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Registry based analysis of cost-of-illness study among stage C heart failure patients at Hospital Queen Elizabeth II, Sabah, Malaysia

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ABSTRACT

Background: Numerous cost-of-illness studies of heart failure (HF) have been published in developed countries, but such knowledge is lacking in Malaysia. To fill the gap, this study estimated the cost of HF in Hospital Queen Elizabeth II (HQEII).
Methods: This study adopted an activity-based costing approach from Ministry of Health's perspective. Data of types and quantities of healthcare components utilized during patient treatment at HQEII between 2013 and 2015 were extracted from the medical records. Censored costing using inverse probability weighted estimators was applied to estimate the mean annual cost of HF.
Results: Ninety-two patients (85.9% male and 14.1% female) with a mean age of 59 (SD 3.5) years were included in this study. There were 451 outpatient clinic visits and 44 admissions, with a mean length of stay of 5.2 (SD 6.0) days. The mean and median annual cost of HF were US$ 5428, 95% CI (5311, 5545) and US$ 591, 95% CI (IQR 819) respectively in 2017. Inpatient cost accounted for 90.6% of the total cost and was mainly attributable to percutaneous coronary intervention (PCI) procedures and hospitalization.
Conclusion: PCI procedures and hospitalization were the cost drivers of HF. This finding indicates a possible opportunity for cost savings through efficient clinical management in the outpatient setting to prevent hospitalization.

Introduction

The high prevalence of heart failure worldwide has become an economic burden, affecting 26 million people worldwide [1]. Rates increase sharply with age. With the aging population, the economic burden of heart failure is expected to rise. Heart failure accounts for one to two percent of the total healthcare budget in many developed countries [2]. Heart failure leads to tremendous healthcare resource utilization and is therefore expensive to treat. Healthcare decision makers are interested to know the economic burden of heart failure so that they can determine research and funding priorities by highlighting areas where inefficiencies may exist and savings may be found. However, most studies on the epidemiology and economic burden of heart failure are from developed countries. For example, 29 out of 35 studies mentioned in a systematic review by Shafie et al. [3] reported the costs of heart failure in developed countries. Very few studies are from developing countries such as Malaysia, due to the lack of infrastructure and financial support for the establishment of easily accessible, continuous big data. Patient medical records are still the main data

Abbreviations: ASIAN-HF Registry, Asian Sudden Cardiac Death in Heart Failure Registry; CRF, Case Report Form; CI, Confidence Interval; CABG, Coronary Artery Bypass Graft; DRG, Diagnosis-Related Group; GLM, Generalized Linear Model; GDP, Gross Domestic Product; HQEII, Hospital Queen Elizabeth II; $S_c(t_i)$, Inverse Probability Of Being Censored; IPW, Inverse Probability Weighted; MOH, Ministry of Health; NYHA, New York Heart Association; PCI, Percutaneous Coronary Intervention; RM, Ringgit Malaysia; SD, Standard Deviation; n, Total Number of Eligible Patients; US$, US dollar.

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source of healthcare resource utilization for cost-of-illness studies in developing countries. For instance, studies reporting the economic burden of heart failure in Nigeria [4] and Brazil [5] were based on patient medical records.

Knowledge on the economic burden of heart failure in Malaysia is still lacking. Therefore, this study aims to estimate the mean annual cost of heart failure Stage C population in Hospital Queen Elizabeth II (HQEII) using the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry [6].

Methods

Overall design

This was a retrospective study utilizing the data of ASIAN-HF registry and medical records in HQEII. The ASIAN-HF registry is a prospective observational registry of patients with symptomatic heart failure (Stage C) in 11 Asian countries. This registry includes patients who are 18 years old and above, with a diagnosis of symptomatic heart failure (Stage C) with left ventricular systolic dysfunction and ejection fraction less than 40.0% on baseline echocardiography. Patients included in the registry must have had at least 1 episode of decompensated heart failure in the past 6 months that required hospitalization.

The registry provided a list of eligible patients which then was used to retrieve the patient's medical records. Healthcare resources utilization information was obtained from patients' medical records. This data was used to estimate the mean annual cost of stage C heart failure in HQEII.

Study location

The HQEII is one of the 4 government-subsidized hospitals located in Kota Kinabalu, the state capital of Sabah with a total population of 462,963 [7]. HQEII is a 400-bedded hospital that serves as the cardiology referral centre for Sabah state.

Ethical consideration

This study was approved by the Medical Research and Ethics Committee with National Medical Research Register registration number NMRR-15-1661-27979.

Population, sample and sampling procedure

Medical record of ninety-two patients recruited into the ASIAN-HF registry between 1 Jan 2013 and 31 May 2015 were included in this study. Data were excluded if the registry case report form (CRF) or patient medical records could not be retrieved.

Procedures in data collection

Identification of cost components

This study adopted/utilized an activity-based costing approach [8] to identify the relevant healthcare resources consumed by the registry patients. The costing pathway was outlined in Fig. 1. Care received in other hospitals or clinics was not taken into account due to difficulties in data tracing and retrieval.

Collection of cost data

Patient medical records were retrieved accordingly based on the patient name list as obtained from the registry. Healthcare resources utilization data such as number of outpatient visits, number of inpatient hospital stays due to heart failure, number of PCI procedures performed, number of diagnostic tests performed and medications utilised between 1 January 2013 and 31 December 2015 were extracted retrospectively from the medical records and documented in a Microsoft Excel file. Data for each resource utilization were then grouped chronologically in 6-month periods from recruitment date.

