






Nationwide trends in incidence, healthcare utilization, and mortality in hospitalized heart failure patients in Taiwan

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Abstract

Aims The objective of this study was to estimate the nationwide annual incidence, healthcare utilization, and mortality among hospitalized heart failure (HF) patients in Taiwan.

Methods and results People aged 20 years or older and having been newly admitted for HF between 2010 and 2015 were identified from Taiwan's National Health Insurance Research Database. For 124 816 patients with incident HF hospitalizations between 2010 and 2012, we further analysed their treatment patterns, healthcare utilizations, and mortality during index hospitalization and within 3 years following discharge from the index hospitalization. The age-stratified incidences were declined by 10–20% in people aged 55 years or older, but increased by ~4% among people younger than 44 years old between 2010 and 2015. For all incident hospitalized HF patients, the percentages of patients visiting the emergency room, were rehospitalized, and treated with guideline-directed medical therapy were highest in the first year. Approximately two-thirds of subsequent hospitalizations were due to non-HF and non-cardiovascular causes. The all-cause mortality rate during index hospitalization was 8.5%, whereas the mortality rates at 30 days, 90 days, 180 days, 1 year, 2 years, and 3 years following discharge were 3.5%, 8.9%, 14.4%, 22.5%, 33.9%, and 42.8%, respectively, for those surviving index HF hospitalization. Non-cardiovascular disease-related deaths accounted for nearly 60% of all deaths.

Conclusions Our study reveals that, in contemporary Taiwan, the >10% annual mortality following the first year of hospitalization, 30% deaths occurring outside the hospital, and 60% non-cardiovascular-related deaths, along with the decreasing use of guideline-directed medical therapy, highlight sectors requiring more attention.

Keywords Incidence; Healthcare utilization; Mortality; Heart failure; Taiwan

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Introduction

Heart failure (HF) is associated with substantial risks of hospitalization and mortality and is regarded as an emerging pandemic, with an estimated 26 million patients worldwide.^{1,2} To identify the management gaps and allocate healthcare resources adequately for HF, contemporary population-level epidemiology with longer-term follow-up information is of vital importance. However, studies regarding population-based

prevalence and incidence of HF and its temporal trends are scarce, particularly in Asia.^{3,4} In the real world, the diagnosis of HF is usually made on clinical grounds,⁵ which casts doubts on the reliability of population-based prevalence data. Hospitalization for HF, compared with HF diagnosed at outpatient settings, is more reliable in disease ascertainment and a powerful predictor of rehospitalization and mortality.⁶

In Taiwan, the crude incidence of HF hospitalization was 271 per 100 000 persons in 2005, according to the random

sample of 1 million people from the National Health Insurance Program.⁷ However, patients with prior history of HF were not excluded, and no adjustment for a standard population was made, rendering comparisons with other studies challenging. Recent epidemiological studies showed a decreasing trend in standardized HF incidence in Western countries,^{8,9} whereas there are no data from Asian countries.⁴ Prior hospital-based registries worldwide consistently demonstrated that, in patients with HF hospitalization, the risks of death and recurrent hospitalization are greatest in the first 30 to 60 days after discharge, with rates approaching 15% and 30%, respectively.^{10,11} Nevertheless, there is a paucity of data concerning longer-term (>2 years) outcomes in patients with HF hospitalization, which might show an even greater discrepancy between hospital-based registry and population-level epidemiology given the various limitations of chronic disease management in real life. Patients with HF are often associated with frailty and malnutrition, portending worse prognosis indirectly related to HF.¹² To assess the impact of HF on morbidity and mortality comprehensively, non-HF-related hospitalization, non-HF-related mortality, and out-of-hospital mortality (deaths occurring outside the hospital) should be emphasized as well.

The objective of the present study was to fill the knowledge gaps regarding the current trends in the incidence of hospitalized HF and its longer-term (3 years) outcomes among patients newly hospitalized for HF from the 23 million people of Taiwan from 2010 to 2015 by using the Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD contains nationwide claims-based data embedded with comprehensive data on healthcare utilization.¹³ Through this analysis, the gaps in real world management of HF would appear.

Methods

Data source

We performed a population-based retrospective longitudinal study based on data from Taiwan's NHIRD between 1 January 2009 and 31 December 2015.

The NHIRD is a nationwide database comprising anonymous eligibility and enrolment information as well as claims for visits, procedures, and prescription medications for more than 99% of the entire population (23 million) of Taiwan. Individual patients are recorded as entering the NHIRD when they are covered by Taiwan's National Health Insurance system, which is a mandatory, single-payer health insurance programme in Taiwan established in 1996. The NHIRD is organized by the government and operated by the National Health Insurance Administration. For each visit, the NHIRD has recorded dates (outpatient visits, admissions, and

discharges), medical resource utilization (outpatient and inpatient visits), costs of services, medication prescriptions, and up to five diagnoses according to the International Classification of Diseases, 9th Edition (ICD-9 CM codes). The completeness and accuracy of the NHIRD are ensured by the Ministry of Health and Welfare and National Health Insurance Administration and maintained by the Health and Welfare Data Science Center. The database has been described in detail elsewhere¹⁴ and has been the source for numerous epidemiological studies published in peer-reviewed journals.¹⁵ Mortality data obtained from the National Death Registry in Taiwan were used to estimate all-cause and cause-specific mortality rates according to the ICD, 10th Edition (ICD-10 CM codes). The accuracy of the coding has been validated by previous studies.^{16,17}

Ethical statement

The identification numbers for all entries in the NHIRD were encrypted to protect the privacy of individual patients. The study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital (No. 201701105W).

Study population

This study is composed of two study designs, including a cross-sectional survey for exploring the nationwide temporal trends and a longitudinal cohort design for assessing the long-term healthcare utilization and cause-specific mortality in incident hospitalized HF patients in Taiwan.

For calculation of nationwide temporal trends, we identified adult patients, legally defined as aged 20 years or older in Taiwan, who had been admitted for HF, defined as a hospitalization with either a primary diagnosis of HF or with one of the first two secondary diagnoses being HF (ICD-9-CM codes: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 428.0, 428.1, and 428.9), in each year between 2010 and 2015 from Taiwan's NHIRD. We defined the incident cases of hospitalized HF as the first record of HF in hospital admission record and no history of HF-related hospitalization or outpatient visits during the previous 1 year.

