REGISTRY BASED ANALYSIS OF COST-OF-ILLNESS STUDY AMONG STAGE C HEART FAILURE PATIENTS AT HOSPITAL QUEEN ELIZABETH II, SABAH, MALAYSIA

by

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LIST OF ABBREVIATIONS

ACA/AHA	American College of Cardiology /American Heart Association
ADHERE	Acute Decompensated Heart Failure National
AF	Atrial Fibrillation
AIC	Akaike's information criterion
APPL	Approved Purchase Product List
ASIAN-HF	Asian Sudden Cardiac Death in Heart Failure
ATR	Alberta Trauma Registry
BIC	Bayesian Information Criterion
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCU	Critical Care Unit
CI	Confidence Interval
CRD	Chronic Respiratory Disease
CRF	Case Report Forms
CRT-BIV	Cardiac Resynchronization Therapy with Biventricular Device
CW	Cardiac Ward
DM	Diabetes Mellitus
ECG	Electrocardiography
ESC	European Society of Cardiology
GLM	Generalized Linear Model
HES	Hospital Episode Statistics
HFOC	Heart Failure Outpatient Clinic
HFpEF	Heart Failure with Preserved Ejection Fraction

HFrEF	Heart Failure with Reduced Ejection Fraction
HPT	Hypertension
ICD	Implantable Cardioverter-Defibrillator
ICU	Intensive Care Unit
Int$	International Dollars
IPW	Inverse Probability Weighted
MAC	Mean Annual Cost
MAIC	Mean Annual Inpatient Cost
MAOC	Mean Annual Outpatient Cost
MDC	Major Diagnostic Classification
MOH	Ministry of Health
MI	Myocardial Infarction
N	Sample Size
NHS	National Health Services
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
OLS	Ordinary Least Squares Estimation
OPTIMIZE-HF	Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure
PAVD	Peripheral Arterial Vascular Disease
PCI	Percutaneous Coronary Intervention
QALY	Quality-Adjusted Life-Year
SD	Standard Deviation
SE	Standard Error

KAJIAN KOS PENYAKIT BERDASARKAN ANALISA DAFTAR PENYAKIT DI KALANGAN PESAKIT KEGAGALAN JANTUNG TAHAP C DI HOSPITAL QUEEN ELIZABETH II, SABAH, MALAYSIA

ABSTRAK

Banyak kajian kos penyakit kegagalan jantung telah diterbitkan di negara-negara maju tetapi terdapat kekurangan pengetahuan tersebut di Malaysia. Pengetahuan tersebut dapat membantu pihak pembuat keputusan kesihatan mengenal pasti kos utama kegagalan jantung. Bagi mengisi jurang tersebut, objektif utama kajian ini adalah untuk menganggarkan kos purata tahunan kegagalan jantung tahap C di Hospital Queen Elizabeth II berdasarkan data daftar penyakit ASIAN-HF. Objektif spesifik adalah untuk mengesahkan data daftar penyakit ASIAN-HF dan untuk meneroka epidemiologi populasi daftar penyakit tersebut. Dalam fasa pertama, pangkalan data elektronik daftar penyakit tersebut telah disahkan dari segi kesempurnaan dan ketepatan dengan membandingkannya dengan borang laporan kes daftar penyakit. Fasa kedua menganggarkan kelaziman kegagalan jantung tahap C dan dan mengenal pasti ciri demografi pesakit, sejarah klinikal, komorbiditi dan peristiwa hasil di kalangan pesakit dengan kegagalan jantung peringkat di Hospital Queen Elizabeth II. Dalam fasa ketiga, data penggunaan sumber penjagaan kesihatan seperti kemasukan ke hospital, lawatan klinik pesakit luar, prosedur intervensi koronari perkutan (PCI), ubat-ubatan dan ujian diagnostik yang berlaku antara 1 Jan 2013 dan 31 Disember 2015 telah diambil secara retrospektif daripada rekod perubatan dan digabungkan dengan data epidemiologi dari fasa kedua untuk menganggarkan kos purata tahunan kegagalan jantung dari perspektif Kementerian Kesihatan Malaysia. Kos unit sumber-sumber tersebut dinilai berdasarkan kajian yang diterbitkan dan tarif

bayaran penuh pesakit kerajaan. Pengekosan tertapis berdasarkan penganggar kebarangkalian songsang digunakan untuk menganggarkan kos tahunan purata kegagalan jantung yang dinyatakan dalam Ringgit Malaysia (RM) 2014. Kajian pengesahan menunjukkan bahawa pangkalan data elektronik daftar penyakit tersebut mempunyai tahap kesempurnaan (99.9%) dan ketepatan (97.8%) yang baik. Dalam kajian epidemiologi, 74.8% daripada pesakit mempunyai nilai dasar New York Heart Association (NYHA) kelas I. Sepanjang tempoh kajian, terdapat 451 lawatan klinik pesakit luar dan 44 kemasukan ke hospital dengan purata tempoh penginapan 5.2 (6.0) hari. Kos tahunan purata kegagalan jantung ialah RM 15,071.00. Pemandu kos utama kegagalan jantung adalah kos pesakit dalam yang menyumbang 90.6% (RM 13,661.00) daripada jumlah kos. Kira-kira 43.9% daripada kos pesakit dalam adalah disebabkan oleh prosedur PCI, diikuti dengan kemasukan ke hospital (40.5%), ujian diagnostik (14.0%) dan ubat-ubatan (1.6%). Kos meningkat dari NYHA kelas I hingga kelas II. Kajian mendapati prosedur PCI dan kemasukan ke hospital adalah pemandu utama kos kegagalan jantung. Maklumat mengenai kos purata tahunan kegagalan jantung tahap C dan bilangan pesakit dengan kegagalan jantung tahap C akan membantu Kementerian Kesihatan Malaysia dalam menganggarkan kos keseluruhan kegagalan jantung tahap C dan setereusnya memperuntukkan pembiayaian yang mencukupi untuk tujuan rawatan.