Cost methodology

This study adopted an annual prevalence-based cost-of-illness approach from the perspective of the Ministry of Health (MOH). In this study, the cost components were grouped according to the two main units of care: inpatient and outpatient. Inpatient cost (Eq. (1)) included healthcare resources such as hospitalizations due to heart failure, PCI procedures, diagnostic tests and medications utilized when patients were admitted into cardiac ward in HQEII, while outpatient cost (Eq. (2)) included outpatient clinic visits, diagnostic tests and medications utilized when patients visited the heart failure outpatient clinic in HQEII. Mean annual cost is the sum of inpatient and outpatient costs (Eq. (3)).

All identified cost items were included in the following general costing framework for analysing the cost of each component.

$$\begin{aligned}&\textbf{Mean annual inpatient cost}\\&=\textbf{Cost of hospitalizations}+\textbf{Cost of PCI procedures}\\&\quad+\textbf{Cost of diagnostic tests}+\textbf{Cost of medications supplied}\end{aligned}\tag{1}$$

$$\begin{aligned}&\textbf{Mean annual outpatient cost}\\&=\textbf{Cost of outpatient clinic visits}+\textbf{Cost of diagnostic tests}\\&\quad+\textbf{Cost of medications}\end{aligned}\tag{2}$$

$$\begin{aligned}&\textbf{Mean annual cost}=\textbf{Mean annual inpatient cost}\\&\qquad+\textbf{Mean annual outpatient cost}\end{aligned}\tag{3}$$

Sources and valuation of cost components

The cost of each component was calculated by multiplying the unit cost with the quantity utilized, as illustrated in Fig. 1. Cost of hospitalizations refers to the cost incurred when registry patients were admitted into the cardiac ward in HQEII due to heart failure, whereas the cost of heart failure outpatient clinic visits was calculated as the cost incurred when registry patients followed up at the heart failure outpatient clinics in HQEII. The cost of medications included both medications supplied during hospitalization and upon discharge as inpatient medication cost, and cost of medications supplied during heart failure outpatient clinic visits as outpatient medication cost. The cost calculations for medications included those medicines for other cardiovascular diseases such as hypertension, coronary artery disease, myocardial infarction and atrial fibrillation, as these are the most common comorbidities among patients with heart failure, in addition to being the primary causes of heart failure [1]. Cost of diagnostic tests was the cost incurred when diagnostic tests were performed on registry patients who were hospitalized and followed up at the heart failure outpatient clinics in HQEII. The cost of PCI procedures was the cost incurred when register patients underwent PCI procedures in HQEII.

The unit cost of cardiac ward per bed day and PCI procedures were valued based on the published work by Lee et al. [9], estimating the cost of elective percutaneous coronary intervention in five public cardiac centres in Malaysia which included HQEII. The unit cost of outpatient clinic visits and diagnostic tests (Appendix) were valued based on the MOH Full Paying Patient Tariff 2014 as provided by the Financial Department, whereas the unit cost of medication was valued based on the 2014 national price list of medicines as provided by the Procurement Unit of the Pharmacy Department of HQEII (Appendix). Information on quantity of healthcare resources utilized was obtained from patient medical records.

