TIME TO READMISSION AND ITS PROGNOSTIC FACTORS AMONG HOSPITALISED HEART FAILURE PATIENTS IN KELANTAN

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UNIVERSITI SAINS MALAYSIA

2024

TIME TO READMISSION AND ITS PROGNOSTIC FACTORS AMONG HOSPITALISED HEART FAILURE PATIENTS IN KELANTAN

by

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Thesis submitted in fulfilment of the requirements
for the degree of
Master of Science (Medical Statistics)

Aug 2024

ACKNOWLEDGEMENT

Bismillah al-Rahman al-Rahim,

In the name of Allah, the most gracious, the most merciful, I would like to express my gratitude to Allah SWT for giving me the time, strength, and opportunity to complete this dissertation. I would like to extend my gratitude to my supervisor Dr Wan Nor Arifin and Assoc. Prof. Dr Sarimah Abdullah for the continuous guidance and advise to ensure the quality of my project. Special thanks to all lectures and staffs in Biostatistics and Research Methodology Unit, USM for all the knowledge that I have acquired throughout my two-year journey in the course. Thanks also to all my colleagues who have been helpful and supportive to each other during learning process.

My appreciation also to head of Clinical Research Centre (CRC) Kelantan, Dr Wan Hasnul Halimi Wan Hassan and fellow colleagues working in CRC Kelantan for providing me adequate space and support to complete this thesis.

Last but not least, this thesis is not possible without the support of my closest family especially my wife, Nurul Amirah, my two little daughters and also both of my parents. They are the source of my strength and passion to overcome all the obstacles.

May Allah reward all the kind and lovely people that help me along the way.

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LIST OF SYMBOLS

A	Accrual period (in sample size calculation)
β	Regression coefficient for Cox regression analysis
F	Follow-up period (in sample size calculation)
R	Hazard ratio (in sample size calculation)

LIST OF ABBREVIATIONS

ACEi	Angiotensin-converting enzyme (ACE) inhibitors
AF	Atrial fibrillation
Alb	Albumin
ARB	Angiotensin II receptor blockers
AST	Aspartate aminotransferase
CKD	Chronic Kidney Disease
CVA	Cerebrovascular accident
DBP	Diastolic blood pressure
DM	Diabetes Mellitus
eGFR	estimated Glomerular Filtration Rate
EF	Ejection Fraction
HF	Heart Failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HRPZII	Hospital Raja Perempuan Zainab II
IHD	Ischaemic heart disease
JEPeM	Jawatankuasa Etika Penyelidikan Manusia
LOS	Length of stay
LVEF	Left ventricular ejection fraction
MREC	Medical Research & Ethics Committee
Pro-BNP	pro-brain natriuretic peptide
SBP	Systolic blood pressure
USM	Universiti Sains Malaysia

LIST OF APPENDICES

MASA UNTUK KEMASUKAN SEMULA DAN FAKTOR PROGNOSTIKNYA DALAM KALANGAN PESAKIT KEGAGALAN JANTUNG DI HOSPITAL DI KELANTAN

ABSTRAK

Kegagalan jantung adalah komorbiditi yang biasa di kalangan populasi dewasa dan ia dikaitkan dengan akibat yang buruk. Satu aspek yang mencabar ialah isu kemasukan berulang ke hospital yang membawa kepada beban penjagaan kesihatan yang ketara. Matlamat kajian ini adalah untuk meneroka kadar kemasukan semula, masa median dan faktor prognostik untuk masa kemasukan semula dalam kalangan pesakit kegagalan jantung selepas discaj dari hospital. Kajian kohort retrospektif ini melibatkan pesakit yang dimasukkan ke hospital disebabkan oleh kegagalan jantung di Hospital Raja Perempuan Zainab II dari Oktober 2021 hingga Disember 2022. Kriteria kemasukan termasuk warganegara Malaysia, berumur 18 tahun dan ke atas dengan keputusan rasmi ekokardiografi dalam tempoh satu tahun dari indeks kemasukan ke hospital. Pesakit yang menghadapi kematian sebagai pesakit dalam, dipindahkan ke hospital lain selepas discaj atau discaj dengan risiko sendiri dan mereka yang mempunyai kanser malignan dikecualikan dari penyelidikan. Kohort telah disusuli sehingga Disember 2023 untuk mengenal pasti peristiwa kemasukan semula yang ditakrifkan sebagai kemasukan akibat penyakit akut. Pesakit yang tiada kemasukan semula, kehilangan susulan atau meninggal dunia telah ditapis. Ciri-ciri sosiodemografi, data klinikal semasa indeks kemasukan ke hospital termasuk keputusan makmal dan ubat semasa discaj telah dikumpulkan. Data dikumpul daripada rekod perubatan elektronik berdasarkan borang pengumpulan data dalam talian dan analisis dilakukan menggunakan RStudio dan StataMP. Faktor prognostik untuk masa