REGISTRY BASED ANALYSIS OF COST-OF-ILLNESS STUDY AMONG STAGE C HEART FAILURE PATIENTS AT HOSPITAL QUEEN ELIZABETH II, SABAH, MALAYSIA

ABSTRACT

Numerous cost-of-illness studies of heart failure have been published in developed countries but such knowledge is currently lacking in Malaysia. Such knowledge can assist the healthcare decision makers to identify the cost driver of heart failure. To fill the gap, the main objective of this study was therefore to estimate the mean annual cost of Stage C heart failure in Hospital Queen Elizabeth II based on the ASIAN-HF registry data. The specific objectives were to validate ASIAN-HF Registry data, to estimate the prevalence of Stage C heart failure and to identify the patient demographic characteristics, clinical history, comorbidities and outcome events among registry patients with Stage C heart failure in Hospital Queen Elizabeth II. In the first phase the registry electronic database was validated in term of completeness and accuracy by comparing them with the registry case report forms. In the second phase the epidemiology of the study population was explored based on the validated registry data. In the third phase health care resources utilization data such as hospitalizations, outpatient clinic visits, percutaneous coronary interventions (PCI) procedures, medications and diagnostic tests that incurred between 1 Jan 2013 and 31 December 2015 were extracted retrospectively from the medical records and combined it with earlier epidemiology results in phase two to estimate the mean annual care cost of heart failure from the perspective of Ministry of Health Malaysia. Unit costs of each of the resources were valued based on published studies and government Full Patient Paying tariff. Censored costing using inverse probability weighted estimators was

applied to estimate the mean annual cost of heart failure which was expressed in Malaysia Ringgit 2014. The validation study showed that the registry electronic database has a good degree of completeness (99.9%) and accuracy (97.8%). Despite unable to provide resource utilization data, the ASIAN-HF registry provided a good starting platform to help to retrieve patient medical records for the same purpose. In the epidemiology study, 74.8% of the patients have baseline NYHA Class I. During the study period there were 451 outpatient clinic visits and 44 admissions with mean length of stay of 5.2 (6.0) days. The mean annual cost of heart failure was RM 15,071.00. The main driver of cost of heart failure was inpatient cost which accounted for 90.6% (RM 13,661.00) of the total cost. Approximately 43.9% of the inpatient cost was due to PCI procedures, followed by hospitalization (40.5%), diagnostic test (14.0%) and medications (1.6%). The cost increased from NYHA class I to class II. This study found that PCI procedures and hospitalization were the main cost drivers of heart failure. Information on the mean annual cost of Stage C heart failure and the number of patients with Stage C heart failure would help the MOH to estimate the total cost of Stage C heart failure and therefore to allocate sufficient funding for treatment purpose.

CHAPTER 1: INTRODUCTION

1.1 Pathophysiology of heart failure

Heart failure is a complex syndrome characterised by reduced heart efficiency in maintaining a sufficient cardiac output to meet the body's demands for blood and oxygen as well as to accommodate venous return (American Heart Association, 2018). Consequently the heart has to contract stronger to pump blood and over time the heart muscles get bigger. The increase in heart muscle mass helps the heart to pump even faster which consequently increases the cardiac output. At the same time the compensation mechanism takes places by which the blood vessels get narrow to maintain the blood pressure and adequate tissue perfusion. This is done by diverting blood away from other organs such as kidney towards heart. Such temporary compensation mechanism is beneficial initially but it can worsen the heart condition in the long term eventually result in heart failure (Kemp and Conte, 2012).

Heart failure is defined in term of which ventricular where the impairment occurs. If dysfunction is seen in left ventricular, the heart failure is termed as left ventricular dysfunction and vice versa for dysfunction affecting right ventricular (Nicholson, 2014). Besides heart failure can also be defined in terms of where the impairment is in the phases of the cardiac cycle – either during contraction (systole) or relaxation (diastole). The former is termed as left ventricular systolic dysfunction and the latter is called as left ventricular diastolic dysfunction.

1.2 Clinical classification and disease progression

Heart failure can be either classified based on New York Heart Association (NYHA) (Committee and Association, 1979) classification system or American College of Cardiology (ACC) and the American Heart Association (AHA) classification system

(Hunt et al., 2001). The former refers the heart failure condition based upon the functional status of the patient due to heart failure whereas the latter classification system emphasizes on the structural defect of heart and the progression of the disease process.

Patients with NYHA Class I heart failure have cardiac disease can perform ordinary physical activities without any limitations or symptoms. Those in NYHA Class II have a slight limitation in performing ordinary physical activity but will result in fatigue, palpitation, dyspnoea or angina. However they are comfortable at rest. NYHA Class III patients are still comfortable at rest but have marked limitation of physical activity with symptoms occurring with less than ordinary activity. NYHA Class IV patients may have symptoms even at rest and cannot to carry out any physical activity without symptoms.

Patients in Stage A are those with risk factors such as hypertension, obesity and diabetes as well as family history who are at high risk for developing heart failure but do not have any structural disorders of the heart. Stage B patients have structural disorder but do not show any symptoms of heart failure. Those in Stage C have past or current symptoms of heart failure which are associated with underlying structural heart disease. Stage D patients are those who have end-stage heart failure who require specialized treatment strategies.

1.3 Global epidemiology of heart failure

Heart failure has become a major public health problem worldwide. It is estimated that heart failure is currently affecting 26 million people worldwide (Ambrosy et al., 2014). Approximately 6.5 million adults in the United States have heart failure between 2011 and 2014, an increase of 14.0% from 5.7 million between 2009 and 2012 (Benjamin