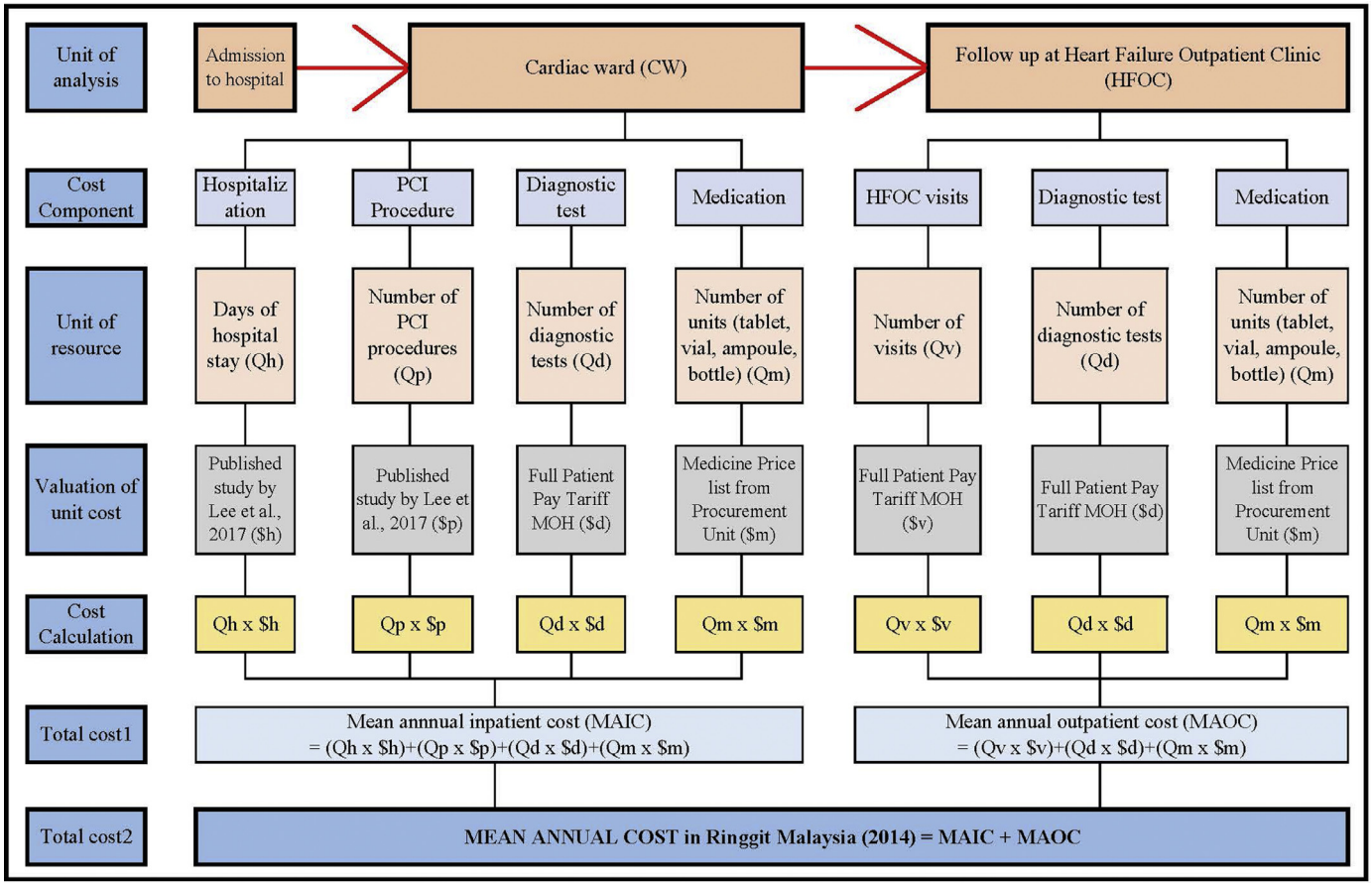

Fig. 1. Costing pathway for mean annual cost of heart failure based on activity-based costing approach.

Estimation of mean annual cost of heart failure

This study employed both standard costing and censored costing methods to estimate the mean annual cost of heart failure. The standard costing method includes simple calculations based on actual events. Censored costing method was applied because some patients were recruited at different point of time throughout the study period. Some were lost to follow up or deceased, resulting in incomplete follow up. Costs cannot be calculated simply by averaging the observed cumulative cost of all patients or of uncensored patients, as this will lead to misleading inference [10]. The exclusion of patients with incomplete cost data may reduce the effective sample size and consequently leads to inaccurate inference especially in studies estimating long term costs of diseases. Furthermore, conducting analysis by employing last observation carried forward and assuming no further incurred cost by patient after being censored would underestimate the actual cost. Censored costing using standard survival analysis method based on Kaplan-Meier estimator may produce bias [10]. Patients who accrued costs at higher rates tend to have larger total costs at both the survival time and censoring time, indicating a positive correlation between total cost and censoring [10]. Hence, this study has employed the inverse probability weighted (IPW) estimator method by Bang and Tsiatis [10] to estimate the healthcare cost of Stage C heart failure in HQEII.

The equation for calculating mean annual cost of heart failure using IPW method is as shown below:

$$\text{Mean annual cost} = \frac{1}{N}\left[\sum_i^n \frac{\Delta_i A_i(t_i)}{S_c(t_i)}\right] \quad (4)$$

N = total sample size of the study, including censored and uncensored patients.

t_i = time of fixed endpoint, death or loss to follow up for each patient

$A_i(t_i)$ = the cumulative cost until time t for patient i

$S_c(t_i)$ = the probability of being uncensored beyond time t

The costs incurred during each interval were calculated by summing up all the cost components such as cost of outpatient clinic visits, cost of hospitalizations, cost of PCI procedures, cost of medications and cost of diagnostic tests incurred within each interval for all censored and uncensored patients. The interval cost was then weighted by multiplying with the inverse probability of being censored $S_c(t_i)$ to adjust for censoring [11]. Consecutively, cost estimates were summed across intervals, then divided by the duration of follow up days accordingly and multiplied by 365 days to annualize a cost estimate for each patient. Subsequently all the weighted annual costs of all patients were summed up and divided by the total number of eligible patients (N) to obtain the mean annual cost of heart failure. For inpatient costs, the weighted annual costs were summed up and divided by the number of patients who experienced hospitalization events to obtain the mean annual inpatient cost. The justification of such calculation for the mean annual inpatient cost was due to the fact that only approximately one-third of the patients were hospitalized throughout the follow up period. Thus, dividing the weighted annual cumulative costs with total number of patients might underestimate the actual inpatient cost.

The annual healthcare cost of heart failure per patient in HQEII calculated was reported in this study as mean and median annual cost in ringgit Malaysia (RM) and US dollars (US$). Gross

domestic product (GDP) deflators were used to inflate the cost estimates to 2017 values [12]. Ringgit Malaysia were then converted to US dollars using the 2017 exchange rate of US$ 1 = RM 4.298 [13].

Statistical methods section

The categorical variables are presented as percentages and the continuous variable are presented in terms of mean with standard deviations [14]. Cost estimates are presented with mean and 95% confidence interval (CI).

