

One-Year Outcomes of Acute Decompensated Systolic Heart Failure in Taiwan: Lessons from TSOC-HFrEF Registry

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Background: Heart failure (HF) is a global health problem. The Taiwan Society of Cardiology-Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry was a multicenter, observational survey of patients admitted with HFrEF in Taiwan. The aim of this study was to report the one-year outcome in this large-cohort of hospitalized patients presenting with acute decompensated HFrEF.

Methods: Patients hospitalized for acute HFrEF were recruited in 21 hospitals in Taiwan. A total of 1509 patients were enrolled into the registry by the end of October 2014. Clinical status, readmission rates and dispensed medications were collected and analyzed 1 year after patient index hospitalization.

Results: Our study indicated that re-hospitalization rates after HFrEF were 31.9% and 38.5% at 6 and 12 months after index hospitalization, respectively. Of these patients, 9.7% of them were readmitted more than once. At 6 and 12 months after hospital discharge, all-cause mortality rates were 9.5% and 15.9%, respectively, and cardiovascular mortality rates were 6.8% and 10.5%, respectively. Twenty-three patients (1.5%) underwent heart transplantation. During a follow-up period of 1 year, 46.4% of patients were free from mortality, HF re-hospitalization, left ventricular assist device use and heart transplantation. At the conclusion of follow-up, 57.5% of patients were prescribed either with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; also, 66.3% were prescribed with beta-blockers and 40.8% were prescribed with mineralocorticoid receptor antagonists.

Conclusions: The TSOC-HFrEF registry showed evidence of suboptimal practice of guideline-directed medical therapy and high HF re-hospitalization rate in Taiwan. The one-year mortality rate of the TSOC-HFrEF registry remained high. Ultimately, our data indicated a need for further improvement in HF care.

Key Words: Beta-blocker • Heart failure • Mortality • Renin-angiotensin blockade • Taiwan • Treatment

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INTRODUCTION

Heart failure (HF) is a major public health concern and is a leading cause of morbidity and mortality. Approximately 1-2% of the adult population in developed countries has HF, with the prevalence rising to more than 10% among persons 70 years of age or older.¹ The HF population is growing quickly worldwide, due to the rapidly aging population and improved survival rate of patients suffered from acute myocardial infarction and various heart diseases.²⁻⁴ This is also a prominent health concern in Taiwan, as the National Health Insurance Administration reported more than 22,000 patients were admitted for HF in 2014.

Many HF patients have multiple comorbidities and present with acute exacerbation of chronic HF. Acute HF is characterized by rapid onset of signs and symptoms of HF secondary to cardiac decompensation. It is often life threatening, and requires urgent therapy. Acute decompensated HF can lead to additional myocyte death, renal injuries and neurohormonal system activation, which therefore create a pathophysiological “vicious cycle”, and contribute to progressive deterioration of HF and increase in mortality.

Patients with HF were described as HF with a reduced ejection fraction (HFrEF) or HF with preserved ejection fraction by measuring the left ventricular ejection fraction (LVEF). Before 1990, 60-70% of HF patients died within 5 years of diagnosis, and re-hospitalization rates due to worsening HF symptoms were high.^{5,6} Later on, several major clinical trials enrolling HFrEF patients showed that the neurohumoral antagonists are fundamentally important in treating these patients, which could not only relieve symptoms but also slow progressive worsening of HF and reduce mortality and hospital admission for HF.⁷⁻¹³ In real world clinical practice observation, effective treatment reduced 30-50% of HF re-hospitalization and increased the median survival period from 6 to 12 months.¹⁴

In Europe and the United States, guidelines for the diagnosis and management of HF were first published in 1995. Thereafter, further updated guidelines were published by the European Society of Cardiology and the American Heart Association based on evidence-based medicine and clinical trials.^{15,16} In 2012, the Heart Failure Committee of the Taiwan Society of Cardiology pub-

lished its own Guideline for the Diagnosis and Treatment of Heart Failure.¹⁷ However, there remains a wide gap between guideline-directed treatment and real world practice in HF management. A recently published report from the Taiwan Society of Cardiology-Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry showed suboptimal use of guideline-directed medical therapy (GDMT): in patients admitted with acutely decompensated systolic HF, renin-angiotensin system (RAS) blockers, beta-blockers and mineralocorticoid receptor antagonists were prescribed in 62.1%, 59.6% and 49.0% of the patients at discharge, respectively.¹⁸ We aimed to describe the one-year outcomes of the TSOC-HFrEF registry.

METHODS

Study designs and patients

The TSOC-HFrEF was a prospective, multicenter, observational survey of patients presenting to 21 hospitals in Taiwan for acute decompensated systolic HF. The Institutional Review Board of each hospital agreed to participate in the registry.

The enrollment of patients, patient population characteristics, and patient management during index hospitalization have been completely described in a previous manuscript.¹⁸ In brief, patients being enrolled in the study were those who presented with either acute new-onset HF or acute decompensation of chronic HF with reduced LVEF. The patients' LVEF had to be documented as less than 40%. Patients enrolled were asked to sign informed consent. Because we used observational methodology, there were no specific protocols or recommendation for evaluation and management of HF.

Data were collected during index hospitalization beginning with the initial point of care, and ending with discharge or death. Outpatient visits were arranged after discharge, and clinical status was ascertained via telephone interview for patients not attending the outpatient clinical visit.