kemasukan semula dikenal pasti menggunakan analisis regresi Cox berganda. Seramai 276 pesakit telah dimasukkan untuk analisis. Purata umur ialah 60.64 tahun. Sebahagian besar daripada mereka adalah Melayu (95.3%) dengan nisbah lelaki yang lebih tinggi (53.6%). Komorbiditi yang dikenalpasti termasuk hipertensi (81.5%), penyakit jantung iskemia (62%), kencing manis (57.2%) dan penyakit buah pinggang kronik (50.4%). Kemasukan semula ke hospital pada 6 Bulan dan 1 tahun selepas discaj adalah 51.8% (95% CI: 45.8, 57.8) dan 63.4% (95% CI: 57.4, 69.0). Kohort mempunyai masa median untuk kemasukan semula selama 118 hari (95% CI: 90,149). Faktor prognostik untuk masa kemasukan semula ialah fibrilasi atrium (HR diselaraskan: 2.06, 95% CI: 1.42, 2.99, P<0.001), penyakit buah pinggang kronik (HR diselaraskan: 1.53, 95% CI: 1.14, 2.04, P=0.004), tahap albumin (HR terlaras: 0.96, 95% CI: 0.94, 0.99, P=0.005), tahap aspartate aminotransferase (HR terlaras: 1.003, 95% CI: 1.001, 1.006, P=0.022) dan EF≤40% (HR terlaras: 1.003 95% CI: 1.03, 1.84, P=0.033). Kesimpulannya, pesakit kegagalan jantung di Kelantan adalah lebih muda dan mempunyai kadar kemasukan semula yang lebih tinggi berbanding angka global pada 6 bulan. Pakar perubatan perlu mengoptimumkan pesakit sebelum discaj dengan perhatian khusus kepada faktor prognostik yang dikenal pasti.

Kata kunci: kegagalan jantung, kemasukan hospital, kemasukan semula, prognosis, faktor risiko

TIME TO READMISSION AND ITS PROGNOSTIC FACTORS AMONG HOSPITALISED HEART FAILURE PATIENTS IN KELANTAN

ABSTRACT

Heart failure (HF) is a common comorbidity among adult population and is associated with poor outcomes. One challenging aspect of it is the issue of recurrent admissions leading to significant healthcare burden. The aim of this study is to explore the proportion of readmission, median time and prognostic factors for time to readmission among hospitalised HF patients in Kelantan. This retrospective cohort study involved patients admitted primarily for HF in Hospital Raja Perempuan Zainab II from October 2021 until December 2022. Inclusion criteria include adult Malaysian citizen, age 18 years old and above with formal echo finding within one year of index hospitalisation. Those with in-patient mortality, transferred to another facility upon discharge or discharge at own risk and those with active malignancy were excluded. The cohort were followed up until December 2023 to identify the event of readmission which is defined as admission due to acute illness. Patients who had no readmission, loss to follow up or passed away were censored. Sociodemographic characteristics, clinical data during index hospitalisation including laboratory result and medication upon discharge were collected. Data was collected from electronic medical record based on standardised online data proforma and analysis was done using RStudio and StataMP. Prognostic factors for time to readmission were identified using multiple Cox regression analysis. A total of 276 patients were included for analysis. Mean age was 60.64 years old. Most of them were Malays (95.3%) with higher proportion of male (53.6%). Common comorbidities include Hypertension (81.5%), ischaemic heart disease (62%), type II diabetes mellitus (57.2%) and chronic kidney disease (50.4%).