et al., 2017). Worldwide, the prevalence of heart failure is ascending at alarming rate. The prevalence of heart failure in the United States is projected to increase by 46.0% from 2012 to 2030, resulting in more than 8 million aged above 18 years old with heart failure (Heidenreich et al., 2013). About 44.0% patients with newly diagnosed cardiovascular disease in sub-Saharan Africa have heart failure (Sliwa et al., 2008) and are much younger age than those in the United States and Europe (Damasceno et al., 2012). The incidence of heart failure increased sharply with age from 5.1 - 15.4 per 1000 person-years in those aged 65 through 69 years old to 41.1 - 42.5 per 1000 person-years in those aged 85 years and older (Barker et al., 2006, Bleumink et al., 2004, Gottdiener et al., 2000). The elderly especially those with several comorbidities such as hypertension, ischaemic heart disease and diabetes face higher risk of heart failure. Heart failure has poor prognosis which gets worse as age advances (Senni et al., 1999, Ho et al., 1993b, Gerber et al., 2015). Patients with heart failure aged above 65 years old have lower survival rate than those aged below 65 years old (Aranda et al., 2002). It has high mortality rate and is 6 to 7 times higher than of the population without heart failure (Ho et al., 1993a). Although survival after heart failure diagnosis has improved between 1979 and 2000 (Roger et al., 2004), only 57.0% to 77.0% survived 1 year after the incident heart failure (Senni et al., 1999, Ho et al., 1993b, Bleumink et al., 2004).

1.4 Economic burden of heart failure

Heart failure can cause heavy economic burden to a country. It was estimated that the global economic burden of heart failure was at $108 billion per year in 2012 (Cook et al., 2014). Patients with heart failure are more frequently admitted to hospital compared with diabetic patients which are mainly treated in primary health care and

therefore incurring a higher cost. This is supported by a study which recruited 1077 patients with heart failure in Olmsted County of which 83.0% patients were hospitalized at least once and 43.0% hospitalized at least 4 times (Dunlay et al., 2009). The lengths of hospital stay due to heart failure range from 4 to 20 days (Gheorghiade et al., 2006, Steinberg et al., 2012, Nieminen et al., 2006, Atherton et al., 2012, Maggioni et al., 2010, Sato et al., 2013, Adams et al., 2005, Kuwabara et al., 2010). Heart failure has high readmission rate (Cowie et al., 1997). A study reported that approximately one-fifth of patients were readmitted after first diagnosis of heart failure during a 6-month follow up (Smith et al., 2003). The main causes of high readmission rate were recurrent heart failure, primary diagnosis of heart failure, heart failure precipitated acute myocardial infarction and uncontrolled hypertension (Gooding and Jette, 1985, Vinson et al., 1990). Besides, short duration of hospital stay and early discharge were reported to be another factor of high readmission (Gooding and Jette, 1985). Inadequate medical management, patient incompliance with medications, lack of social support system and inadequate follow up after discharge were the factors identified for high readmission rate among patients with heart failure (Gooding and Jette, 1985, Vinson et al., 1990). Heart failure is therefore accounted for 1.0% - 2.0% of the total health care budget in many developed countries and is expected to rise in the future (Berry et al., 2001).

1.5 Use of registries

Decision makers increasingly request more information on the epidemiology and economic burdens of heart failure before deciding on health care resource allocation. Such information could be obtained from various data sources. Disease registry is one of the data sources which holds the promise of providing information over a clinical

decision support such as physician's written notes, prescriptions, medical imaging, laboratory, pharmacy, insurance, disease surveillance and population health management. Registry is defined an organized, observational system that collects long term data for a population with a particular disease or condition for scientific, clinical, or policy purposes (Gliklich et al., 2014).

In the past decade, the registry data has been incorporated as part of burden of illness studies such as leukaemia (Lee et al., 1998), chronic obstructive pulmonary disease (Alkins and O'Malley, 2000), arrhythmias (Foutz and Sayre, 2000, Greenberg et al., 2002), end-stage renal disease (Holohan, 1995) and coronary artery bypass grafting (Boyd et al., 1999), as part of cost-effectiveness studies such as prenatal screening (Cunningham and Tompkinson, 1999), as part of cost-utility studies as cost per quality-adjusted life-year (QALY) (Kobelt et al., 2002) for cataract surgery and cost per QALY for lung transplantation (Ramsey et al., 1995). Registry data is retrospectively employed in pharmacoeconomics analysis include clinical outcomes, discharge or admission data for which cost data is separately calculated. Furthermore registry data also helps to identify patients for economic analysis which depend on retrospective review of patient medical records.

The use of registries in collecting pharmacoeconomics data in the last decade has been encouraging as more nations have increasingly demanded such information for use in regulatory procedures such as for pricing and reimbursement decisions (Kennedy and Craig, 2004).

1.6 ASIAN-HF registry

The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry is a prospective observational registry of patients with symptomatic heart failure (Stage C) in 11 Asian countries. This registry involves 44 medical centres in Malaysia, Singapore, Indonesia, Japan, China, India, Hong Kong, Korea, Philippines, Taiwan and Thailand. There were 4 medical centres in Malaysia participating in this ASIAN-HF registry; National Heart Institute, University Malaya Medical Centre, Sarawak General Hospital and Hospital Queen Elizabeth II. This registry recruits patients who are 18 years old and above, with a diagnosis of symptomatic heart failure (Stage C) regardless of functional status with left ventricular systolic dysfunction and ejection fraction less than 40.0% on baseline echocardiography. Patients need to have at least 1 episode of decompensated heart failure in the past 6 months that required a hospital admission or follow up in an outpatient clinic. Patients are recruited over 2 years and followed at 6 months, 1 year, 2 years and 3 years for outcomes of death or hospitalization. There is a central event adjudication committee which will adjudicate the mode of death and cause of hospitalization using pre-specified criteria. This registry collects data on demographic characteristics, clinical history, NYHA functional status, date of heart failure diagnosis, prior cardiovascular investigations and clinical risk factors.

1.7 Problem statement

Heart failure has become an epidemic worldwide in the last decades and its burden is increasing. It was estimated that the overall annual cost of heart failure in Malaysia was $ 194.00 million (Cook et al., 2014) in 2012, which accounted for 1.9% of Malaysia's total health expenditure ($ 10,747.00 million / RM 41,913.00) in 2012 (Central Bank of Malaysia, 2018, Ministry of Health Malaysia, 2018). Heart failure

therefore requires tremendous amount of health care resource utilization and therefore is expensive to treat. Health care decision makers are interested to know the economic burden of heart failure so that they can be guided in decision-making in future budget allocation and drafting effective health care strategy to curb such epidemic. However most studies on the epidemiology and economic burden of heart failure are from 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. These findings are not suitable to be applied on local setting due to differences in demographic background and health care policies. The knowledge on the epidemiology and economic burden of heart failure in Malaysia is still lacking.