Statistical analysis

All patients enrolled were included in the analysis. Descriptive summaries were presented for all patients, and also for subgroups of patients. The quantitative

data were expressed as the mean value \pm standard deviation, or as median and inter-quartile range (IQR); categorical variables were reported as percentages. The Student's *t*-test or the Mann-Whitney U-test was used for comparisons between the continuous data, and the Chi-square test was used for comparisons between the categorical data. A Kaplan-Meier survival analysis was used to present the survival curves. Multivariate Cox regression analysis with forward selection was performed to assess predictability of variables on survival presented as hazard ratios (HR) and 95% confidence intervals (CI) using $p < 0.05$ in univariate analyses for inclusion. Receiver operating characteristic (ROC) curves were used to find the optimal cutoff levels of predictors. A *p*-value of < 0.05 was considered statistically significant. The statistical analyses were performed using SPSS Statistics 17.0 software (Chicago, IL, USA).

RESULTS

Index hospitalization

From May 2013 to October 2014, 1509 hospitalized patients (age 63.9 ± 16.1 years, 72.4% male) from 21 hospitals were included in the TSOC-HFrEF registry. The most common etiology of HF was ischemic cardiomyopathy (44.1%), followed by dilated cardiomyopathy (32.9%), and valvular heart disease (7.9%). The rates of moderate (NYHA Fc II) and severe HF (NYHA Fc III and IV) were 11.8% and 88.2% at the time of admission, respectively. The median length of hospital stay was 8 days (IQR 5~15); most patients improved after treatment, and the rates of NYHA Fc I and II HF were 12.9% and 58.1% at discharge, respectively. Approximately 30% of patients were discharged with severe HF symptoms (NYHA Fc III-IV). Thirty-six patients (2.4%) died during the index hospitalization, and 63.9% of patient deaths were due to cardiovascular (CV) mortality. Figure 1 showed the comparison of in-hospital mortality with other multi-center HF registries.¹⁹

Clinical presentations at hospital entry and during follow-up

Upon entry to the hospital, patient mean systolic blood pressure (SBP) was 130.9 ± 27.6 mmHg, mean diastolic blood pressure (DBP) was 80.7 ± 19.5 mmHg, and

mean heart rate was 92.7 ± 22.2 bpm. Sinus rhythm was detected in 66.7% of patients on electrocardiography. At discharge from index hospitalization, mean SBP was 119.2 ± 19.0 mmHg, DBP was 71.8 ± 13.6 mmHg, and heart rate was 80.4 ± 15.0 bpm. These three vital signs at discharge were significantly lower than those upon hospital admission ($p < 0.005$). A total of 14% of the patients had SBP lower than 100 mmHg, and 76.6% of patients had heart rate faster than 70 bpm at discharge. The mean body weight at discharge was 64.5 ± 15.9 kg.

At the 12-month follow-up, the mean SBP was 125.3 ± 20.9 mmHg, DBP was 73.1 ± 13.6 mmHg, and heart rate was 80.7 ± 16.0 bpm. Sinus rhythm was found in 66.6% of patients. A total of 8.2% of patients had SBP lower than 100 mmHg, and 76.9% of patients had heart rate above 70 bpm at 12-month. The mean body weight at 12-month was 67.5 ± 16.6 kg. Changes in vital signs over time were shown in Figure 2.

Echocardiographic results and laboratory studies during follow-up

At index hospitalization, the mean LVEF was $28.5 \pm 8.7\%$, the mean left ventricular end diastolic diameter was 60.8 ± 10.0 mm and the mean left atrial diameter was 46.3 ± 8.7 mm. The mean LVEF was $38.0 \pm 15.8\%$ and $39.4 \pm 15.3\%$ at 6- and 12-months, respectively. The mean left ventricular diastolic diameter was 59.7 ± 14.0 mm and 59.1 ± 10.9 mm at 6- and 12-months, respectively. The mean left atrial diameter was 46.3 ± 9.3 mm and 45.7 ± 9.0 mm at 6- and 12-month, respectively.

At index hospitalization, mean serum creatinine

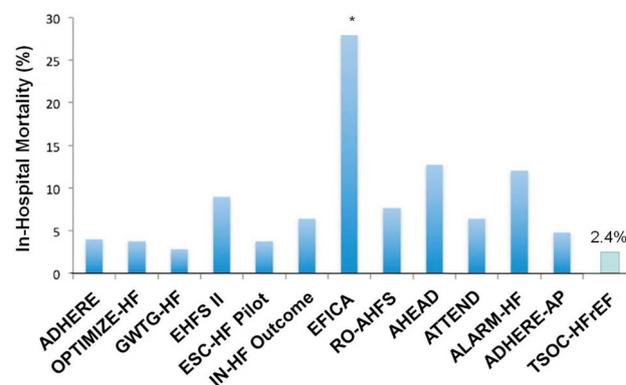


Figure 1. Comparison of in-hospital mortality between TSOC-HFrEF and other multi-center HF registries (Modified from Ambrosy AP, et al. *J Am Coll Cardiol* 2014;63:1123-33.) * Indicated 4-week mortality.

level was 1.9 ± 1.8 mg/dL, and the mean estimated glomerular filtration rate (eGFR) was 55.5 ± 40.2 mL/min/