To assess long-term healthcare utilization and cause-specific mortality in hospitalized HF patients in Taiwan, we identified incident hospitalized HF patients between 2010 and 2012 as a cohort. The cohort entry date was defined as the admission date of the incident HF hospitalization, and the index date was defined as the discharge date of incident HF hospitalization. After cohort identification, patients were followed from the index date to whichever of the following events came first: (i) death, (ii) the

end of 3 year follow-up since index date, or (iii) the end of the observation period (31 December 2015).

Measurement of healthcare utilization

We collected detailed information about health service use, including pharmacological treatments, non-pharmacological treatments, outpatient visits, emergency department visits, and inpatient hospitalizations during the incident hospitalization and within 1, 2, and 3 years after the index date (*Table 1*). To comprehensively understand the current treatment performances of HF, the pharmacological treatment evaluated in this study consisted of guideline-directed medical therapy (GDMT), treatment for symptom targets, and treatment for underlying diseases. The American College of Cardiology Foundation/American Heart Association foundation launched the term 'GDMT' to represent those Class I recommended therapies defined by the American College of Cardiology Foundation/American Heart Association in 2013.¹⁸ The GDMT, currently deemed one of the major performance measures for optimal treatment of HF, includes the use of any beta-blockers, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), loop diuretics, thiazide diuretics, and aldosterone antagonist.¹⁸ To assess the indirect impact of HF on morbidity, non-HF-related hospitalization, including hospitalization for other cardiovascular diseases and other diseases (except HF and cardiovascular diseases), was also analysed.

Measurement of mortality

To estimate all-cause and cause-specific mortality during incident HF hospitalization and within 30 days, 90 days, 180 days, 1 year, 2 years, and 3 years after the index date, we used the National Death Registry in Taiwan, which records the cause of death for all deceased citizens. Causes of death and their corresponding codes are presented in *Table 2*. In addition to the overall mortality, in-hospital and out-of-hospital mortality were also reported to assess the impact of HF on mortality comprehensively. In-hospital mortality was defined as a death in a patient who was hospitalized on the day of death. Because a substantial number of patients would have terminal discharge¹⁹ under critical conditions, which is also called impending death discharge²⁰ or going home to die²¹ and is a traditional custom in Taiwanese society, patients discharged within 3 days before the day of death were also considered as in-hospital mortality.²⁰ Out-of-hospital mortality, death occurring outside the hospital, was defined as a death in a patient who was not hospitalized within 3 days before the day of death. A death in a patient brought to the emergency room (ER) on the day of death was also defined as out-of-hospital mortality.

Statistical analysis

Age-stratified (20–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years) and calendar year-stratified crude incidence rates of hospitalized HF from 2010 to 2015 in Taiwan were reported as estimates per 100 000 person-years at risk. Age-standardized overall and sex-stratified incidence rates were calculated annually using the direct standardized method, and the standard population was from the World Health Organization in 2000.²² Poisson regression adjusted for age and calendar year was adopted to estimate the relative risk of HF between men and women. The annual percentage change in incidence between 2010 and 2015, stratified by age and sex, was calculated by using Joinpoint Trend Analysis software (National Cancer Institute, Bethesda, Maryland, USA).²³

Information on the baseline characteristics was retrieved from claims data from outpatient and inpatient visits 1 year prior to the index date. Data were presented as number (*n*) and frequencies (%) for categorical data, mean and standard deviation (SD) for normally distributed continuous data, or medians and inter-quartile range for non-normally distributed continuous data.

Results

Trends in the incidence of hospitalized heart failure from 2010 to 2015

The age-standardized, overall annual incidence of hospitalized HF decreased by 13% during the study period in Taiwan (from 204.1 per 100 000 people in 2010 to 177.2 per 100 000 people in 2015) (*P* for trend <0.05), and the overall decline was consistent across sex groups (*Figure 1*). The incidence of hospitalized HF was 17% higher in men than that in women in general [relative risk of incidence between men and women = 1.17 (1.16, 1.18); *P* < 0.0001]. Because of steeper declines in incidence in women during the study period, the incidence of hospitalized HF was ~10% higher in men compared with that in women in 2010 and was 25% higher in men in 2015 (*Figure 1*). Age-stratified estimates showed that the incidence declined by 13.1%, 19.8%, 18.9%, and 10.7% among people aged 55–64, 65–74, 75–84, and 85+, respectively (*P* < 0.005, *Figure 2*). However, the incidence remained the same for people aged 45–54 and even increased by ~4% in people younger than 45 years old (*P* for trend = 0.0108). Despite the decreasing trend in the age-standardized incidence of hospitalized HF, the absolute annual number of individuals presenting with incident HF hospitalization increased by 3.6% (from 44 631 in 2010 to 46 109 in 2015).

Table 1 Healthcare utilization of incident hospitalized HF cases during index hospitalization and within 3 years after discharge