There was only 1 published literature (Chong et al., 2003) reported the prevalence of heart failure (6.7%) in a single hospital in Malaysia back in 2003 but it did not estimate the cost of heart failure. Besides the findings on the prevalence and epidemiology of heart failure were not generalized enough for Sabah's population. Population in Sabah and Peninsula have different racial and demographic background which could affect health outcomes (Lua et al., 2007). Besides its limited generalizability was also due to its short duration of 4 weeks prospective study of acute medical admission of primary diagnosis of heart failure to the Emergency Department of Hospital Kuala Lumpur. No new study was conducted since 2003 to explore the epidemiology of heart failure in Malaysia. On the other hand, registry has potential to fill the knowledge gap by providing the necessary real world data to assist the decision makers in future budget allocation and strategy planning to effectively curb the rising epidemic of heart failure. Despite the advantages of registry, establishing and maintaining a registry is however too costly for developing countries like Malaysia to

afford. The quality of the registry data is too important to be ignored and hence its utilization in health care decision requires extra caution.

1.8 Research Question

The extent of ASIAN-HF registry in Hospital Queen Elizabeth II in providing useful information on the epidemiology of Stage C heart failure and health care resource utilization is unexplored. There is a need to determine the prevalence of Stage C heart failure in Hospital Queen Elizabeth and to assess the patient demographic characteristics, clinical history, comorbidities and outcome events among registry patients with Stage C heart failure in Hospital Queen Elizabeth II. However, before the registry data can be confidently utilized to provide the epidemiological and health care resource utilization data, it is necessary to explore the validity of the registry electronic data in terms of accuracy and completeness. Furthermore this study also sought to explore the extent of using the registry data to estimate the cost of illness of Stage C heart failure Hospital Queen Elizabeth II. Lastly, combining the epidemiological and health care utilization data, this study also sought to estimate the mean annual cost (MAC) of Stage C heart failure population in Hospital Queen Elizabeth.

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology of heart failure

2.1.1 Incidence

Incidence refers to the number of new cases observed over a specified period in a defined population. The age-adjusted incidence estimates of heart failure range from 3.4 to 26.2 cases per 1000 person-years in men and from 2.1 to 14.6 cases per 1000 person-years in women (Gerber et al., 2015, Gottdiener et al., 2000, Ho et al., 1993b, Roger et al., 2004, Barker et al., 2006). On the other hand, the crude incidence estimates range from 1.4 to 17.6 cases per 1000 person-years s in men and from 1.3 to 12.6 cases per 1000 person-years in women (Bleumink et al., 2004, Cowie et al., 1999).

The incidence of heart failure increases sharply with age from 5.1 - 15.4 per 1000 person-years in those aged 65 through 69 years old to 41.1 - 42.5 per 1000 person-years in those aged 85 years and older as reported by published population-based studies (Barker et al., 2006, Bleumink et al., 2004, Gottdiener et al., 2000). The Hillingdon study which identified new cases of heart failure based on acute hospital admissions due to heart failure and referral from general practitioners over 20 months period (Cowie et al., 1999) reported lower incidence estimates for each age group as compared to those population-based studies whose study populations were randomly selected from the general population with longer study periods (Barker et al., 2006, Ho et al., 1993b, Bleumink et al., 2004, Gottdiener et al., 2000). The increasing trend in the incidence of heart failure with age is also exhibited in both genders in prior studies (Cowie et al., 1999, Barker et al., 2006, Senni et al., 1999, Ho et al., 1993b, Bleumink et al., 2004). Gerber et al. (2015) who evaluated incidence trends in heart failure with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF) concluded that the latter was more predominant in women.

Majority of the studies reported that the incidence of heart failure was higher in men than women (Cowie et al., 1999, Barker et al., 2006, Roger et al., 2004, Ho et al., 1993b, Bleumink et al., 2004, Gottdiener et al., 2000, Gerber et al., 2015) but a few studies established that the trend of incidence behaved differently over decades. The Framingham study (Ho et al., 1993b) reported that there was a significant drop by 31.0% to 40.0% in the incidence of heart failure between 1948 and 1988 among women but such decline was less pronounced in men for the same period of time. The possible explanation was a decline in the prevalence of hypertension (Burt et al., 1995) which was the main risk factor of heart failure in women (Ho et al., 1993b, Levy et al., 1997) and improved pharmacological management of hypertension has resulted in the reduction of incidence of heart failure among women. On the other hand, the improvement in the clinical and surgical management of ischaemic heart disease such as myocardial infarction (Stevenson et al., 1993), a main risk factor for heart failure among men (Ho et al., 1993b), which has subsequently increased surviving pool of older patients with residual myocardial damage who were more susceptible to left ventricular dysfunction, therefore putting them at higher risk of developing heart failure later in their lives. However there were some studies which reported conflicting findings. Another population-based cohort study in Olmsted County, United States between 1979 and 2000, the Rochester study (Roger et al., 2004) reported that the incidence of heart failure did not change significantly over 22 years in both genders. Advantages of this study as compared to the earlier Framingham study were it used both Framingham guideline and ejection fraction examination to identify patients with heart failure from outpatient setting (42.0%) and it has larger sample size than the Framingham study with sufficient power to detect a change in the incidence of heart failure of 0.8% per year. The lack of significant change in the incidence observed over

long term period was also demonstrated by a population-based study of two cohorts in 1981 and 1991 (Senni et al., 1999). The design of this study may however possibly underestimate the incidence estimates due to smaller size of the study population and patients with heart failure were identified based on signs and symptoms information abstracted from medical record review. In a study comparing the incidence of heart failure between two cohorts in 1970-1974 and 1990-1994 among persons aged 65 years old and above using the data from the Kaiser Permanente system (Barker et al., 2006), there was an 14.0% increase in the incidence which was greater for men and for older persons. The Olmsted study (Gerber et al., 2015) found a substantial decline over time in both HFpEF and HFrEF, and the decline was greater in the former.