Predictors of cost of heart failure

A generalized linear model (GLM) with log link and gamma distribution [15–17] was employed in this study to examine the unadjusted relationships between covariates such as patient demographic characteristics or clinical history and mean annual cost. In this study, certain patients accrued no or very low expenses throughout the follow up period, while some patients utilized more health care resources and hence accrued higher expenses, making the distribution of expenses skew strongly to the right [15]. Thus, if linear regression using ordinary least squares estimation (OLS) were used to examine the relationship between cost and covariates, the cost data would tend to exhibit variability, which then tends to increase as the mean cost increases, violating the assumption of homoscedasticity (constant variance) [18]. Hence, GLM with log link function and gamma distribution was used in this study to take both the non-negativity and skewed distribution of costs into account and to avoid heteroscedasticity in simple least-squares models [15,19]. Log link was used, as it restricted predicted costs to positive values and produced final model coefficients that were straightforward to interpret. Gamma distribution was used because of the skewed distribution of health care expenses [18]. The coefficient estimates derived from generalized linear models with logarithmic link functions are interpretable as the logarithm of the relative change in mean cost associated with a one-unit change in the predictor variable [15,18]. Coefficient estimates can be interpreted directly in a manner similar to that for the odds ratios obtained from the proportional hazards models [15]. Ratio below 1 indicates the percentage of reduction in the mean cost for each unit change in the predictor whereas ratio above 1 indicates the opposite [20]. A value of $p < 0.05$ was considered statistically significant. The statistical software SPSS version 21 was used to run this model.

Results

Epidemiology of the study population

Ninety-two patients (85.9% male and 14.1% female) with a mean age of 59 (SD 3.5) years were included in this study. Chinese patients accounted for slightly more than one-quarter of the study population, followed by Kadazan. A majority (78.3%) had secondary education or lower, and 58.7% earned a monthly household income less than RM 1000.00 (US$ 232.68).

A majority of the study population (73.9%) had a baseline New York Heart Association (NYHA) class I. A total of 67.4% of them were former or current smokers while 38.0% of them were former or current alcohol drinker. A majority (79.3%) were diagnosed with heart failure less than five years ago. The main aetiology of heart failure among the patients was non-ischaemic heart failure (52.2%). Dilated/idiopathic heart failure was the main non-ischaemic aetiology, affecting 22.8% of the study population. The prevalence of comorbidities among the study population was high: 58.7% with hypertension; 55.4% with coronary artery disease; 32.6% with

Table 1a
Health care resource utilization by patients with heart failure in Hospital Queen Elizabeth II throughout follow up period from the recruitment until 31 December 2015 and distribution of cost of heart failure according to the cost components (presented in RM).

Setting	Cost Component	Unit	Source of Utilization Data	Total Utilization Throughout Follow Up Period ($n = 92$)	Annual Utilization per Patient, Mean[a]	Unit Cost (RM)	Source of Unit Cost Valuation	Annual Cost per Patient (RM) [Mean (95% CI), Median (IQR)]	Annual Cost per Patient (RM) [Mean (95% CI), Median (IQR)]	Annual Cost per Patient (RM) [Mean (95% CI), Median (IQR)]
Outpatient	Clinic visits	Each	Medical Records	451	3.3 (2.4)	185.76	MOH Full Paying Patient Tariff 2014	Mean: 745 (625, 867) Median: 594 (451)	Mean: 2183 (1930, 2435) Median: 1337 (871)	Mean: 23329 (22826, 23833) Median: 1641 (2273)
	Medications	Tablet/Vial/ Ampoule		11,572	72.2 (24.3)	Refer Appendix	2014 national price list of medicines	Mean: 794 (667, 919) Median: 602 (582)		
	Diagnostic tests	Each		653	4.5 (6.1)	Refer Appendix	MOH Full Paying Patient Tariff 2014	Mean: 642 (512, 772) Median: 469 (686)		
Inpatient	Hospitalizations	Bed-day	Medical Records	44	1.6 (1.5)	932.57	published literature data [9]	Mean: 8564 (3630, 13500) Median: 3039 (6404)	Mean: 21147 (19532, 22761) Median: 3825 (10924)	
	Medications	Tablet/ Vial/ Ampoule		409	13.2 (9.3)	Refer Appendix	2014 national price list of medicines	Mean: 330 (147, 512) Median: 180 (291)		
	Diagnostic Tests	Each		746	29.0 (27.6)	Refer Appendix	MOH Full Paying Patient Tariff 2014	Mean: 2979 (1556, 4404) Median: 1171 (3049)		
	PCI Procedures	Each		6	0.6 (0.2)	16,078.09	published literature data [9]	Mean: 9273 (7183, 11365) Median: 0 (0)		

[a] Resource utilization in outpatient setting was divided by follow up period of each individual patient, multiplied by 365 and divided by total number of patients ($n = 92$) to obtain the mean annual resource utilization. For inpatient setting, only patients who experienced hospitalization events were taken into consideration.

diabetes mellitus; 20.7% with atrial fibrillation; and 16.3% with prior stroke.

Epidemiology of the patients who have hospitalization events and PCI procedures

Only 30 of 92 patients had hospitalization events throughout the study period (Table 3). Among these, 6 had undergone PCI procedures. Comparing to the study population, this patient group had a younger mean age (57.3 vs 59), lower proportion of male (83.3% vs 85.9%), lower proportion of baseline NYHA class I (56.7% vs 73.9%), lower proportion of heart failure less than 5 years (73.3% vs 79.3%), lower proportion of hypertension (56.7% vs 58.7%) and lower proportion of diabetes mellitus (30.0% vs 32.6%). A higher proportion of these patients had coronary artery disease (56.7%) and atrial fibrillation (23.3%).