	Index hospitalization		First year		Second year		Third year	
	n	%	n	%	n	%	n	%
All patient number	124 816	100.00%	114 253	100.00%	88 489	100.00%	75 402	100.00%
Pharmacological treatments (n, %)								
Any GDMT	107 119	85.82%	104 300	91.29%	74 593	84.30%	62 201	82.49%
ACEIs	32 046	25.67%	33 514	29.33%	17 753	18.93%	11 873	15.75%
ARBs	30 956	24.80%	49 106	42.98%	33 841	38.24%	27 869	36.96%
Beta-blockers	43 885	35.16%	62 672	54.85%	44 890	50.73%	37 920	50.29%
ACEI/ARB + beta-blockers	26 039	20.86%	43 298	37.90%	26 855	30.35%	21 381	28.36%
Loop diuretics	90 323	72.36%	81 261	71.12%	49 017	55.39%	38 256	50.74%
Thiazide diuretics	6380	5.11%	14 463	12.66%	8167	9.23%	6062	8.04%
Aldosterone antagonist (ARA)	33 651	26.96%	40 011	35.02%	22 474	25.40%	17 460	23.16%
Treatment for symptom target								
Inotropic agents	19 917	15.96%	22 094	19.34%	9857	11.14%	7061	9.36%
Digoxin	24 647	19.75%	30 115	26.36%	17 769	20.08%	13 903	18.44%
Hydralazine	7041	5.64%	8509	7.45%	4812	5.44%	3545	4.70%
Organic nitrates	63 062	50.52%	61 372	53.72%	38 257	43.23%	30 521	40.48%
Treatment for underlying disease								
Dihydropyridine, calcium-channel blockers	38 204	30.61%	52 959	46.35%	37 030	41.85%	30 174	40.02%
Non-dihydropyridine, calcium-channel blockers	18 312	14.67%	24 974	21.86%	14 829	16.76%	11 860	15.73%
Statins	19 718	15.80%	30 851	27.00%	24 439	27.62%	22 339	29.63%
Fibrates	2071	1.66%	5620	4.92%	4995	5.64%	4346	5.76%
Ezetimibe	156	0.12%	416	0.36%	405	0.46%	401	0.53%
Biguanides	12 282	9.84%	19 150	16.76%	12 984	14.67%	10 524	13.96%
Sulfonylureas	14 542	11.65%	21 825	19.10%	14 707	16.62%	11 672	15.48%
α -Glucosidase inhibitors	5031	4.03%	9385	8.21%	6393	7.22%	5139	6.82%
Thiazolidine	1510	1.21%	3352	2.93%	2215	2.50%	1838	2.44%
Meglitinides	7303	5.85%	12 263	10.73%	8179	9.24%	6610	8.77%
DPP4 inhibitors	5465	4.38%	11 845	10.37%	10 797	12.20%	10 577	14.03%
Insulin	28 893	23.15%	32 246	28.22%	20 821	23.53%	17 240	22.86%
Aspirin	53 006	42.47%	60 919	53.32%	40 778	46.08%	33 341	44.22%
Clopidogrel	26 701	21.39%	30 184	26.42%	16 606	18.77%	13 282	17.61%
Ticlopidine	2885	2.31%	5724	5.01%	3904	4.41%	3197	4.24%
Ticagrelor	0	0.00%	29	0.03%	235	0.27%	561	0.74%
NOACs	126	0.10%	733	0.64%	1629	1.84%	2853	3.78%
Warfarin	9332	7.48%	14 467	12.66%	10 229	11.56%	8738	11.59%
Non-pharmacological treatment								
Echocardiogram	67 807	54.33%	51 051	44.68%	36 155	40.86%	29 835	39.57%
Electrocardiogram	83 007	66.50%	86 085	75.35%	56 759	64.14%	46 609	61.81%
BNP/pro-BNP test	24 279	19.45%	29 126	25.49%	18 915	21.38%	16 583	21.99%
Biochemistry examination	115 093	92.21%	102 578	89.78%	76 069	85.96%	64 474	85.51%
Chest X-ray	102 055	81.76%	90 295	79.03%	60 131	67.95%	49 352	65.45%
Angiocardiology	12 517	10.03%	7077	6.19%	3269	3.69%	2577	3.42%
Cardiac output	3786	3.03%	3666	3.21%	1271	1.44%	1027	1.36%
Cardiac catheterization	18 528	14.84%	11 103	9.72%	5233	5.91%	4136	5.49%
Percutaneous coronary intervention (PCI)	8338	6.68%	5680	4.97%	2675	3.02%	2091	2.77%
Coronary artery bypass graft (CABG)	1009	0.81%	1238	1.08%	245	0.28%	175	0.23%
Ventricular assist device (VAD)	11	0.01%	17	0.01%	17	0.02%	15	0.02%

(Continues)

Table 1 (continued)

	Index hospitalization		First year		Second year		Third year	
	n	%	n	%	n	%	n	%
Heart implantation	29	0.02%	80	0.07%	45	0.05%	28	0.04%
ECMO	289	0.23%	229	0.20%	94	0.11%	71	0.09%
Cardiopulmonary bypass	1849	1.48%	2312	2.02%	528	0.60%	390	0.52%
ICD/CRT	261	0.21%	329	0.29%	138	0.16%	126	0.17%
Outpatient visit			111 130	97.27%	85 973	97.16%	73 241	97.13%
Number of visit, mean (SD)			34.5	(24.4)	34.7	(24.3)	34.7	(24.4)
Number of visit, median (IQR)			30	(30)	30	(29)	29	(30)
ER visit			70 319	61.55%	46 832	52.92%	38 115	50.55%
Number of visit, mean (SD)			3.0	(3.7)	2.8	(3.6)	2.8	(3.5)
Number of visit, median (IQR)			2	(3)	2	(2)	2	(2)
Total hospitalizations	124 816	100.00%	71 733	62.78%	44 730	50.55%	35 370	46.91%
Number of admission, mean (SD)	1.0	(0.0)	2.3	(1.8)	2.2	(1.8)	2.2	(1.7)
Number of admission, median (IQR)	1	(0)	2	(2)	2	(2)	2	(2)
Length of stay, mean (SD)	16.5	(72.4)	31.3	(44.8)	30.7	(50.9)	28.6	(47.1)
Length of stay, median (IQR)	7	(8)	16	(30)	14	(29)	13	(25)
In-hospital mortality	10 563	8.46%	18 414	25.67%	9911	22.16%	7502	21.21%
Hospitalization for HF	124 816	100.00%	35 275	30.87%	18 004	20.35%	13 137	17.42%
Number of admission, mean (SD)	1.0	(0.0)	1.6	(1.1)	1.6	(1.1)	1.5	(1.0)
Number of admission, median (IQR)	1	(0)	1	(1)	1	(1)	1	(1)
Length of stay, mean (SD)	16.5	(72.4)	20.6	(33.8)	22.7	(45.1)	20.1	(38.4)
Length of stay, median (IQR)	7	(8)	11	(17)	10	(16)	9	(15)
In-hospital mortality	10 563	8.46%	4886	13.85%	2441	13.56%	1738	13.23%
Hospitalization for cardiovascular diseases (exp HF)			8746	7.65%	4413	4.99%	3441	4.56%
Number of admission, mean (SD)			1.2	(0.6)	1.2	(0.7)	1.2	(0.6)
Number of admission, median (Q1, Q3)			1	(1, 1)	1	(1, 1)	1	(1, 1)
Length of stay, mean (SD)			11.6	(18.9)	10.2	(18.3)	10.0	(19.4)
Length of stay, median (IQR)			6	(11)	5	(9)	5	(9)
In-hospital mortality			1014	11.59%	494	11.19%	359	10.43%
Hospitalization for other diseases (exp HF and cardiovascular diseases)			50 316	44.04%	33 461	37.81%	27 066	35.90%
Number of admission, mean (SD)			2.0	(1.6)	1.9	(1.6)	1.9	(1.5)
Number of admission, median (SD)			1	(1)	1	(1)	1	(1)
Length of stay, mean (SD)			28.2	(40.1)	27.5	(45.4)	26.3	(43.9)
Length of stay, median (IQR)			14	(27)	13	(24)	12	(22)
In-hospital mortality			12 643	25.13%	7045	21.05%	5449	20.13%