2.1.2 Prevalence of heart failure

The overall prevalence estimates of heart failure reported in population-based studies range from 1.8% to 17.6% (median prevalence 4.7%) (Sánchez et al., 2008b, Abhayaratna et al., 2006, Ceia et al., 2002, van Riet et al., 2014, Alehagen et al., 2009, Mureddu et al., 2012, Tiller et al., 2013, Mosterd et al., 1999, Davies et al., 2001, Redfield et al., 2003). Heart failure is hardly found in population younger than 50 years old but it increases progressively with age. In a cross-sectional survey of 2042 residents in Olmsted County (Redfield et al., 2003), the overall prevalence of heart failure was 2.2% which rose from 0.7% in persons aged 45 through 54 years to 8.4% for those aged 75 years or older. Other population-based studies also reported the increasing trend of prevalence of heart failure with age (Sánchez et al., 2008b, Abhayaratna et al., 2006, Ceia et al., 2002, van Riet et al., 2014, Alehagen et al., 2009, Mureddu et al., 2012, Tiller et al., 2013, Mosterd et al., 1999, Davies et al., 2001). The prevalence of heart failure increases rapidly with age in both genders, from between

0.2% and 3.0% in the age group below 50 year old to between 8.0% and 22.0% in those aged 75 or over as reported in prior population-based studies (Sánchez et al., 2008b, Davies et al., 2001, Ceia et al., 2002, Tiller et al., 2013).

Generally speaking, there is no difference in prevalence rates observed between genders but some studies indicated that women have higher prevalence of heart failure than men. A community-based epidemiological study involving subjects aged over 25 year attending primary care centres in Poland (Ceia et al., 2002) reported that the prevalence of heart failure was slightly higher in men than in women up to the age of 70. The same study also reported that the prevalence of heart failure in the 70 - 79 years old age group was higher in women than in men. Studies (Abhayaratna et al., 2006, Ceia et al., 2002, van Riet et al., 2014, Alehagen et al., 2009, Mureddu et al., 2012, Tiller et al., 2013) showed that the HFpEF (median prevalence 4.0%, range 1.7% to 12.0%) is more prevalent than HFrEF (median prevalence 3.2%, range 1.3% to 4.4%). More men are affected by HFrEF than women whereas HFpEF affected more women than men (Tiller et al., 2013).

2.1.3 Prevalence of NYHA class

The prevalence of New York Heart Association (NYHA) class among patients with heart failure differs across various studies (Sakata et al., 2014, Davies et al., 2001, Fischer et al., 2003, Alehagen et al., 2009, Kuwabara et al., 2010, Delgado et al., 2014, Biermann et al., 2012, Peters-Klimm et al., 2012, Agvall et al., 2005, Ondrackova et al., 2009, Parissis et al., 2015) depending on the study design. NYHA class II (median prevalence 44.0%, range 28.7% to 65.4%) is the most prevalent among patients with heart failure as compared to other NYHA classes. The median prevalence estimates are similar in NYHA class I (median prevalence 27.6%, range 7.3% to 47.0%), class

III (median prevalence 26.7%, range 7.0% to 44.7%) and is lowest in class IV (median prevalence 4.6%, range 0.3% to 25.4%). However in a registry-based study of 17,912 patients treated in hospital in Japan (Kuwabara et al., 2010), the prevalence of NYHA class IV was as high as 25.4% in more than 80.0% of its patients aged above 80 years old. Besides, studies which included patients with heart failure following up at primary care clinics (Delgado et al., 2014, Peters-Klimm et al., 2012, Agvall et al., 2005) reported that the prevalence of NYHA class II (range 51.0% to 65.4%) was as twice as higher than the studies which included hospitalized patients with heart failure (range 28.7% to 38.3%) (Kuwabara et al., 2010, Ondrackova et al., 2009, Parissis et al., 2015). This indicates that primary care clinics play an important role in identifying and managing more patients with stable heart failure in the population to reduce the hospitalization events. Furthermore, similar observation was also reported in 3 population-based studies (Davies et al., 2001, Fischer et al., 2003, Alehagen et al., 2009) which established that the prevalence of NYHA class II ranged between 29.9% and 44%, were slightly higher than the prevalence estimates in studies involving hospitalized patients with heart failure. This was maybe due to the fact that only those with worsening symptoms of heart failure were hospitalized for further treatment and the remaining were symptomless, resulting in lower prevalence estimates.

There are several factors contributing to the observed variability in the prevalence estimates across different studies. One of the contributors is the variation in recruitment age of the study population. Studies with younger, wider age distribution generally showed lower prevalence of heart failure and vice versa for studies with older age distribution. The studies (Mureddu et al., 2012, van Riet et al., 2014, Di Bari et al., 2004, Demirovic et al., 2001, Morgan et al., 1999, Sánchez et al., 2008a) that recruited participants aged 65 years and older only showed a higher a

median crude prevalence at 7.9% (range 5.6% to 15.7%) as compared to those studies who have younger population with a median crude prevalence at 2.2% (range 1.2% to 6.8%) (Ceia et al., 2005, Ceia et al., 2002, Ohlmeier et al., 2015, Zarrinkoub et al., 2013, Mair et al., 1996, Ni, 2003, Sánchez et al., 2008b, Mosterd et al., 1999, Redfield et al., 2003).