Resource utilization of healthcare components

The mean follow-up period was 629 (SD 320) days. As illustrated in Table 1a and b, a total of 451 outpatient clinic visits were made throughout the period, with a mean of 3.3 (SD 2.4) visits per patient per year. Approximately one-third of the patients were hospitalized with a total of 44 admissions and mean length of hospital stay of 5.2 (SD 6.0) days. Patients visiting outpatient clinic consumed higher amount of medicines with a total of 11,572 items and a mean of 72.2 (SD 24.3) items per year, as compared to 409 medicines with a mean of 13.2 (SD 9.3) medicines by hospitalized patients. However, hospitalized patients utilized more diagnostic tests (746 tests) with a mean of 29 (SD 27.6) tests per year as compared to outpatient patients (653 tests) with mean 4.5 (SD 6.1) tests. A total of 6 procedures were performed throughout the follow up period.

Comparison of cost estimation using standard costing and censored costing methods

As shown in Table 2, there was no significant difference in the annual cost of heart failure estimated using both methods ($p = 0.702$).

Distribution of cost of heart failure according to the cost components

The annual data were aggregated across a study period between January 2013 and December 2015 (Table 1a and b). The mean annual cost of heart failure in 2014 was RM 23,329, 95% CI (22,826, 23,833) [US$ 5428, 95% CI (5311, 5545)]. Mean annual inpatient costs accounted for approximately 90.6% of the total cost of heart failure at RM 21,147, 95% CI (19,532, 22,761) [US$ 4920, 95% CI (4545, 5296)], followed by the mean annual outpatient cost (9.4%) of RM 2183, 95% CI (1930, 2435) [US$ 508, 95% CI (449, 567)]. Approximately forty-four percent of the mean annual inpatient costs were due to cost of PCI procedures, followed by cost of hospitalization (40.5%), cost of diagnostic tests (14.0%) and cost of medications (1.6%). The composition of cost components was rather equally distributed in outpatient cost. Each outpatient cost component accounted for approximately one-third of the mean annual outpatient cost.

Individual variation in the cost distribution

The annual cost of heart failure varied substantially among the study population, with the highest cost being approximately 303-fold higher than the lowest cost. The mean annual outpatient cost showed narrower range between RM 240 (US$ 36) and RM 8597 (US$ 1292) as compared to the mean annual inpatient cost which ranged broadly from RM 793 (US$ 119) to RM 64,145 (US$ 9642).

Table 1b
Health care resource utilization by patients with heart failure in Hospital Queen Elizabeth II throughout follow up period from the recruitment until 31 December 2015 and distribution of cost of heart failure according to the cost components (presented in USD).

Setting	Cost Component	Unit	Source of Utilization Data	Total Utilization Throughout Follow Up Period ($n = 92$)	Annual Utilization per Patient, Mean[a]	Unit Cost (USD)	Source of Unit Cost Valuation	Annual Cost per Patient (USD) [Mean (95% CI), Median (IQR)]	Annual Cost per Patient (USD) [Mean (95% CI), Median (IQR)]	Annual Cost per Patient (USD) [Mean (95% CI), Median (IQR)]
Outpatient	Clinic Visits	Each	Medical Records	451	3.3 (2.4)	27.92	MOH Full Paying Patient Tariff 2014	Mean: 173 (146, 202) Median: 138 (105)	Mean: 508 (449, 567) Median: 482 (314)	Mean: 5428 (5311, 5545) Median: 591 (819)
	Medications	Tablet/Vial/Ampoule		11,572	72.2 (24.3)	Refer Appendix	2014 national price list of medicines	Mean: 185 (155, 214) Median: 140 (135)		
	Diagnostic Tests	Each		653	4.5 (6.1)	Refer Appendix	MOH Full Paying Patient Tariff 2014	Mean: 149 (119, 180) Median: 109 (160)		
Inpatient	Hospitalizations	Bed-day	Medical Records	44	1.6 (1.5)	140.18	published literature data [9]	Mean: 1993 (845, 3141) Median: 707 (1490)	Mean: 4920 (4545, 5296) Median: 1378 (3935)	
	Medications	Tablet/Vial/Ampoule		409	13.2 (9.3)	Refer Appendix	2014 national price list of medicines	Mean: 77 (34, 119) Median: 42 (68)		
	Diagnostic Tests	Each		746	29.0 (27.6)	Refer Appendix	MOH Full Paying Patient Tariff 2014	Mean: 693 (362, 1025) Median: 273 (709)		
	PCI Procedures	Each		6	0.6 (0.2)	2416.78	published literature data [9]	Mean: 2158 (1671, 2644) Median: 0 (0)		

[a] Resource utilization in outpatient setting was divided by follow up period of each individual patient, multiplied by 365 and divided by total number of patients ($n = 92$) to obtain the mean annual resource utilization. For inpatient setting, only patients who experienced hospitalization events were taken into consideration.

Table 2
Comparison of annual cost estimation using standard costing and censored costing methods.

Variable	Standard costing method $n=92$ Median (IQR)	Censored costing method $n=92$ Median (IQR)	Z statistics[a]	P value[a]
Annual cost of heart failure (RM)	1622 (2480)[b]	1641 (2452)[b]	−0.38	0.702

[a] Mann-Whitney Test.
[b] Skew to the right.

Table 3
Subgroup analysis of the patients who have hospitalization events.