Proportion of readmission at 6 Month and 1 year post discharge was 51.8% (95% CI: 45.8, 57.8) and 63.4% (95% CI: 57.4, 69.0) respectively. The cohort had median time to readmission of 118 days (95% CI: 90,149). Prognostic factors for time to readmission were atrial fibrillation (adjusted HR: 2.06, 95% CI: 1.42, 2.99, $P<0.001$), chronic kidney disease (adjusted HR: 1.53, 95% CI: 1.14, 2.04, $P=0.004$), albumin level (adjusted HR: 0.96, 95% CI: 0.94, 0.99, $P=0.005$), aspartate aminotransferase level (adjusted HR: 1.003, 95% CI: 1.001, 1.006, $P=0.022$) and ejection fraction ≤40% (adjusted HR: 1.37, 95% CI: 1.03, 1.84, $P=0.033$). In conclusion, HF patients in Kelantan were relatively younger and had a higher rate of readmission compared to global figures at 6-month. Clinicians need to optimise patients prior to discharge with particular attention to the identified prognostic factors.

Keywords: heart failure, hospitalization, readmission, rehospitalisation, prognosis, risk factors,

CHAPTER 1

INTRODUCTION

1.1 Background

Heart failure (HF) is a common non-communicable disease among adult population worldwide. HF is defined as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion (Bozkurt *et al.*, 2021). This is the universally accepted definition of HF established during the international scientific conference in 2021 that involve major heart associations across the world. There is no gold standard in the diagnosis of HF and it is mainly a clinical diagnosis based on careful history and physical examination. Nevertheless, there are several diagnostic criteria being used in previous studies particularly the Framingham criteria, the Boston criteria, the Gothenburg criteria, and the European Society of Cardiology criteria (Roger, 2013). Among those aforementioned diagnostic criteria, only the European Society of Cardiology criteria require objective evidence of cardiac dysfunction by echocardiography.

HF is a complex syndrome with different aetiologies. Patient can present with same symptoms or signs, but further investigations might lead to different causes. Ischaemic heart disease (IHD) remains the most common cause of HF. Approximately 40% of HF cases worldwide are contributed by IHD (Savarese et al., 2023). Data in Malaysia showed that IHD is responsible for almost half (49.5%) of HF cases (Chong et al., 2003). Other causes of HF include hypertension, valvular and rheumatic heart disease, idiopathic dilated cardiomyopathy, chagas cardiomyopathy, chemotherapy and radiotherapy induced cardiomyopathy and congenital heart disease.

In term of disease burden, HF is a global pandemic affecting about 64.3 million people worldwide (Savarese et al., 2023). The prevalence of HF ranges between 1 – 3% in among adult population in developed nation (Savarese et al., 2023). Regionally, our neighbouring countries in Southeast Asia reported wide range of HF prevalence. Philippine reported quite similar prevalence of 1-2%, Thailand had lower prevalence (0.4%) while Indonesia had highest prevalence at 5% (Reyes et al., 2016). Malaysia had one of the highest HF prevalence rates in Southeast Asia, with 721 cases per 100,000 persons in 2017 which is an increase of 7.7% compared to data in 1990 (Bragazzi et al., 2021).

The prevalence of HF is generally projected to increase. This might be the result of better access to healthcare and diagnostic tool that facilitate early diagnosis of HF. Another contributing factor is continuous improvement in medical care including treatment of HF means that patients are receiving better care, and this will improve survival of the patients. HF is generally a disease of older people; therefore, the global issue of ageing population is also important factor for increasing prevalence of HF (Roger, 2013).

The prognosis of HF is poor with mortality rate similar to many forms of cancer (Straw, McGinlay & Witte, 2021). A large community-based prospective study in England reported the 10-year survival rate was 26.7% for those with definite HF and 37.6% for those with left ventricular dysfunction (Taylor et al., 2012). Advancement in the treatment of HF has partly contributed to improve survival of HF patients especially after the addition of angiotensin-converting enzyme inhibitors and β-blocker into standard management of HF (Roger, 2013). However, improvement in survival is relatively modest in absolute measure.

HF imposes significant economic burden, and this burden is anticipated to grow as the prevalence of heart failure continues to rise. Annual health care costs per HF patient amount up to €25 000 in the Western world. A cost analysis study in Malaysia reported spending for chronic HF patient as USD 1,971 per patient per year (Ong et al., 2022). Majority of the costs are linked with directs costs that include inpatient care and readmission. Among developed nation, HF represented about 1-2% of all hospital admission and approximately 50% are re-admitted within 1 year of their initial hospitalisation (Savarese et al., 2023). A study in Sweden highlighted that recurrent HF hospitalizations were associated with an increased risk of cardiovascular and all-cause mortality (Lindmark et al., 2021). Therefore, optimizing care for HF patient is important to reduce hospitalization and readmission.