Besides, the wide variation in the prevalence estimates reported in the literatures is also due to use of different sets of disease definition and diagnostic criteria of heart failure. Most studies employed either the Framingham (McKee et al., 1971) or the European Society of Cardiology (ESC) principles to diagnosis heart failure. The Framingham instrument defines heart failure based on the presence of either 2 major or 1 major and 2 minor criteria representing the signs and symptoms of heart failure while the ESC principles refer to a combination of symptoms, objective evidence and response to heart failure medications. The information on the signs and symptoms of heart failure is obtained by either self-report questionnaires or clinical evaluation by physician in some studies. Bleumink et al. (2004) claimed that studies that employed the Framingham criteria for case ascertainment reported higher age-specified prevalence estimates of heart failure than those using ESC principles. Such claim is however not consistent in other studies which employed the same criteria as there are factors which can contribute to variation in the prevalence estimates. On the other hand, case ascertainment of heart failure by signs and symptoms based on the Framingham criteria might not be able to detect some patients without any symptoms of heart failure as 50.0% of the heart failure population were asymptomatic (McDonagh et al., 1997, Redfield et al., 2003, Mosterd et al., 1999). A combination of symptoms and objective evidence of cardiac dysfunction is therefore useful in detecting patients with symptomless heart failure. Besides, some studies employed additional criteria such as

the presence of cardiac diseases or an increase of the N-terminal pro-brain natriuretic peptide (NT-proBNP) serum concentration above 220 pg/ml to ascertain the diagnosis of heart failure. However there were studies which did not apply these instruments to diagnose heart failure. Instead such information of heart failure diagnosis is obtained directly either from patient medical records, administrative health database or self-report by patients themselves. Such practice might have provided incorrect, invalidated information on the diagnosis of heart.

2.1.4 Comorbidities

Cardiac comorbidities such as ischaemic heart diseases, atrial fibrillation, myocardial infarction and hypertension are the most common and often co-existing illness in patients with heart failure (Ambrosy et al., 2014). It was established that both coronary artery disease and myocardial infarction were the main causes of systolic dysfunction among patients hospitalized with heart failure. (Ambrosy et al., 2014). Other non-cardiac comorbidities included chronic obstructive pulmonary disease, renal disease, obstructive sleep apnoea and diabetes (Mosterd and Hoes, 2007). The presence of comorbidities can increase the risk for death and rehospitalization for heart failure (Liu et al., 2014).

2.1.5 Aetiology

Ischaemic heart diseases, hypertension and diabetes are the major aetiologies of heart failure (Mosterd et al., 1999, Davis et al., 2002, McDonagh et al., 1997). Early population-based Framingham study reported that hypertension is the main cause of heart failure (McKee et al., 1971, Ho et al., 1993b) in over 70.0% of cases but Hillingdon study (Cowie et al., 1999) and Cardiovascular Health study (Gottdiener et

al., 2000) reported that ischaemic heart disease is the main cause of heart failure instead whereas McDonagh et al. (1997) demonstrated that a combination of ischaemic heart disease and hypertension is a powerful predictor of heart failure. Such discrepancy is due to the different criteria used to determine aetiology across studies. For instance 2 sets of blood pressure (≥160/95 mmHg and ≥140/90 mmHg) were used to define hypertension being used across studies. Besides, data that was used to define the aetiology of heart failure was obtained from hospital-based medical records whereas the diagnosis of ischaemic heart diseases such as myocardial infarction, atrial infarction and angina were based on medical records of physician diagnosis or echocardiogram assessment reports. Information obtained from medical records of physician diagnosis may not clearly state which clinical guidelines the physician used to make diagnosis. This is especially obvious when there was a new definition of myocardial infarction by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) (Thygesen et al., 2007). Furthermore it was reported that some patients in prospective Euro-Heart Survey of Acute Coronary Syndromes were diagnosed with unstable angina inaccurately (Hasdai et al., 2003). These examples showed that the extent of accuracy of definition of the aetiology of heart failure largely depends on the extent of accuracy of diagnosis of ischaemic heart diseases.

2.1.6 Prognosis

Heart failure has poor prognosis which gets worse with age (Senni et al., 1999, Ho et al., 1993b, Gerber et al., 2015). The Framingham study established that the mortality rate increased by 27.0% per decade of age in men and 61.0% per decade of age in women (Ho et al., 1993b), therefore those patients with heart failure aged 65 years old and older have lower survival rate than those aged 65 years old and younger (Aranda

et al., 2002). It has high mortality rate and is 6 to 7 times higher than of the population without heart failure (Ho et al., 1993a). Heart failure has poor prognosis which is further proven in some studies by which only 57.0% to 77.0% survived 1 year after the incident of heart failure (Senni et al., 1999, Ho et al., 1993b, Bleumink et al., 2004). The median survival ranges between 1.7 and 2.1 years (Ho et al., 1993b, Bleumink et al., 2004). The survival rate declines further to between 25.0% and 35.0% at 5 years after heart failure has developed (Senni et al., 1999, Ho et al., 1993b, Bleumink et al., 2004). The Framingham study (Ho et al., 1993b) reported that the survival did not improve significantly after onset of heart failure during 40 years of follow up between 1948 and 1988. This finding was further supported by the Rochester study (Senni et al., 1999) which showed that the 10-year survival remained the same in its two cohorts in 1981 and 1991 except there was an improvement in the survival rate in NYHA class I and II groups. It was however reported that the 5-year survival for men aged 65 years old and older showed a significant improvement but not in women between 1970-1974 and 1990-1994 (Barker et al., 2006). In another population-based study of 4,537 residents with diagnosis of heart failure Olmsted County between 1979 and 2000 (Roger et al., 2004), the 5-year survival improved over time between 1979-1984 and 1996-2000. Lack of significant improvement in the long term survival observed in earlier studies such as the Framingham study (Ho et al., 1993b) and the Rochester study (Senni et al., 1999) was hypothetical because angiotensin-converting enzyme (ACE) inhibitors which were beneficial for heart failure were only available in the market after 1983. However, the findings on the survival in men and women have been inconsistent across studies. While women have been reported to survive better than men (Ho et al., 1993b, Roger et al., 2004), some studies have reported survival in women was similar (Bleumink et al., 2004, Senni et al., 1999) or worse than in men

(Barker et al., 2006, Goda et al., 2009). Conflicting findings are also observed across studies regarding the prognosis between patients with HFrEF and HFpEF. A 6-month follow up of hospital-based study (Smith et al., 2003) with 413 patients with heart failure between 1996 and 1998 reported that those with HFrEF has better survival than those with preserved ejection fraction. Similar observation was reported by a registry-based study of 2,906 unselected consecutive patients with heart failure who were admitted to hospitals in 1995 and 1997 (Philbin et al., 2000). In a hospital-based study with longer follow up of 2.4 years with 172 patients with heart failure (Tsutsui et al., 2001), there was no significant difference between patients with HFrEF and preserved ejection fraction. Similar finding was observed in other studies (Owan et al., 2006, Kapłon-Cieślicka et al., 2016). The hypothetical explanation for such disparity is due to lower percentage of patients with left ventricular ejection fraction measurement in some studies (Smith et al., 2003, Philbin et al., 2000) which resulted in exclusion of potential cases which might affect the outcome.