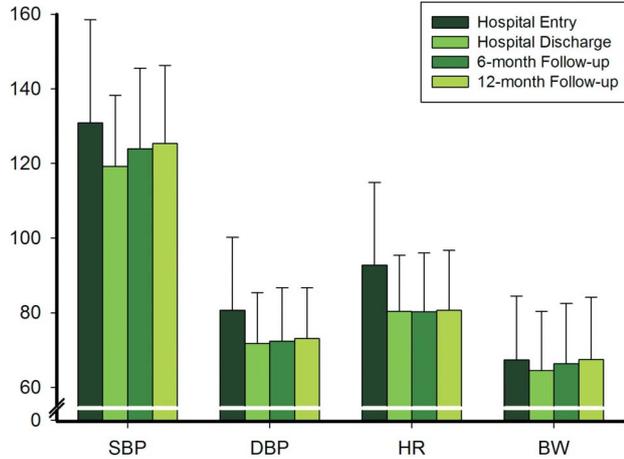


Figure 2. Changes of blood pressure, heart rate and body weight in HF patients over time. BW, body weight; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

m^2 . A total of 36.6% of patients had stage III chronic kidney disease (CKD, eGFR 30-60 mL/min/ m^2) and 27.4% of the patients had stage IV/V chronic kidney disease (eGFR < 30 mL/min/ m^2). At 6 months, the mean eGFR was 56.9 ± 38.4 mL/min/ m^2 . The percentages of stage III and stage IV/V CKD were 33.8% and 27.1%, respectively. At 12 months, mean eGFR was 57.1 ± 9.3 mL/min/ m^2 . The percentages of stage III and stage IV/V CKD were 39.4% and 23.4%, respectively.

Anemia (hemoglobin level < 12 g/dL) was noted in 34.9% of the patients at index hospitalization, 49.0% at 6-month and 48.8% at 12-month. Hyponatremia (serum sodium < 135 mEq/L) was noted in 19.9% of the patients at index hospitalization, 17.1% at 6-month and 16.0% at 12-month. Hyperkalemia (serum potassium ≥ 5.5 mEq/L) was noted in 2.6% of the patients at index hospitalization, 3.8% at 6-month and 3.2% at 12-month. Detailed laboratory findings were shown in Table 1.

Table 1. Laboratory findings of TSOC-HFrEF registry patients

	Index Hospitalization		6-month		12-month	
	Mean/percentage	Median (IQR)	Mean/percentage	Median (IQR)	Mean/percentage	Median (IQR)
BUN (mg/dL)	32.2 ± 23.3	24.7 (17.3-38.0)	37.7 ± 26.8	29.0 (19.0-47.0)	35.2 ± 25.3	25.6 (17.9-45.6)
Creatinine (mg/dL)	1.9 ± 1.8	1.3 (1.0-1.9)	2.0 ± 2.1	1.3 (1.0-2.1)	2.0 ± 2.1	1.3 (1.0-1.9)
eGFR (mL/min/ m^2)	55.5 ± 40.2	48.0 (27.9-73.7)	56.9 ± 38.4	48.6 (29.0-79.9)	57.1 ± 39.3	46.4 (30.9-75.5)
Stage III CKD	36.6%		33.8%		39.4%	
Stage IV or V CKD	27.4%		27.1%		23.4%	
Sodium (mEq/L)	137.7 ± 4.6	138 (135-140)	138.1 ± 4.3	138 (136-141)	138.3 ± 4.8	139 (136-141)
Hyponatremia (< 135 mEq/L)	19.9%		17.1%		16.0%	
Potassium (mEq/L)	4.0 ± 0.6	4 (3.6-4.4)	4.2 ± 0.7	4.2 (3.8-4.6)	4.2 ± 0.6	4.2 (3.8-4.6)
Hyperkalemia (≥ 5.5 mEq/L)	2.6%		3.8%		3.2%	
Hgb (g/dL)	12.9 ± 2.4	13 (11.2-14.7)	12.0 ± 2.4	12.0 (10.2-13.7)	12.2 ± 2.5	12.1 (10.1-13.9)
Anemia (< 12 g/dL)	34.9%		49.0%		48.8%	
Blood glucose (mg/dL)	149.5 ± 81.7	125 (103-169)	130.8 ± 61.0	115 (95-142)	132.1 ± 57.6	114 (95-148)
HbA1c (%)	7.0 ± 1.7	6.5 (5.9-7.6)	7.2 ± 2.7	6.7 (5.9-7.6)	7.0 ± 1.8	6.5 (5.9-7.5)
Total bilirubin (mg/dL)	1.4 ± 2.0	1 (1-2)	2.0 ± 3.9	0.9 (0.5-1.7)	1.9 ± 4.1	0.9 (0.5-1.5)
AST (U/L)	87.3 ± 364.0	30 (23-47)	71.7 ± 334.7	27 (20-37)	39.0 ± 91.1	25 (20-33)
ALT (U/L)	69.5 ± 224.4	26 (17-45)	51.7 ± 299.4	21 (15-30)	27.6 ± 50.9	19 (14-27)
Free T4 (ng/mL)	1.9 ± 3.1	1.3 (1.1-1.5)	1.5 ± 1.7	1.3 (1.1-1.6)	1.7 ± 1.8	1.3 (1.1-1.6)
TSH (μ U/mL)	2.7 ± 4.3	1.7 (0.9-3.0)	4.2 ± 5.9	2.4 (1.1-4.5)	3.1 ± 3.6	1.9 (1.0-3.7)
BNP (pg/mL)	1749 ± 1589	1250 (554-2487)	1744 ± 2423	893 (285-2436)	1486 ± 1958	720 (287-2135)
NT-PRO-BNP(pg/mL)	4887 ± 5066	3534 (1896-6338)	8381 ± 10546	3734 (1178-10750)	9125 ± 12540	3532 (854-9825)
Troponin-I (μ g/L)	2.8 ± 21.9	0.09 (0.04-0.32)	-	-	-	-
Uric acid (mg/dL)	8.6 ± 2.9	8.5 (6.6-10.3)	7.9 ± 3.2	7.5 (5.9-9.6)	7.5 ± 2.7	7.1 (5.6-8.8)
Ferritin (ng/mL)	285 ± 367	152 (84-365)	285 ± 262	184 (96-386)	301 ± 250	297 (83-457)
Iron (μ g/dL)	67.9 ± 52.4	54 (36-85)	75.6 ± 67.7	58 (41-86)	70.1 ± 36.9	65 (44-88)
TIBC (μ g/dL)	307.3 ± 85.2	298 (248-366)	284.3 ± 102.9	283 (201-341)	254.2 ± 79.5	242 (210-303)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urine nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; NT-PRO-BNP, N-terminal pro-brain natriuretic peptide; TIBC, total iron-binding capacity; TSH, thyroid stimulating hormone.