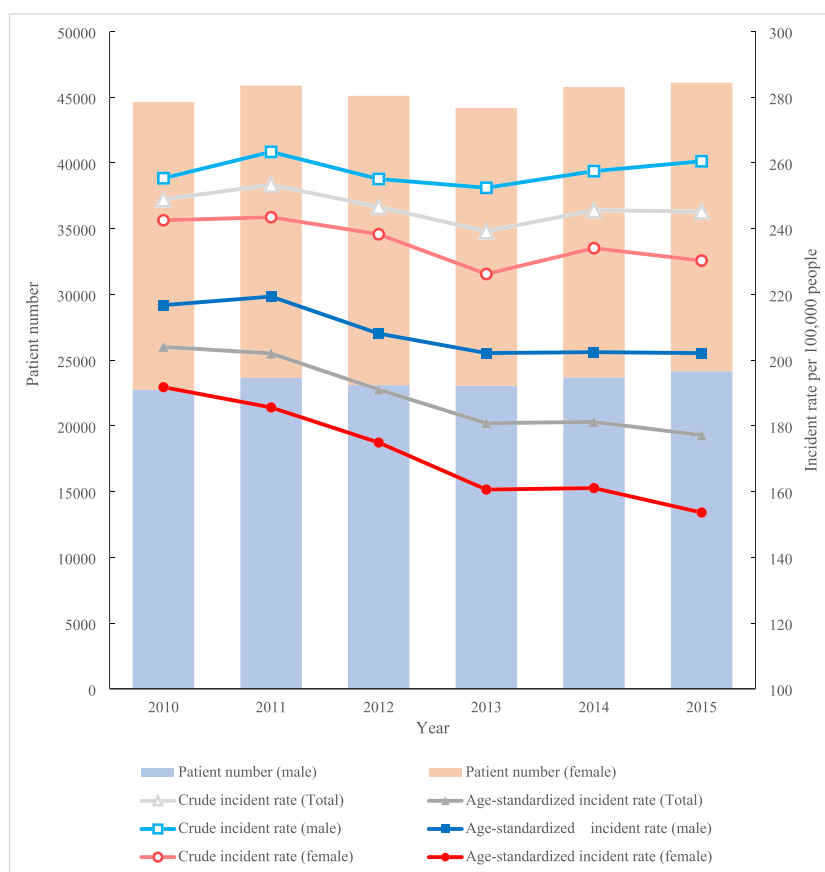
ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronization therapy; DPP4, dipeptidyl peptidase-4; ECMO, extracorporeal membrane oxygenation; ER, emergency room; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; NOACs, novel oral anticoagulants; SD, standard deviation; IQR, interquartile ranges.

Table 2 Mortality rates during index HF hospitalization and within 30 days, 90 days, 180 days, 1 year, 2 years, and 3 years after discharge from the index hospitalization among incident hospitalized HF patients

Cause of death	Index hospitalization (N = 124 816)		Post-discharge day of index hospitalization (N = 114 253)											
	n	% ^a	30 days		90 days		180 days		1 year		2 years		3 years	
			n	% ^b	n	% ^b	n	% ^b	n	% ^b	n	% ^b	n	% ^b
All-cause death	10 563	8.46%	3979	3.48%	10 157	8.89%	16 462	14.41%	25 688	22.48%	38 768	33.93%	48 907	42.81%
All cardiovascular disease (I)	5032	4.03%	1606	1.41%	3955	3.46%	6301	5.51%	9790	8.57%	14 639	12.81%	18 459	16.16%
HF (I50)	1453	1.16%	348	0.30%	892	0.78%	1393	1.22%	2140	1.87%	3079	2.69%	3822	3.35%
Valvulopathy (I05–09 and I34–39)	266	0.21%	109	0.10%	271	0.24%	414	0.36%	626	0.55%	930	0.81%	1150	1.01%
Cardiomyopathy (I42–43 and I25.5)	88	0.07%	30	0.03%	80	0.07%	128	0.11%	195	0.17%	291	0.25%	372	0.33%
Ischaemic heart diseases (I20–25)	1631	1.31%	485	0.42%	1157	1.01%	1851	1.62%	2904	2.54%	4295	3.76%	5403	4.73%
Atrial fibrillation (I48)	46	0.04%	7	0.01%	24	0.02%	38	0.03%	58	0.05%	93	0.08%	134	0.12%
Stroke (I60–64)	431	0.35%	124	0.11%	327	0.29%	571	0.50%	915	0.80%	1409	1.23%	1836	1.61%
COPD and chronic respiratory failure (J40–44 and J96.1)	444	0.36%	182	0.16%	461	0.40%	771	0.67%	1277	1.12%	2022	1.77%	2554	2.24%
Pulmonary embolism (I26)	13	0.01%	13	0.01%	22	0.02%	28	0.02%	37	0.03%	50	0.04%	62	0.05%
Diabetes mellitus (E10–14)	716	0.57%	343	0.30%	919	0.80%	1526	1.34%	2503	2.19%	3833	3.35%	4860	4.25%
Pneumonia (J12–18)	835	0.67%	346	0.30%	880	0.77%	1388	1.21%	2163	1.89%	3170	2.77%	3981	3.48%
Dementia (F01–03)	24	0.02%	16	0.01%	30	0.03%	50	0.04%	75	0.07%	122	0.11%	177	0.15%
Parkinson (G20)	19	0.02%	13	0.01%	29	0.03%	47	0.04%	65	0.06%	104	0.09%	135	0.12%
Renal disease (N00–N07, N17–N19, and N25–N27)	551	0.44%	188	0.16%	516	0.45%	879	0.77%	1445	1.26%	2235	1.96%	2922	2.56%
Neoplasms (C)	870	0.70%	375	0.33%	1063	0.93%	1763	1.54%	2721	2.38%	4043	3.54%	5049	4.42%

COPD, chronic obstructive pulmonary disease; HF, heart failure.