2.1.7 Hospitalization for heart failure

2.1.7(a) Length of hospital stay

The median length of hospital stay due to heart failure is 7 days (range 4 to 20 days) (Gheorghiade et al., 2006, Steinberg et al., 2012, Nieminen et al., 2006, Atherton et al., 2012, Maggioni et al., 2010, Sato et al., 2013, Adams et al., 2005, Kuwabara et al., 2010). Findings obtained from Acute Decompensated Heart Failure (ADHERE) national registry, Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry and Medicare data in the United States showed that the lengths of hospital stay were 4.3, 6.4 and 5.5 days respectively (Aranda et al., 2009, Adams et al., 2005, Gheorghiade et al., 2006). The possible

reason for the lower length of hospital stay as observed in ADHERE registry (Adams et al., 2005) was due to its lower percentage of coronary artery disease as compared to OPTIMIZE-HF (Gheorghiade et al., 2006) registry and its younger population as compared to Medicare heart failure population (Aranda et al., 2009). This indicates the positive association of comorbidities especially coronary heart disease and age with length of hospital stay. Two studies in the Japan reported that the lengths of hospital stay were few times longer, ranged between 18 and 21 days (Sato et al., 2013, Kuwabara et al., 2010). Such observation was mainly because the health care system in Japan was publicly financed whereas 66 percent of residents in the United States received health insurance coverage from private voluntary health insurance (Mossialos et al., 2016) and therefore Japanese patients can afford to stay longer in hospital. Besides, Japanese hospitals also provide inpatient disease management such as rehabilitation which results in longer hospitalization. The lengths of hospital stay in the European countries (Nieminen et al., 2006, Maggioni et al., 2010) and Asia Pacific countries (Atherton et al., 2012) were 8 – 9 days and 6 days respectively. Chong et al. reported that the length of hospital stay due to heart failure in Hospital Kuala Lumpur, Malaysia was four days (Chong et al., 2003).

There is no significant difference in the lengths of hospital stay between HFrEF and HFpEF (Malki et al., 2002, Kapłon-Cieślicka et al., 2016, Yancy et al., 2006, Fonarow et al., 2007b). However significant difference between these two groups was observed when the duration of stay was more than 4 days as reported in the Get With the Guidelines–Heart Failure study (Steinberg et al., 2012). The length of hospital stay among Medicare patients decreased steeply from 8.81 days to 6.33 days between 1993 and 2006 (Bueno et al., 2010). Similar downward trend was observed in another study involving Medicare patients with heart failure (Baker et al., 2003). The former reported

that the adjusted 30-day relative risk of readmission over the same time period increased by 11.0% (Bueno et al., 2010), indicating negative association between length of hospital stay and risk of 30-day readmission as confirmed by Eapen et al. (Eapen et al., 2013) in their clinical trial data analysis.

2.1.7(b) In-hospital mortality

Heart failure has a median in-hospital mortality rate of 4.9% (range 3.8% to 15.0%) (Steinberg et al., 2012, Nieminen et al., 2006, Atherton et al., 2012, Maggioni et al., 2010, Sato et al., 2013, Fonarow et al., 2007b, Baker et al., 2003, Nicol et al., 2008, Yancy et al., 2006, Goda et al., 2009, AlHabib et al., 2014, Kapłon-Cieślicka et al., 2016). The much higher in-hospital mortality rate at 15.0% as reported by National Health Services (NHS) Heart Failure Survey of acute heart failure in England, Wales and Northern Island (Nicol et al., 2008) was due to higher proportion (75.0%) of patients hospitalized with moderate to severe heart failure. Registry-based studies (Nieminen et al., 2006, AlHabib et al., 2014) that selected patients who were admitted to critical care unit (CCU) and intensive care unit (Investigators) also reported higher in-hospital mortality rate between 6.5% and 6.6%. These observations demonstrated that the in-hospital mortality rate was higher among those patients with severe condition of heart failure and required hospitalizations. Contrary, lower in-hospital mortality rate ranging between 3.6% and 3.8% was observed in those registry-based studies (Goda et al., 2009, Maggioni et al., 2010, Kapłon-Cieślicka et al., 2016) which included patients in outpatient and inpatient settings. The reason for lower in-hospital mortality rate in these registry-based studies was the exclusion of some patients without any echocardiogram examinations and hence reducing the potential cases of heart failure. For those studies which ascertained cases of heart failure based on

discharge diagnosis (Fonarow et al., 2007b, Yancy et al., 2006, Steinberg et al., 2012), the inconsistent diagnosis coding might cause the investigators to miss some potential heart failure case and hence lower in-hospital mortality rate was reported. Three studies (Yancy et al., 2006, Fonarow et al., 2007b, Steinberg et al., 2012) reported that the in-hospital mortality of HFrEF (range 3.0% to 3.9%) was higher than HFpEF (range 1.6% to 2.9%). But both HFrEF and HFpEF have similar survival. The in-hospital mortality dropped from 6.4% to 3.0% as reported in four studies in the United States between 1991 and 2010 (Fonarow et al., 2007b, Baker et al., 2003, Yancy et al., 2006, Steinberg et al., 2012). Similar downward trend of in-hospital mortality rate was also showed by two European studies (Nieminen et al., 2006, Maggioni et al., 2010). This could be attributed to higher usage of renin–angiotensin–aldosterone system inhibitors and beta-adrenergic inhibitors which improves the condition of heart failure as well as higher rate of assessment of left ventricular ejection fraction in more recent studies to identify patients with left ventricular systolic dysfunction and hence providing them with proper management of heart failure.