Pharmacological treatments for HF

The pharmacological treatments at discharge, 6 months and 12 months were shown in Table 2. Diuretics were the most commonly prescribed medication and were used in 82.2% of the patients at discharge. The prescription of diuretics decreased over time, and 75.9% of the patients were under diuretics treatment at the 1-year follow-up.

The renin-angiotensin system blockers were prescribed in 62.1% of the patients upon discharge, and were prescribed in 56.8% and 57.5% of the patients at 6-month and 12-month, respectively. Angiotensin converting enzyme inhibitors (ACEIs) were prescribed in 27.5% of the patients at discharge, but they were used in only 16.8% of the patients at 12 months. The most commonly used ACEIs were Ramipril, Captopril and Enalapril. Different from ACEIs, prescribing trends of angiotensin receptor blockers (ARBs) increased over time.

They were prescribed in 34.6% of the patients at discharge and 40.7% of the patients at 12-month. The most commonly prescribed ARBs were Candesartan, Valsartan and Losartan.

Prescribing rates of beta-blockers increased from 59.6% of the patients at discharge to 66.3% of the patients at 12-month; Bisoprolol was the most commonly prescribed beta-blocker. Mineralocorticoid receptor antagonists (MRA) were prescribed in 49.0% of the patients at discharge from index hospitalization. They were prescribed in 40.8% of the patients at the 1-year follow-up.

A total of 20.6% of patients received all three types of GDMT. On the contrary, 10.7% of the patients did not receive any GDMT, and 29.0% of the patients received only a single type of GDMT. (See Figure 3)

Surgical procedures and device therapies for HF

During follow-up, 20 patients (1.4%) received coro-

Table 2. Prescribed pharmacological treatments for heart failure over time

	At discharge		At 6 months		At 12 months	
	Rate of use	Dosage (mg)	Rate of use	Dosage (mg)	Rate of use	Dosage (mg)
ACEIs	27.5%		17.5%		16.8%	
Ramipril	33.8%	4.6 ± 4.5	37.4%	4.2 ± 3.7	44.2%	4.6 ± 4.4
Captopril	30.3%	28.8 ± 23.1	19.4%	28.1 ± 22.1	15.3%	31.1 ± 20.8
Enalapril	23.6%	8.1 ± 8.9	24.2%	8.8 ± 7.4	20.2%	12.3 ± 11.9
Others	12.2%		19.0%		20.2%	
ARBs	34.6%		39.3%		40.7%	
Candesartan	39.7%	6.9 ± 4.1	37.8%	7.1 ± 4.5	32.9%	6.6 ± 4.3
Valsartan	35.0%	117.1 ± 70.6	35.7%	112.2 ± 56.6	40.3%	112.6 ± 61.7
Losartan	16.4%	41.4 ± 29.1	17.5%	40.9 ± 25.0	16.5%	40.5 ± 18.8
Others	8.9%		9.1%		10.3%	
ACEIs or ARBs	62.1%		56.8%		57.5%	
Beta-blockers	59.6%		67.3%		66.3%	
Bisoprolol	57.9%	2.7 ± 2.5	60.6%	2.7 ± 1.9	62.0%	2.7 ± 1.9
Carvedilol	37.5%	13.4 ± 14.1	36.3%	14.2 ± 13.7	33.7%	14.7 ± 12.6
Metoprolol	1.3%	40.0 ± 26.2	2.0%	40.6 ± 28.0	2.8%	48.6 ± 36.1
MRA	49.0%		43.9%		40.8%	
Spironolactone	98.7%	33.7 ± 29.1	98.1%	32.8 ± 29.3	99.5%	32.7 ± 29.4
Eplerenone	1.3%	52.8 ± 19.5	1.9%	52.5 ± 18.4	0.5%	
Diuretics	82.2%		76.5%		75.9%	
Digitalis	25.9%		25.5%		24.0%	
Antiplatelets	59.4%		58.0%		57.3%	
Anticoagulants	21.3%		21.1%		23.7%	
Nitrates	36.4%		32.3%		32.2%	
Hydralazine	4.9%		4.6%		4.2%	
Anti-arrhythmic drugs	15.7%		16.0%		14.8%	

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonist.

nary artery bypass surgery, and 16 patients (1.1%) received valvular surgery. A total of 4 patients (0.3%) received surgical anterior ventricular endocardial restoration. Six patients (0.4%) received left ventricular assist device implantation; three of these patients died within 2 weeks after the procedure, while the other 3 patients survived till the end of follow-up. Twenty-three patients (1.5%) received heart transplantation, and 5 of them died during follow-up.