^aThe ratio of the number of deaths to the number of total incident hospitalized HF patients (N = 124 816).^bThe ratio of the number of deaths to the number of patients discharge from index hospitalization (N = 114 253).

Figure 1 2010–2015 annual incidence of heart failure hospitalization in Taiwan, overall and sex stratified.

Characteristics of patients with incident heart failure hospitalization

We identified 124 816 patients with incident HF hospitalization between 2010 and 2012 as a cohort and estimated their healthcare utilization during index hospitalization and within 3 years after discharge. The detailed baseline characteristics are summarized in Supporting Information, *Table S2*. Mean age of patients at index hospitalization was 74.0 years (SD 13.9), and 48.8% were women. Among these patients, 33.7% had ischaemic heart disease, 65.5% had hypertension, 19.9% had hyperlipidaemia, 37.1% had diabetes mellitus, 25.9% had chronic obstructive pulmonary disease, 17.5% had nephropathy, 11.0% had atrial fibrillation, and 11.8% had other cardiac dysrhythmias excluding AF.

Treatment patterns and healthcare utilization

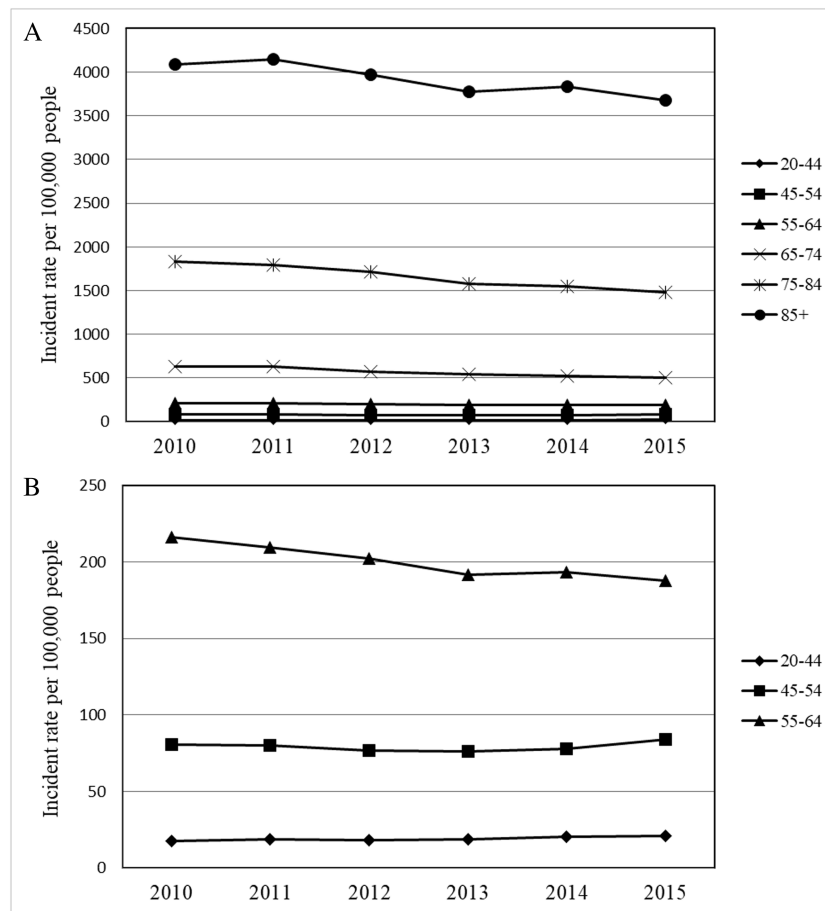
The detailed information of treatment patterns and health care utilization was summarized in Table 1. During the index

hospitalization, 85.8% of the 124 816 incident HF patients had been treated with GDMT (25.7% received ACEI, 24.8% received ARB, 35.2% received beta-blockers, and 27.0% received aldosterone antagonist), and 77.2% had been managed with treatments for symptom targets. Only 20.9% of patients had been treated with both ACEI/ARB and beta-blockers. The in-hospital mortality during the index hospitalization was 8.5%.

In the first year, 97% and 62% of the incident hospitalized HF patients had outpatient visits and ER visits, respectively. The mean numbers of outpatient visits and ER visits were 34.5 (SD 24.4) and 3.0 (SD 3.7), respectively. The percentages of patients having outpatient visits remained stable in the second and third years, whereas the percentages of patients having ER visits decreased to ~50%.

During the first year, the average number of admissions was 2.3, with a median length of stay of 16 days, in 114 253 (91.5%) patients surviving the index hospitalization. Hospitalizations directly related to HF constituted only 34% of all hospitalizations, whereas 61% of hospitalizations were due to non-HF and non-cardiovascular causes.

Figure 2 2010–2015 incidence of heart failure (HF) hospitalization in Taiwan, age stratified. (A) Incidence of HF hospitalization in the entire population. (B) Incidence of HF hospitalization in people aged <65 years. The incidence of HF hospitalization is stratified by age groups.



During the second and third years, the average numbers of admissions were similar to the number in the first year, but the percentages of patients with recurrent hospitalizations decreased (50.6% and 46.9% for 88 489 and 75 402 patients surviving the first and second years, respectively). Only 29.3% and 25.3% of hospitalizations during the second and third years were directly related to HF, whereas 64.6% and 66.1% of hospitalizations were due to non-HF and non-cardiovascular causes.