Patient Characteristics ($n=30$)		
Age (years), mean		57.3 (10.2)
Male, *n* (%)		25 (83.3%)
Baseline NYHA Class, *n* (%)	NYHA Class I	17 (56.7%)
	NYHA Class II	12 (40.0%)
	NYHA Class III	1 3.3%)
Duration of Heart Failure Diagnosis, *n* (%)	<5years	22 (73.3%)
	>5 years	8 (26.7%)
Aetiology of Heart Failure, *n* (%)	Ischaemic	16 (53.3%)
	Non-Ischaemic	14 (46.6%)
Comorbidity, *n* (%)	Hypertension	17 (56.7%)
	Coronary Artery Disease	17 (56.7%)
	Diabetes Mellitus	9 (30.0%)
	Atrial Fibrillation	7 (23.3%)

Table 4
Predictors of MAC of heart failure using GLM.

Variable	Model 1			
	Rate Ratio	95% CI%		*p*-value
		Lower	Upper	
Age	0.951	0.927	0.976	<0.0001*
Male	0.197	0.093	0.418	<0.0001*
Bumiputera	0.963	0.673	1.379	0.839
Education higher than secondary level	0.838	0.409	1.716	0.629
Monthly Income < RM 1000.00	0.950	0.524	1.720	0.865
Monthly Income RM 1000.00–2999.00	3.579	1.949	6.571	<0.0001*
Baseline NYHA Class I	0.903	0.474	1.723	0.758
Improving NYHA Class	0.904	0.438	1.869	0.786
Worsening NYHA Class	0.965	0.615	1.512	0.876
Ex & Current smoker	0.701	0.457	1.075	0.103
Ex & Current alcohol drinker	1.437	1.022	2.022	0.037*
Duration of heart failure diagnosis				
1 till 5 years	1.172	0.783	1.754	0.442
>5 years	1.762	1.072	2.896	0.026*
Ischaemic Aetiology	0.187	0.092	0.378	<0.0001*
History of Defibrillator	19.850	4.858	81.107	<0.0001*
Coronary Artery Disease				
Myocardial Infarction	0.850	0.568	1.271	0.428
Coronary Artery Disease with Prior PCI	0.511	0.331	0.787	<0.0001*
Atrial Fibrillation	0.712	0.379	1.339	0.292
Hypertension	1.881	1.459	2.425	<0.0001*
Post Stroke	0.734	0.509	1.057	0.097
Peripheral Artery Vascular Disease	0.694	0.310	1.556	0.375
Chronic Respiratory Disease	0.079	0.031	0.201	<0.0001*
Diabetes Mellitus	0.515	0.351	0.757	<0.0001*
Hospitalization	2.055	1.544	2.737	<0.0001*
Length of hospital stay	1.158	1.031	1.300	0.013*

Such a huge variation in the mean annual inpatient cost was due to the 44 hospitalizations that took place during the follow up period, involving less than one-third of the study population. This resulted in the huge variation of annual cost of heart failure from RM 240 (US$ 36) to RM 72,742 (US$ 10,934).

Determination of cost predictor using GLM

Table 4 displays the results of model III from GLM analysis. Thirteen variables were found to be significant predictors of the cost of heart failure. Older, male patients were significantly associated with a 4.9% and 80.3% reduction in MAC of heart failure, respectively, as compared to younger, female patients. Ischaemic heart failure was also significantly associated with 81.3% lower cost as compared to non-ischaemic heart failure. Patients with comorbidities such as coronary artery disease with prior PCI, chronic respiratory disease and diabetes mellitus were significantly associated with 48.9%, 92.1% and 48.5% reduction in cost of heart failure, respectively.

Others significant predictors of higher cost included earning between RM 1000 and RM 2999 monthly (rate ratio 3.579; 95% CI, 1.949 – 6.571; $P < 0.0001$) and former or current consumption of alcohol beverages (rate ratio 1.437; 95% CI, 1.022 – 2.022; $P=0.037$). Patients who were diagnosed with heart failure for more than five years (rate ratio 1.762; 95% CI, 1.072 – 2.896; $P=0.026$), had a history of defibrillator use (rate ratio 19.850; 95%

CI, 4.858 – 81.107; $P < 0.0001$) or had hypertension (rate ratio 1.881; 95% CI, 1.459 – 2.425; $P < 0.0001$) were significantly associated with higher cost of heart failure as well. Length of hospital stay (rate ratio 1.158; 95% CI, 1.031 – 1.300; $P = 0.013$) and hospitalization events (rate ratio 2.055; 95% CI, 1.544 – 2.737; $P < 0.0001$) were two additional significant predictors of higher costs of heart failure.

Discussion

Differences of cost estimates using both standard costing and IPW costing method

The differences of cost estimates calculated using both methods were insignificant. This could be due to fact that the study duration was not long enough to observe a significant difference. This was pointed out by Basu and Manning [21], as with short study duration there is no censoring, and the differential effects of grade on survival are small.

Variation in the individual cost distribution

The mean annual cost of heart failure ranged widely from RM 239.94 (US$ 36.07) per person to RM 72,742.16 (US$ 10,934.25). Such substantial variations in costs were due to the observation that slightly more than two-third of the study population were not hospitalized, which led to low expenses throughout the follow up period, whereas other subjects utilized more healthcare resources due to hospitalization. As such, the distribution of expenses was highly skewed to the left [15]. Similar patterns were reported in other studies [22,23].