A total of 26 patients (1.8%) received cardiac implantable electronic device implantation during the fol-

low-up period: nine of them received permanent pacemaker implantation, 8 received implantable cardioverter defibrillator, 8 received cardiac resynchronization therapy pacemaker, and 1 received cardiac resynchronization therapy defibrillator.

Mortality and re-hospitalization

All-cause mortality rates were 9.5% and 15.9%, and CV mortality rates were 6.8% and 10.5% at 6 and 12 months after hospital discharge, respectively. Kaplan-Meier survival curves for all-cause mortality and CV death were shown in Figure 4.

Re-hospitalization rates for HF were 31.9% and 38.5% at 6 and 12 months after index hospitalization, respectively. One hundred and forty-three patients (9.7%) were admitted more than 1 time within one year. Overall, 46.4% of patients were free from death, hospitalization for HF, left ventricular assist device and heart transplantation at one year.

Table 3 showed the multivariate Cox regression model: longer index hospitalization stay (HR 1.01, 95% CI 1.00-1.02, p = 0.007), smaller body weight index (BMI, HR 0.95, 95% CI 0.91-0.99, p = 0.02), history of hypothyroidism (HR 3.97, 95% CI 1.96-8.05, p < 0.001), severe HF symptoms at discharge (NYHA Fc III/IV) (HR 1.88, 95% CI 1.28-2.77, p = 0.001), hyponatremia (HR 1.86, 95% CI 1.27-2.72, p = 0.001) and prescription of less than 2 types of GDMT (HR 1.59, 95% CI 1.07-2.38, p = 0.02) could independently predict the all-cause mortality in this registry. After an-

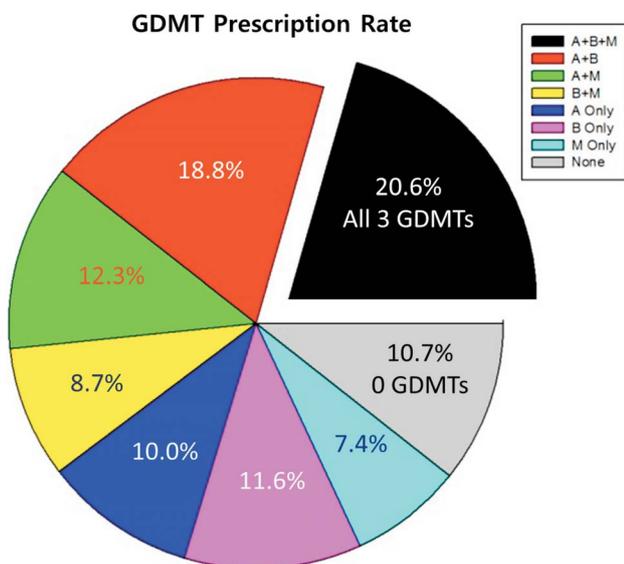


Figure 3. Different types of guideline-directed medical therapy (GDMT) prescribed to the patients. A, renin-angiotensin system blockers; B, beta-blockers; M, mineralocorticoid receptor antagonists.

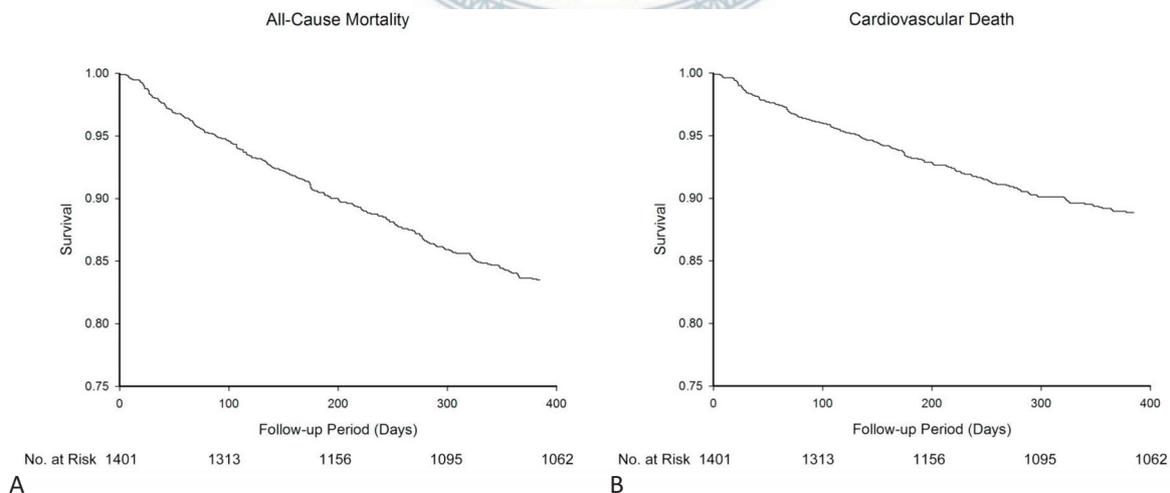


Figure 4. One-year survival in patients discharged alive; (A) all-cause mortality; (B) cardiovascular mortality.