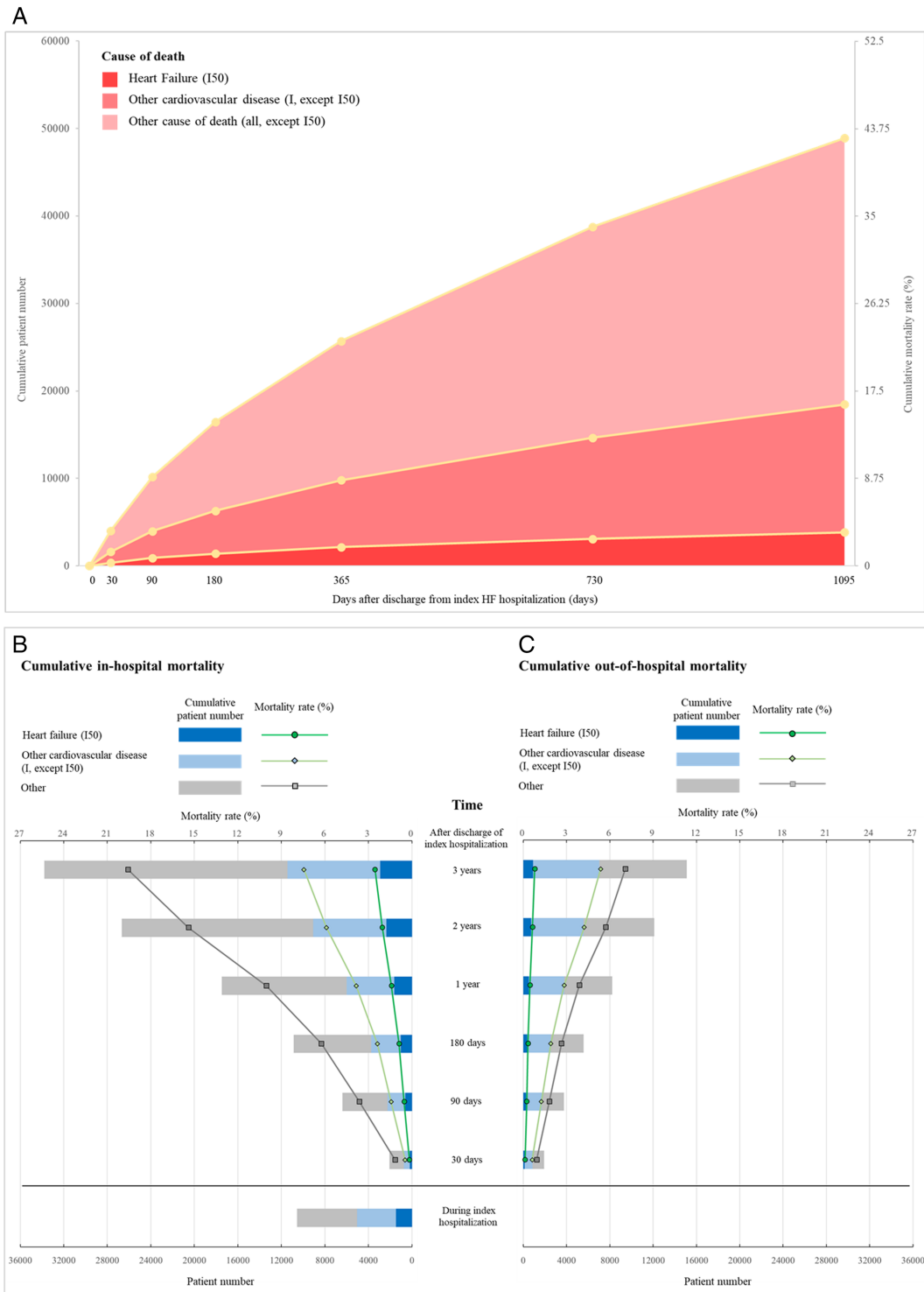
For pharmacological treatments, the percentages of patients treated with GDMT and receiving treatments for symptom targets were both highest in the first year and declined gradually in the second and third years. For instance, the percentage of the combined use of ACEI/ARB and beta-blockers was 20.9% during the index hospitalization, 37.9% in the first follow-up year, and 28.4% in the third follow-up year. However, treatments for underlying diseases such as statins, dipeptidyl peptidase-4 inhibitors, and new oral anticoagulants increased across the years.

Mortality rates of incident hospitalized heart failure patients

Among the 114 253 patients surviving the index hospitalization, the 30 day, 90 day, 180 day, 1 year, 2 year, and 3 year cumulative all-cause mortality rates were 3.5%, 8.9%, 14.4%, 22.4%, 33.9%, and 42.8%, respectively (Figure 3A and Table 2). For the whole 124 816 incident hospitalized HF patients, the index hospitalization, 30 day, 90 day, 180 day, 1 year, 2 year, and 3 year cumulative mortality rates were 8.5%, 11.7%, 16.6%, 21.7%, 29.0%, 39.5%, and 47.7%, respectively. The cumulative annual mortality was highest in the first year (22.5%) and remained above 10% in the second and third years (14.8% and 13.4% for 88 489 and 75 402 patients surviving the first and second years, respectively).

Notably, patients who died outside the hospital (out-of-hospital death) accounted for ~30% of all mortality cases (32.0%, 31.2%, and 30.9% of all deaths in the first, second, and third years, respectively) (Figure 3B and 3C).

Figure 3 Three year overall, in-hospital, and out-of-hospital mortality rates after discharge from the index heart failure (HF) hospitalizations (2010–2012) in Taiwan. (A) Three year overall mortality rates after discharge. (B) The cause-specific in-hospital mortality rate during the index hospitalization and 3 year in-hospital mortality rates after discharge from the index hospitalizations. (C) Three year cause-specific out-of-hospital mortality rates after discharge.



and Supporting Information, *Figures S1* and *S2*). Non-cardiovascular disease-related deaths accounted for nearly 60% of all deaths during the entire study period. Approximately one-fourth of cardiovascular disease-related deaths were due to ischaemic heart diseases, and another one-fourth were HF related in general. The detailed information about cause-specific in-hospital and out-of-hospital mortality is shown in Supporting Information, *Tables S1* and *S2*.