Cost distribution by outpatient and inpatient cost components

The mean annual inpatient cost, RM 21,147, 95% CI (19,532, 22,761) [US$ 4920, 95% CI (4545, 5296)], estimated by this current study was similar to the cost estimates reported by Lee et al. [9]. The result also showed that the mean annual inpatient cost was approximately 10 times higher than mean annual outpatient cost, RM 2183, 95% CI (1930, 2435) [US$ 508, 95% CI (449, 567)], indicating that there is an opportunity for cost saving if healthcare providers can focus on providing good outpatient care of heart failure. Heart failure is classified by Agency for Healthcare Research and Quality as an ambulatory cares-ensitive condition, of which proper clinical management in the outpatient setting might avoid worsening condition [24]. Good outpatient care of heart failure is therefore important as it ensures early intervention which prevents complications or more severe diseases and hence reducing the hospitalization events. Shifting cost from inpatient care to outpatient care could possibly create opportunity of cost saving.

The total percentage of cost of diagnostic tests incurred in both inpatient and outpatient settings estimated in this current study was 15.5% of the total cost which was congruent to findings from other studies (range 6–18%) [5,25]. Cost of diagnostic tests incurred in inpatient setting was 4 times higher than in outpatient setting, similar to the findings reported by Ogah et al. [4]. Such observation was expected because hospitalized patients were generally sicker and therefore required frequent and more types of diagnostic tests for disease diagnosis and monitoring.

Furthermore, the cost of medications in outpatient setting was found to be as twice as high as in inpatient setting, as reported in previous study [4]. Possible explanation was the larger amount of medications needed to be supplied continuously throughout the year to patients following up at outpatient clinic as compared to the short supply of medications to hospitalized patients during hospital stay.

Cost driver

This study showed that the mean annual inpatient costs were the main driver of the cost of heart failure. The aforesaid result was generally in line with previous studies [2,4,9,22,26–36] which concluded that mean annual inpatient cost accounted for more than half of total cost of heart failure. It is important to note that these published literatures exhibited substantial variations in term of costing methodologies such as perspective, study population, costing methodology and healthcare system. The result of this study further extend these findings, suggesting that with the cost of PCI procedures and cost of hospitalization being the greatest contributor to the mean annual inpatient cost [2,27], the cost of PCI procedures and cost of hospitalization were therefore the main cost drivers of the total cost of heart failure.

The cost of PCI procedures accounted for 43.9% of the total cost of heart failure. This cost estimate does not include other expensive interventional procedures such as coronary artery bypass graft (CABG) and antiarrhythmic interventions. In other studies which included those expensive interventional procedures, the percentage of cost of procedures was as high as 49.7% [37] or even 72.0% [38] of the total cost, respectively, indicating that the cost of PCI procedures was the cost driver instead of cost of hospitalization.

Extent of usability of the ASIAN-HF registry in estimation of cost-of-illness of heart failure

The ASIAN-HF registry electronic database did not contain sufficient information on healthcare resource utilization. Additionally, medication profiles were overwritten each time the registry electronic data was updated and therefore did not contain much information on medications previously prescribed. Furthermore, the registry CRFs were only filled in whenever patients attended the follow up visits for the registry data collection purpose and did not capture any medications supplied or diagnostic tests performed during hospitalization and outpatient clinic visits. The main reason for all these limitations is that it is not the objective of this registry to estimate the economic burden of heart failure in the first place [6]. Therefore its protocol does not require its data collectors to document any healthcare resources consumed during either hospitalization or outpatient clinic visits.

Comparison of annual cost of heart failure according to national income across countries

Cost estimates reported by other studies performed in various countries were compared in the work by Shafie et al. [3]. The annual cost of heart failure varies across different countries, ranging from US$ 2496.00 to US$ 84,434.00 per patient [4,5,20,22,25,29,31–33,35,36,38]. Such findings have several implications. Firstly, the variation of cost across different studies can be viewed from the perspective of national income of the countries of the studies [39]. Lower income country such as Nigeria [4] generally spent less in heart failure than those high income countries [20,22,25,29,31,33,35,36,40] and upper middle-income countries [5,32,38]. Secondly, the cost estimates of heart failure cannot be generalized across different countries due to methodological differences. There are variations in terms of objectives, perspectives, costing methods and disease definition adopted across studies. For example, when compared to other studies which employed diagnosis-related group (DRG) codes [36] to estimate heart failure specific hospitalization costs, this study used an average cost per bed day [9] as the unit of hospitalization and included other cost components such as medications, diagnostic tests and PCI procedures to estimate the inpatient cost. Furthermore, a study by Agvall et al. [25] included only primary care patients, whereas

this study has included patients diagnosed in both inpatient as well as outpatient settings. Patients in primary healthcare have more stable heart failure and less need of inpatient care [25]. The costs incurred in an inpatient setting will certainly utilize more healthcare resources as compared to outpatient care and therefore incurs higher cost.

Determinant of cost predictors

This study used GLM to identify factors associated with higher costs to target those patients for cost-saving interventions. GLM was favoured over other types of regression models such as linear regression, linear regression on log-transformed cost and cox proportional hazard regression. The linear regression model was not employed as the assumption of uniform variance (homoscedasticity) required by this model is violated with cost data distribution which tends to be positively skewed. The drawback with linear regression on log-transformed cost is that the regression coefficients interpreted as the logarithm of the relative or proportional change in a median cost with a one-unit increase in a predictor variable. These results are difficult to interpret and may lead to bias in estimated predictions on the untransformed scale if the conditional distribution is either non-normal or heteroscedastic. Cox proportional hazard regression was not used as the assumption of non-informative censoring would potentially be violated.