Table 3. Predictors of one-year all-cause mortality in TSOC-HFrEF registry

	Univariate analysis			Multivariate analysis	
	Mortality	Alive	p value	HR (95% CI)	p value
Baseline and hospitalization characteristics					
Age (y/o)	69.0 ± 14.1	62.8 ± 16.2	< 0.001		
Hospital length (day)	17.9 ± 18.1	11.5 ± 12.3	< 0.001	1.01 (1.00-1.02)	0.007
Systolic blood pressure (mmHg)	126.3 ± 27.2	131.8 ± 27.3	0.006		
Body mass index (kg/m ²)	23.9 ± 5.1	25.5 ± 5.0	< 0.001	0.95 (0.91-0.99)	0.02
ICU admission	40.4%	31.1%	0.006		
Severe symptoms at discharge (NYHA Fc III/IV)	41.8%	25.6%	< 0.001	1.88 (1.28-2.77)	0.001
Past and personal history					
Current smoker	12.9%	25.2%	< 0.001		
Diabetes mellitus	55.1%	41.7%	< 0.001		
Chronic kidney disease	45.8%	28%	< 0.001		
Atrial fibrillation	31.6%	25.2%	0.05		
Peripheral arterial disease	10.7%	5.9%	0.009		
COPD/asthma	16%	9.8%	0.006		
Hypothyroidism	6.2%	1.3%	< 0.001	3.97 (1.96-8.05)	< 0.001
Valvular surgery	8.4%	4.2%	0.006		
ICD/CRT implantation	9.8%	2.1%	< 0.001		
Coexisting problem during index hospitalization					
Infection	21.8%	16.1%	0.04		
Acute kidney injury	22.2%	12.6%	< 0.001		
COPD/asthma with acute exacerbation	6.7%	2.4%	0.001		
Electrocardiography					
QRS duration (msec)	120.3 ± 31.9	111.6 ± 29.1	< 0.001		
Laboratory studies					
BUN (mg/dL)	41.9 ± 27.5	29.8 ± 21.5	< 0.001		
Severe CKD (eGFR ≤ 30 mL/min/m ²)	42.7%	24.0%	< 0.001		
Hyponatremia (serum Na ≤ 135 meq/L)	35.7%	23.8%	< 0.001	1.86 (1.27-2.72)	0.001
Hemoglobin (g/dL)	12.2 ± 2.4	13.1 ± 2.4	< 0.001		
Glucose (mg/dL)	161.0 ± 73.8	146.3 ± 81.7	0.04		
Discharge medication					
RAS blockade	50.5%	63.5%	< 0.001		
Beta blocker	50.0%	61.9%	0.001		
MRA	40.8%	49.6%	0.02		
Guideline-directed medical therapy ≤ 1 type	56.9%	36.8%	< 0.001	1.59 (1.07-2.38)	0.02
Digoxin	32.6%	24.8%	0.02		
Anti-arrhythmic drugs	21.1%	14.9%	0.02		

COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; NYHA, New York Heart Association; RAS, renin-angiotensin system.

analyses of receiver operating characteristic curves, six factors (hospital length ≥ 8 days, BMI ≤ 22.4, severe HF symptoms at discharge, hyponatremia, history of hypothyroidism, and ≤ 1 GDMT prescription) were identified. Figure 5 showed the Kaplan-Meier curves in the registry patients presenting with different numbers of risk factors.

DISCUSSION

In the past, the characteristics and long-term outcome of acutely decompensated HF patients in Taiwan were poorly defined despite the high prevalence rate and public health concern. The TSOC-HFrEF registry is the first large-scale, prospective multicenter database

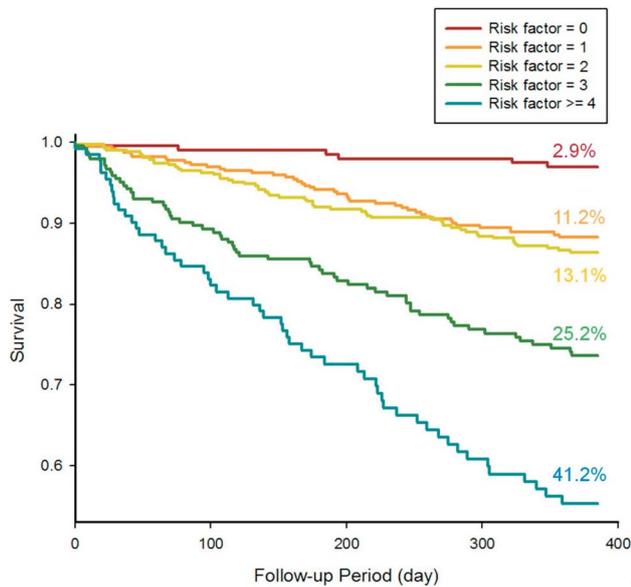


Figure 5. Kaplan-Meier curves in the registry patients presenting with different numbers of risk factors.

involving patients hospitalized for HF in Taiwan, and it provided important insights into the current clinical management and outcome of hospitalized HF patients in Taiwan.

In-hospital mortality and one-year outcome: comparison with other HF registries

Over the past years, patient survival rate after the onset of HF has improved. In-hospital mortality rate was ranging from 3-10% in most multi-center HF registries (Figure 1). The current TSOC-HFrEF registry demonstrated the lowest in-hospital mortality. This could not be explained by disease severity, in that one-third of TSOC-HFrEF patients were admitted into intensive care unit, more than 10% of the patients received mechanical ventilator, and 2.7% of the patients warranted intra-aortic balloon pump support.¹⁸

Early population-based studies have shown that HF was associated with a high 1-year mortality rate of 30% before 1990.²⁰ Later on, EHFS from Europe and OPTIMIZE-HF from the United States of America reported high 3-month all-cause mortality rates of 12% and 9.8%, respectively.^{21,22} The reported 1-year mortality rates of patients hospitalized for acute HF in Italy (IN-HF Outcome Registry) and Europe (EHFS-2) were 24.4% and 21.9%, respectively.^{23,24}

In Asia, the JCARE-CARD from Japan and the KorHF

registry from Korea showed that the 1-year all-cause mortality rates were 8.9% and 9.2%, respectively.^{25,26}

The recently published Hong Kong Heart Failure Registry demonstrated a 1-year mortality rate of 19.5%.²⁷ In our study, a relatively higher 1-year mortality rate of 15.9% was noted.