Discussion

Our study provides nationwide, 'real-world' longitudinal follow-up estimates regarding annual incidence, healthcare utilization, treatment patterns, and mortality among incident hospitalized HF patients in contemporary Taiwan. There are four major observations. First, the age-standardized incidence of hospitalized HF declined over time during the study period, especially in women and people aged 55 years or older. However, the absolute number of incident hospitalized HF increased slightly, mainly due to the more pronounced increase in ageing populations. The slight increase in age-standardized incidence of hospitalized HF in people younger than 45 years of age merits attention. Second, among patients with incident hospitalized HF, the average number of admissions remained the same, while the proportions of patients with recurrent hospitalizations and ER visits decreased across the years. This finding indicates that patients with recurrent hospitalization beget hospitalization, thus a much higher risk. Third, we found that the cumulative 1 year mortality (including deaths during index hospitalization) was nearly 30% and the annual mortality remained above 10% in the second and third years. The persistently high mortality is in contrast to the decreased prescription of GDMT across the years. Finally, it is noteworthy that ~30% of deaths occurred outside the hospital and 60% of deaths were due to non-cardiovascular causes across the years. These sectors are often overlooked in clinical cares of HF from the country's perspective.

Incidence trends in hospitalized heart failure patients

There are several recent nationwide studies investigating the disease burden of HF worldwide that are similar to our study. Christiansen and colleagues reported a decreased incidence of new HF hospitalization among patients older than 50 years from 1995 to 2012 by using the Danish nationwide database.⁹ They also noted an increased incidence in the younger population. There are other similar findings between our work and the study of Christiansen *et al.* First, they found that the mean age of incident HF hospitalization of men was younger

than that of women (men: 72 vs. women: 78 years). In our study, the mean age at incident HF hospitalization was 72 and 76 years for men and women, respectively. Second, the percentage of female HF patients decreased from 49% in 1995 to 44% in 2012 in Demark. In our study, the percentage of women in the incident HF population decreased from 51% in 2010 to 49% in 2015. Third, the percentage of younger (≤ 50 years of age) patients in the HF population doubled from 3% in 1995 to 6% in 2012 in Demark, while the proportion of HF patients younger than 45 years increased from 3.4% in 2010 to 3.9% in 2015 in our cohort. Recently, Conrad *et al.*⁸ assessed the temporal trends in incidence of HF, based on both inpatient and outpatient diagnoses from the Clinical Practice Research Database in the UK. From 2002 to 2014, the age-standardized incidence of HF also decreased from 358 to 332 per 100 000 person-years. Likewise, the absolute number of new HF patients increased from 750 127 to 920 616. Overall, the findings about the decreasing trend in the age-standardized incidence of HF and the increased absolute number of incident HF patients were consistent across studies. The increase in incidence of HF in younger people could result from suboptimal awareness and less effective control of cardiovascular risk factors.

Treatment patterns

The prescription of all kinds of GDMT was still suboptimal in contemporary Taiwan. Compared with previous studies evaluating GDMT in HF populations, the prescription of combined ACEI/ARB and beta-blockers was almost half of that in the USA (61%)²⁴ and in older Japanese patients (67%),²⁵ but was similar to that in patients in India (30%).²⁶ Further, we showed that the use of these medications was more frequent in the first year and then declined in the second and third years. The declining trend in GDMT use is consistent with the declining proportions of patients with recurrent hospitalization and mortality. However, the annual rates of both recurrent hospitalization (>45%) and mortality (>10%) following 1 year after index hospitalization are still high. In other words, the warranty for freedom from recurrent hospitalization and mortality does not exist within 3 years following HF hospitalization. Efforts focusing on physicians and patients to enhance the long-term adoption of GDMT in patients with incident HF hospitalization should be exerted. In situations with improvements of haemodynamic status in HF patients, physicians should implement complete GDMT, which might not be tolerable initially, and uptitrate the doses to the optimal levels, rather than be inert to adjust or even withdraw GDMT.^{18,27} Long-term adherence to GDMT should be emphasized and routinely assessed for every HF patient no matter how stable he or she looks like.²⁸

Healthcare utilization

In contrast to the suboptimal prescription of GDMT, over 97% of incident HF patients had an average 35 outpatient visits annually throughout the 3 year follow-up period, which reflects the effective coverage of national health insurance programme in Taiwan. However, the extensive outpatient visits among patients with HF did not translate into better outcomes. In this nationwide claim-based study, we showed a high first-year readmission rate of 62.8%. This number is similar to the 59% first-year readmission rate in the claim-based population-level study of patients with incident hospitalization for HF in the Italian region of Lombardy in 2011.²⁹ Despite a decreasing trend in recurrent hospitalization and ER visits across the years, the readmission rate herein remained 46.9% at the third year following index hospitalization, which is even higher than the 10–44% first-year readmission rates observed in registry-based studies.^{11,29}

Regarding the causes of readmission, it is noteworthy that 60–66% of readmissions were due to non-cardiovascular causes across the 3 year follow-up period, whereas the proportions of readmissions directly due to HF declined from one-third in the first year to one-fourth in the third year. This finding is similar to the observation obtained among incident HF patients in Olmsted County from 1987 to 2006, which showed that 62% of readmissions were attributed to non-cardiovascular causes.³⁰ These findings indicate that non-cardiovascular co-morbidities make an important contribution to the burden of recurrent hospitalization in patients with HF. Both cardiovascular and non-cardiovascular co-morbidities should be meticulously managed to ameliorate the grave prognosis of HF.

Mortality

We found an 8.5% mortality rate during the index hospitalization among the incident hospitalized HF patients. This result is similar to those reported in a recent review, which showed that in-hospital mortality varied from 3% to 10% in multicentre HF registries and nationwide database.¹¹ Our finding regarding the mortality rate of 22.5% in the first year after HF discharge echoes previous studies in other countries.^{31,32} Chen *et al.*³³ conducted a nationwide cross-sectional study in the USA and reported that the risk-adjusted 1 year mortality in prevalent hospitalized HF patients was 31.7% in 1999 and 29.6% in 2008. Yeung *et al.*³² conducted a population-based cross-sectional study in Ontario, indicating that the 30 day and 1 year mortality rates were ~16% and 34% for hospitalized HF patients. In general, the 1 year mortality following discharge from HF hospitalization ranges from 9% to 34% among studies^{9,11} and shows no definite evidence of declining worldwide.