2.1.7(c) Readmission

Heart failure has high readmission rate (Cowie et al., 1997). Approximately one-fifth of patients with heart failure were readmitted after first diagnosis of heart failure during a 6-month follow up (Smith et al., 2003). The readmission rate rose to 41.0% in a 2.4 years follow up study of 170 patients with heart failure (Tsutsui et al., 2001). The 30-day readmission rates range between 26.9% and 28.0% (Jencks et al., 2009, O'connor et al., 2010, Epstein et al., 2011) but another study (Schrager et al., 2013) reported a much lower 30-day readmission rate at 13.8%. Such difference was because the latter has younger population with 63.0% of them aged 65 years old and below and

this study considered readmission due to heart failure only. The readmission rates increase to 34.0% (Epstein et al., 2011) and approach to 37.0%, respectively, within 60 days (Epstein et al., 2011) and 90 days (Epstein et al., 2011) after discharge. Another study (Aranda et al., 2009) indicated that heart failure patients aged 75 years old and below were more likely to have readmission while there is an opposite conclusion of which patients older than 65 years old were at higher risks of having readmission (Kossovsky et al., 2000). The readmission rate between patient with HFrEF and HFpEF showed no significant difference as observed in several studies (Smith et al., 2003, Tsutsui et al., 2001, Malki et al., 2002) which were limited by small sample size and selected population.

Nevertheless readmission can cause heavy economic burden to health care provided. Unplanned readmission costs Medicare $ 17 billion annually (Jencks et al., 2009). Patients who have recurrent heart failure, primary diagnosis of heart failure, heart failure precipitated acute myocardial infarction and uncontrolled hypertension have higher risk of readmission (Gooding and Jette, 1985, Vinson et al., 1990). Inadequate medical management, patient incompliance with medications, lack of social support system and inadequate follow up after discharge were the factors identified for high readmission rate among patients with heart failure (Gooding and Jette, 1985, Vinson et al., 1990). Given that approximately 50.0% of the readmissions due to heart failure are preventable (Vinson et al., 1990), it is vital to have a better understanding of the demographic characteristics and clinical outcomes of patients with heart failure to improve the clinical management of heart failure. The desired treatment outcomes aim at improving patient compliance and maintaining an optimally compensated state so that can decrease the need for heart failure readmissions and shorten hospital stays.

2.1.8 Comparison with other published studies

Ethnicity has been shown as one of the factors for causing the significant differences in the prevalence and outcome of heart failure reported in the previous studies (Thomas et al., 2011, Bibbins-Domingo et al., 2009, Bahrami et al., 2008, Alexander et al., 1999). Compared to western population, Asian patients are at risk of heart failure at younger age but patients in South East Asia are generally younger than those in East Asia (Atherton et al., 2012). Single-centre studies in Malaysia (Chong et al., 2003) and Singapore (Ng and Niti, 2003) reported higher prevalence of heart failure (4.5% and 6.7% respectively) than western population-based studies (0.5% - 2.0%) (Ponikowski et al., 2014) and China estimates (1.3%) (Yang et al., 2010). In recent decades, studies have demonstrated an increasing trend towards ischemic aetiology and comorbidities such as diabetes mellitus and hypertension in Asian populations. Such prevalence is however not as great as in western populations. The prevalence of hypertension in heart failure in Japan is 74.0% (Shiba et al., 2011) while it is much lower in Malaysia at 19.0% (Chong et al., 2003).

In comparing 2 similarly designed large, multicenter registries of patients hospitalized with heart failure conducted in the United States and Asian countries, Atherton et al. (2012) reported that Asian populations have higher in-hospital mortality rate and longer length of hospital stay (Atherton et al., 2012) as compared to United States population. Such observation was due to the lower use of positive inotropes, higher use of b-blockers and higher rates of left ventricular function assessment in United States hospitals (Fonarow et al., 2007a) as compared to hospitals in Asian countries. Realizing the presence of the differences in clinical, social backgrounds and management of heart failure across geographical regions, it is difficult to generalize western and Asian data for local context.

2.2 Economic burden of heart failure

2.2.1 Cost estimates of heart failure using prevalence approach

The prevalence approach estimates the cost of heart failure at a certain point in time regardless of the date of onset (Segel, 2006). In studies adopting prevalence approach, the cost estimates of heart failure are reported in term of annual cost per patient, ranging from International Dollars (Int$) 2,496.00 to Int$ 84,434.00 with a median cost at Int$ 12,355.00 (Parissis et al., 2015, Ogah et al., 2014, Czech et al., 2012, Agvall et al., 2005, Araujo et al., 2005, Whellan et al., 2010, Peters-Klimm et al., 2012, Biermann et al., 2012, Delgado et al., 2014, Tatari et al., 2015, Corrao et al., 2014, Bogner et al., 2010, Kuwabara et al., 2010, Bharmal et al., 2008, Stålhammar et al., 2014, Wijeysundera et al., 2014). Cost estimates of heart failure are also presented in term of cost per hospitalization, ranging between Int$ 3,780.00 and Int$ 34,233.00 with a median cost at Int$ 11,340.00 (Wang et al., 2010, Hauptman et al., 2008, Titler et al., 2008, Sözmen et al., 2015, Joshi et al., 2004, Ziaeian et al., 2015, Claes et al., 2008, Korves et al., 2012, Lagu et al., 2013, Rihova et al., 2013, Ondrackova et al., 2009).

Studies that adopt societal perspective by combining medical costs, indirect costs such as informal care cost, out-of-pocket payments or productivity loss costs (Haddix et al., 2003, Luce et al., 1996) show a range of cost estimates from In$ 2,612.00 to In$ 39,837.00. Productivity loss ranges between In$ 1,155.00 (Ogah et al., 2014) and In$ 40,447.50 (Araujo et al., 2005) whereas informal care cost ranges between In$ 908.00 (Joo et al., 2015) and In$ 8,779.00 (Delgado et al., 2014).