According to previous reports, the 1-year readmission rates for HF ranged from 9.8% in the KorHF registry to 30.1% in IN-HF outcome registry. The readmission rate was higher in the TSOC-HFrEF registry (38.5%), when compared to other registries.

Differences between TSOC-HFrEF & other HF registries: characteristics & management

The risk of mortality and readmission across several studies was variable because of the heterogeneity of the demographic factors of the population and difference in clinical management. When comparing the TSOC-HFrEF registry with recent large-scale HF registries, several important differences were noted (see Table 4). First of all, there was a significantly lower prevalence of hypertension. Lower blood pressure might suggest the severity of HF indirectly, and it might also hinder the physicians' ability to up-titrate guideline-directed medical therapy. In the OPTIMIZE-HF study, the mean systolic blood pressure at admission in patients with left ventricular systolic dysfunction was 135.2 ± 30.9 mmHg, which was about 5 mmHg higher than that of the TSOC-HFrEF registry. The OPTIMIZE-HF study showed the poorest prognosis in patients with low systolic blood pressure of less than 120 mmHg at admission despite medical therapy.²⁸ The paradoxical effect of higher systolic blood pressure on mortality in HF patients was also demonstrated in a meta-analysis.²⁹

The prevalence rates of diabetes mellitus and chronic renal failure in the current registry were both higher than 40%. Diabetes and chronic renal failure were both associated with major CV events. Moreover, poor renal function is an important barrier for prescribing RAS blockers and MRA for HF patients. This could explain the lower prescription rate of ACEI or ARB in TSOC-HFrEF registry when compared with other recent HF registries.

Randomized controlled trials showed that ACEI could reduce mortality and HF hospitalization,^{7,8} whereas ARB could reduce mortality and morbidity in patients with HF not treated with ACEI.³⁰ According to current HF

Table 4. Comparison of characteristics and outcomes among recent HF registries in patients with HF

	OPTIMIZE-HF	EHFS-2*	IN-HF	JCARE-CARD	KorHF	Hong Kong HF registry	TSOC-HFrEF registry
Baseline characteristics							
Year of enrollment	2003~04	~2005	2007~09	2004~05	2004~09	2005~12	2013~14
Patient numbers, n	20,118	2,981	1,292	847	1,527	383	1,509
Age, y/o	70.4	71.7	71	66.6	69.1	72.2	63.9
Male	62%	61.6%	66.4%	72.2%	55.9%	59.8%	72.4%
BMI kg/m ²	NA	26.8	27.4	22.7	23.2	NA	25.2
LVEF, %	24.3	38.4	31.6	27	28.7	NA	28.5
Comorbid conditions							
Hypertension	66%	62.1%	55.6%	50.4%	42.0%	60.3%	34.5%
Diabetes mellitus	39%	33.1%	41.0%	33.3%	31.4%	36.0%	43.6%
Chronic renal failure	NA	16.5%	34.0%	10.4%	7.3%	8.9%	31.5%
Coronary artery disease	54%	53.6%	NA	39.8%	40.1%	34.2%	41.8%
Atrial fibrillation	28%	38.6%	32.7%	24.5%	20.8%	31.3%	26.0%
Guideline-directed medication therapy at discharge							
ACEI or ARB	NA	80.2%	NA	83.5%	68.0%	68.6%	62.1%
ACEI	62%	71.1%	57.3%	44.2%	45.6%	NA	27.5%
ARB	11%	10.4%	20.5%	45.9%	24.5%	NA	34.6%
Beta-blocker	73%	61.8%	67.1%	65.9%	40.9%	48.2%	59.6%
Aldosterone antagonist	18%	47.3%	60.4%	45.9%	37.5%	12.2%	49.0%
Outcomes after discharge							
Follow-up period	60 ± 90 days	1 year	1 year	1 year	1 year	1 year	1 year
All-cause mortality	9.8%	21.9%	24.4%	8.9%	9.2%	19.5%	15.9%
Re-hospitalization	29.9%	NA	30.1%	23.7%	9.8%	NA	38.5%

* Includes patients with preserved EF.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; LVEF, Left ventricular ejection fraction.

guideline, ARB should be given to patients unable to tolerate ACEI.¹⁵ In TSOC-HFrEF registry, another observation was that the prescription rate of ACEI was significantly lower than ARB. This was in contrast to the data in most other HF registries, in which ACEI was more frequently prescribed. In the JCARE-CARD registry, the ACEI and ARB were prescribed at a similar percentage. During follow-up, the prescribing rate of ACEI decreased further over time (from 27.5%-16.8%), and the prescribing rate of ARB increased from 34.6%-40.7%, indicating that physicians in Taiwan were less likely to be prescribing ACEI as the first line HF medication, they also tended to switch ACEI to ARB after patients suffered from ACEI-related adverse effects, such as cough and angioedema.