Our study further examined the 3 year longitudinal changes in the mortality in incident hospitalized HF patients. We herein showed that the mortality in the second and third years remained substantial (14.8% and 13.4% for surviving HF patients, respectively). According to official information from the Taiwanese government,³⁴ the annual mortality rate was 0.7% in the general population. The remaining >10% annual mortality within 3 years following hospitalization in HF patients highlights the importance of continued GDMT optimization and adherence in the long run.

There are another two features regarding mortality in HF patients worth mentioning. First, deaths due to non-cardiovascular causes accounted for nearly 60% of all deaths among our HF patients. This finding is consistent with the 60–66% readmissions being attributed to non-cardiovascular causes and reminds us that, in addition to GDMT, non-cardiovascular co-morbidities should be properly managed. Second, a consistent 30% of deaths occurred outside the hospital during the 3 year follow-up period. Even though the exact nature of these 'out-of-hospital' deaths was not certain, we assume that sudden cardiac death may contribute substantially. To curtail out-of-hospital death, optimization of GDMT and more widespread adoption of implantable cardioverter defibrillator (ICD) in symptomatic HF with reduced ejection fraction (HFrEF) patients should be emphasized. Because of the limitation in reimbursement criteria in Taiwan, there were only <1% HF patients undergoing ICD implantation throughout 3 year follow-up period.

Strengths and limitations

The major strength of this study is that this is the first study to use a contemporary population-level, country-specific database to explore the temporal trends in the incidence of hospitalized HF and to assess the longitudinal healthcare utilization, treatment patterns, and modes and causes of mortality within 3 years after the incident HF hospitalization in the Asian population. Most studies regarding the epidemiology of HF reported only the incidence and mortality and did not examine treatment patterns, healthcare utilization, and modes of mortality. Considering the high disease burden of HF worldwide and limited HF epidemiology information in Asia, results from this study fill this knowledge gap and could be more reliably generalized to other Asian countries and ethnic Chinese populations, compared with other surveys and registries. Further, the experiences learned from this study, like low GDMT implementation and persistently high rehospitalization and mortality despite high frequencies of outpatient visits, could be referenced for countries with similar universal health coverage and be taken as an example to refine the medical care of HF in a country-specific manner.

There are several limitations in this study. First, because there is no validation study to assess the accuracy of the

diagnostic codes for HF in outpatient claims in the NHIRD, our study only focused on hospitalized HF patients. In other words, the interest of our study is in new HF hospitalizations rather than *de novo* HF. To avoid including patients with recurrent HF hospitalizations, those with either inpatient or outpatient diagnoses of HF in the previous 1 year were excluded. Given the >97% rates of outpatient visits in patients with HF in Taiwan, the inclusion of patients with prior HF should be very limited in this study. Second, owing to the advances in pharmacological treatment, the proportion of HF patients managed exclusively in the outpatient setting is increasing. Hence, inpatient data could not capture all HF cases, particularly for milder ones. Third, because of the lack of information about left ventricular ejection fraction and other laboratory data like N-terminal pro-brain natriuretic peptide, we could not assess disease severity and distinguish the types of HF (preserved, mid-range, or reduced ejection fraction). This not only limits the comparability of this study but also prevents us from assessing whether more accurate ways of diagnosing HF could partly explain the decreasing trend in incidence of HF hospitalizations during these years. Fourth, we included only adult patients in this study, which precludes the applicability of our findings to non-adult populations. Finally, because terminal discharge (going home to die) is a well-adopted tradition in Taiwan, we therefore adjusted our definition of in-hospital mortality as death occurring during hospitalization or within 3 days after discharge. Therefore, some HF patients who died outside the hospital might be erroneously assigned as in-hospital deaths. The average 30% out-of-hospital mortality across the 3 year follow-up period might be underestimated.

Conclusions

By analysing the population-level, claim-based, country-specific NHIRD in Taiwan between 2010 and 2015, we showed a decreasing trend in the standardized annual incidence of HF hospitalization in people aged 55 years or older. On the other hand, both the standardized annual incidence of HF hospitalization in patients younger than 45 years of age and the absolute annual number of incident HF hospitalizations remain increasing, thus portending a rising burden on health care. The persistently high annual rates of mortality (>10%), mortality due to non-cardiovascular causes (~60% of all deaths), mortality occurring outside the hospital (~30% of all deaths), recurrent hospitalization (~50%), and hospitalizations due to non-cardiovascular causes (>60% of all hospitalizations) in the second and third years following initial HF hospitalization highlight the substantial unmet needs in HF management in Taiwan, where the universal health coverage programme has been successfully implemented for decades.

Our findings suggest that, in addition to more complete and widespread adoption of GDMT in patients with HF, the more appropriate use of ICD and control of non-cardiovascular risk factors should be emphasized to further curtail the healthcare burden of HF and improve its grave prognosis.

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Conflict of interest

T-D.W., S-T.H., C-Y.W., F-J.L., H-M.C., and F-Y.H. received a research grant sponsored by Novartis. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

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Author contributions

T-D.W., S-T.H., C-Y.W., F-J.L., and F-Y.H. designed the research, drafted the article, revised it critically for important intellectual content, and approved the final version to be published. H-M.C. performed the analysed data. T-D.W., F-J.L., and F-Y.H. provided critical methodological and statistical inputs. T-D.W. contributed to the clinical interpretation. F-Y.H. acted as a guarantor of the study.

Supporting information

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

Figure S1. The percentage of in-hospital mortality and out-of-hospital mortality contributing to total mortality.

Figure S2. The Kaplan–Meier curves of overall, in-hospital, and out-of-hospital mortality after discharge from the index heart failure (HF) hospitalizations (2010–2012) in Taiwan.

Table S1. 2010–2015 annual incidence of heart failure hospitalization in Taiwan, overall and sex-stratified.

Table S2. Baseline characteristics of patients with incident heart failure (HF) hospitalization between 2010 and 2012.

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