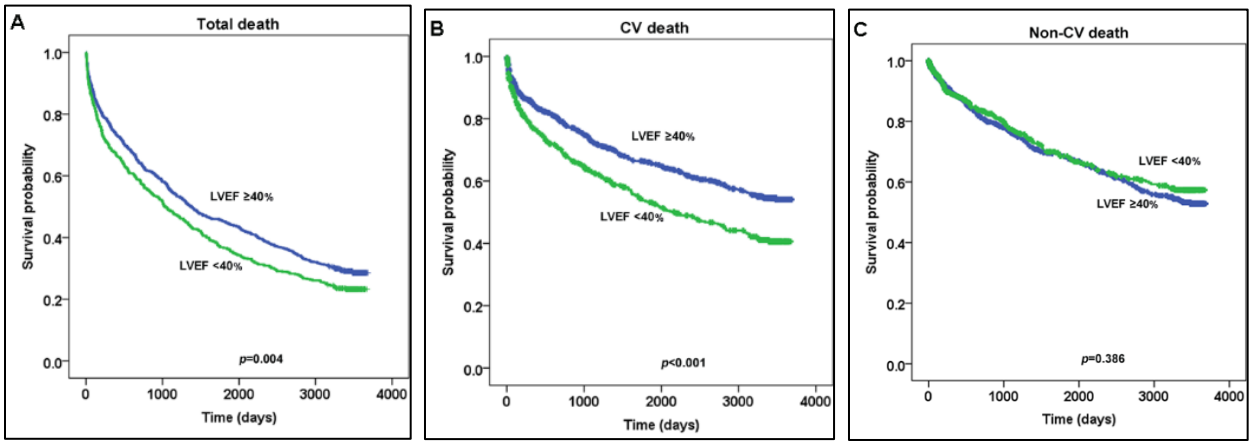

Fig. 3 Survival graphs show (a) all mortality; (b) CV; and (c) non-CV mortality rates over time of patients with low LVEF (< 40%) and preserved LVEF (≥ 40%). CV: cardiovascular; LVEF: left ventricular ejection fraction