Another noteworthy finding was that the prescription rate of MRA in TSOC-HFrEF registry was higher than most other registries except IN-HF. The current guideline suggests RAS blockers and beta-blockers as a first-line therapy, and MRA is recommended for patients with persisting symptoms and LVEF ≤ 35%, despite first-line therapy. The current registry showed that 11.6% of pa-

tients received MRA alone without ACEI, ARB or beta-blockers. As mentioned above, lower prevalence of hypertension may partially explain why some physicians favored MRA to ACEI /ARB, as MRA had less of an effect on hypotension than RAS blockers.

Improvement in HF care and novel anti-heart failure treatment

Present TSOC-HFrEF registry showed the suboptimal results of 1-year re-hospitalization rate for HF and mortality rate. Implementation of new measures to improve the quality of HF care is an issue that will be further addressed in the future. In fact, a registry itself might help to improve outcomes. In the ADHERE registry, beta-blocker usage increased by 30%, and in-hospital mortality decreased from 4.5% to 3.2% over a 3-year period. This indicated that participating in the registry with a better understanding of the unmet need could improve HF care by participating physicians.³¹ Moreover, HF nurse-directed, multidisciplinary disease management programs had been demonstrated to reduce HF re-hos-

pitalization rates and mortality in Europe, the United States, and in a single center in Taiwan.³²⁻³⁴ Therefore, implementing an HF management program to care for the growing number of HF patients could potentially improve the quality of care and reduce costs.

Several novel HF medications had been developed in recent years, which may provide an additional benefit in HF care. In the SHIFT trial, Ivabradine significantly reduced the risk of CV death or hospitalization for worsening HF compared to placebo, in addition to optimal therapy.³⁵ The PARADIGM-HF trial showed that Valsartan/Sacubitril was superior to Enalapril therapy in reducing the risk of CV death or hospitalization for HF.³⁶ In the 2016 updated European HF Guideline, these 2 new medications are recommended for symptomatic HF patients with LVEF \leq 35% after standard triple therapy with ACEI (or ARB), beta-blocker and MRA.¹⁵ These 2 new drugs were not available during the enrollment period of TSOC-HFrEF registry; hence, we did not collect the prescription rates of these drugs.

Ivabradine could be considered for patients with sinus rhythm and heart rate more than 70 bpm. In our study population, two-third of the patients were in sinus rhythm and about 75% patients had heart rate faster than 70 bpm. The data suggested that approximately 50% of the patients might be suitable candidates for Ivabradine treatment. However, although 66.3% of the patients were on beta-blockers at 12-months, the mean heart rate was 80.7 ± 16.0 bpm, indicating there was still a need for further drug up-titration.

Valsartan/Sacubitril use is generally limited by hypotension and hyperkalemia, especially for patients who are unable to tolerate high doses of ACEI or ARB. In our study population, about 8-10% of patients had systolic blood pressure lower than 100mmHg, and about 3-4% of patients had hyperkalemia. Once again, the prescription rates of ACEI or ARB were lower than for patients in other HF registries. Factors hindering the titration of ACEI/ARB might be the potential barriers for switching to Valsartan/Sacubitril.

Empagliflozin is a highly selective SGLT2 inhibitor for treatment of type 2 diabetes mellitus. In the EMPA-REG OUTCOME trial, patients with type 2 diabetes at high CV risk, including about 10% HF patients, were randomly assigned to receive Empagliflozin or placebo in addition to standard care.³⁷ In the Empagliflozin group, there

were significantly lower rates of CV death (3.7% vs. 5.9% in the placebo group; $p < 0.001$), hospitalization for HF (2.7% and 4.1%, respectively; $p < 0.002$), and all-cause mortality (5.7% and 8.3%, respectively, $p < 0.001$). The exact mechanism of CV benefit is currently unclear, but weight loss, blood pressure reduction without increases in HR, and reduction of arterial stiffness are important features of Empagliflozin.³⁸ Since the prevalence of diabetes mellitus in TSOC-HFrEF registry exceeded 40%, this new SGLT2 inhibitor may have a potential role for HF patients with diabetes.

Study limitations

This study had several limitations. First, although participating sites and their coordinators were encouraged to follow-up patients via outpatient visits or telephone interviews, a total of 70 patients (4.6%) were lost to follow-up and their health status could not be obtained. Second, due to study design, some baseline characteristics and laboratory studies were not available in every patient. Although natriuretic peptides can predict death and cardiac events in patients with HF, brain natriuretic peptide and N-terminal pro-brain natriuretic peptide were only available in 30.0% and 20.9% of the patients in our registry, respectively, which limited their use in predicting adverse events and mortality. Standardization of data collection in the future HF registry could avoid this limitation. Third, in 2014, a total of 22,511 patients were admitted due to HF in Taiwan.³⁹ Although only a relatively small amount of HF patients (1509 patients) were included in the current registry, 21 participating centers in this registry were distributed throughout Taiwan, including Northern, Central, Southern and Eastern region. Moreover, nearly all Taiwanese citizens were covered by National Insurance and participated in the same healthcare system. We believe that data in the current registry could still represent the real-world practice of HF care in Taiwan.

CONCLUSIONS

The TSOC-HFrEF registry is the largest national database to date involving acute decompensated HFrEF patients in Taiwan. Despite a low (2.4%) in-hospital mortality rate, the 1-year HF re-hospitalization rate and mortality rate has remained high, indicating the need for

further improvement in HF care.

CONFLICT OF INTEREST

All of the authors declare they have no conflict of interest.

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