This study found diagnoses of heart failure more than 5 years, or histories of defibrillator and hypertension were significantly associated with higher mean cost of heart failure. Hospitalization events and length of hospital stay were also significant predictors of higher mean cost of heart failure. These findings indicate that preventing hospitalization event can lead to cost saving. This could be achieved by providing efficient clinical management of heart failure at the outpatient setting.

This study found that age can significantly impact the cost of heart failure. The GLM showed that older patients were significantly associated with lower mean cost of heart failure. Such findings were however different than other studies [20,37,41] showing that age was not a significant predictor of the costs of heart failure. Note that in those studies, the mean ages of the study populations were younger than 65 years old. It is unclear whether the absence of such association was due to the lack of cost data for those patients aged 65 years and above in those studies. This older cohort may be too old or too sick to seek treatment in hospitals, and thus not be captured in the observation. However, in other studies which supported that age was indeed a significant predictor of lower cost of heart failure [27,42], the mean age of their study populations was above 75 years old.

Various studies have provided conflicting conclusions on which factors should be significant predictors of higher or lower cost of heart failure. For example, this study has shown that gender was a statistically significant predictor for lower mean cost of heart failure. Other studies [27,41,42], however, have demonstrated no association between gender and mean cost of heart failure. On the other hand, Wijeysundera et al. [20] reported that the mean cost of heart failure was higher for males. Such variation could be contributed to the fact that these studies have different study designs and objectives. For instance, Dunlay et al. measured the lifetime costs of medical cost after heart failure diagnosis, while Wijeysundera et al. estimated one-year post-discharge health care costs [20].

Study limitations

The present study bears some limitations. The costs of heart failure estimated by this study can be generalized to patient population with NYHA Class I and Class II heart failure. Nevertheless, these cost estimates cannot be generalized in a patient population with more severe conditions, as the cost of heart failure increases with disease severity [29,31,41,43]. Furthermore, the generalizability is also limited by the hospital characteristics. It is important to note that government-subsidized hospitals in Malaysia consists of state hospitals, major specialist hospitals, minor specialist hospitals, special hospital/institution, and non-specialist hospitals which differ in terms of types and extent of speciality of services provided [44]. A study estimating cost of elective percutaneous coronary intervention in five public cardiac centres in Malaysia conducted by Lee et al. [9] reported that the average hospitalisation cost ranged between RM 17,756.75 (US$ 2669.10) and RM 22,391.37 (US$ 3365.76). The difference in cost estimates was attributed to different ownership and administration characteristics of the participated cardiac centres. Moreover, differences in the ethnic background of the Sabah population might compromise the extent of its generalizability to the population in Peninsular Malaysia.

Another study limitation is its retrospective nature. This study was unable to determine whether the diagnosis was a primary or secondary diagnosis of heart failure. Cost estimates could differ between primary and secondary diagnosis of heart failure. Besides, this study did not capture healthcare resource utilization incurred if patients seek medical treatment in other government hospitals or clinics. Therefore, this may underestimate the true economic burden of heart failure.

Conclusion

The mean annual cost of heart failure in HQEII in 2017 was estimated at RM 23,329, 95% CI (22,826, 23,833) [US$ 5428, 95% CI (5311, 5545)]. The costs of PCI procedures and hospitalizations were the main cost drivers for heart failure. Combining with the prevalence data of heart failure, these cost estimates will allow the healthcare providers to estimate the economic burden of heart failure.

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Conflict of interest

None declared.

Ethical approval

This article did not contain any studies with human participants performed by any of the authors.

Informed consent

Informed consent was not needed as there was no human participant involved in this study.

Appendix

Table A1
Unit price of diagnostic test.

Diagnostic Test	Unit Cost Per Test (RM in 2017)	Unit Cost Per Test (US$ in 2017)
Blood Gas Test	100.62	15.12
Blood Urea Serum Electrolytes Test	58.82	8.84
Bone Chemistry Calcium, Phosphate & Magnesium Test	85.14	12.80
Cardiac Enzyme Test	74.30	11.17
Chest Xray	61.92	9.31
Coronary Angiogram	619.19	93.07
Cortisol Test	85.14	12.80
Doppler Ultrasound - Arteries Per Region	386.99	58.17
Echocardiogram	356.03	53.52
Electrocardiogram	123.84	18.61
Fasting Blood Glucose Test	30.96	4.65
Ferritin Test	201.24	30.25
Full and Microscopic Examination of Urine Test	61.92	9.31
Full Blood Count Test	61.92	9.31
Gamma Glutamyl Transferase Test	46.44	6.98
Holter Monitoring (24 Hours Echocardiogram Monitoring)	707.42	106.34
Iron Test	38.70	5.82
Lipid Test	167.18	25.13
Liver Function Test	154.80	23.27
Pacemaker Follow Up	445.82	67.01
Platelet Agregation Test	162.54	24.43
Platelet Function Test	518.88	78.00
Proothrombin Time/Partial Thromboplastin Time/International Normalised Ratio Test	46.44	6.98
Random Blood Sugar Test	30.96	4.65
Stress Test	588.23	88.42
Thyroid Function Test	154.80	23.27
Thyroid-Stimulating Hormone Test	92.88	13.96
Thyroxine 3 Test	92.88	13.96
Thyroxine 4 Test	61.92	9.31
Total Bilirun Test	30.96	4.65
Total Iron Binding Capacity Test	46.44	6.98
Troponin I Test	265.63	39.93

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