1.2 Problem Statement

HF is a major public health issue worldwide because of its increasing prevalence, high mortality risk and high cost (Fischer *et al.*, 2015). Hospitalisation is one of the critical issues of HF contributing to significant economic and healthcare burden.

Frequent readmissions are associated with poorer health outcomes and reduced quality of life for heart failure patients (Heidenreich *et al.*, 2013). They are often indicative of ongoing or unresolved health issues that can lead to deteriorating health outcomes. Each hospital readmission exposes patients to potential hospital-acquired infections, procedural complications, and the psychological stress associated with repeated hospital stays (Chang, 2019). These factors collectively contribute to a decline in the overall health and well-being of the patient. Additionally, frequent hospitalizations disrupt the continuity of care and can hinder effective long-term

management of heart failure, leading to a vicious cycle of recurrent admissions. The instability caused by frequent readmissions not only exacerbates the patient's physical health but also negatively impacts their quality of life, limiting their ability to perform daily activities and maintain social relationships (Heidenreich *et al.*, 2013). This diminished quality of life highlighted the importance of identifying and mitigating the factors that contribute to repeated hospitalizations, thereby improving both the clinical outcomes and the overall life satisfaction of heart failure patients.

Identifying the predictors for readmission is a crucial step in reducing the risk of readmission for HF patient (Bradford *et al.*, 2017). While there have been many published articles on HF readmission, data within Malaysian population is still limited. Several local studies examine readmission as secondary analysis and did not explore the potential predictors for readmission. Only two studies that focus on determining the predictors of readmission, one study is based on a discharge database that is limited to sociodemographic variables, while another was conducted in a specialized cardiology center, which does not represent the general population. (Lim *et al.*, 2022; Mohd Ghazi, Teoh & Abdul Rahim, 2022).

1.3 Study rationale

Assessing readmission among HF patients can be an indicator on overall quality of hospital care or delivery of healthcare services (Fischer *et al.*, 2015). High readmission rates often indicate issues with patient management, discharge planning, or follow-up care, highlighting areas needing improvement. By identifying key predictors of readmission, healthcare providers can develop targeted strategies to improve those area with the aim of reducing readmission. Reducing readmissions can

consequently alleviate the burden on hospitals, allowing for better allocation of resources and improved patient care.

This study also provided additional knowledge on heart failure readmissions, providing valuable local findings that can be compared with findings from other regions and countries. It has helped fill the gap in the literature regarding the specific predictors of readmission within Malaysia population, particularly in Kelantan. Kelantan population is known to have lower socioeconomic status compared to other regions in Malaysia (Tafran, Tumin & Farid Osman, 2020). Lower socioeconomic status is known to be associated with negative impact on cardiovascular health (Schultz *et al.*, 2018). It is therefore necessary to explore this issue among HF patients in Kelantan to assess the disease burden associated with readmission. The findings from this study can inform health policies aimed at reducing readmission rates, thereby improving the efficiency of the healthcare system. Policymakers can use the data to tailor a program or intervention to tackle the issue and promote better short and long-term outcome for heart failure patients post discharge.

This study aimed to determine the time to readmission and its prognostic factors among hospitalized heart failure patients in Kelantan, incorporating both demographic and clinical parameters, including laboratory values. The results of this study provided local clinicians an insight regarding the pattern of HF readmission in the local population.

1.4 Research Questions

1. What is the proportion of readmission among hospitalised heart failure patients?

2. What is the median time to readmission among hospitalised heart failure patients?
3. What are the prognostic factors for time to readmission among hospitalised heart failure patients?

1.5 Research Objectives

1.5.1 General

To examine the time to readmission and its prognostic factors among hospitalised heart failure patients in Kelantan

1.5.2 Specific

1. To estimate the proportion of readmission among hospitalised heart failure patients at 6-month and 1-year post discharge.
2. To estimate the median time to readmission among hospitalised heart failure patients
3. To identify the prognostic factors for time to readmission among hospitalised heart failure patients.

1.6 Research hypothesis

The prognostic factors for time to readmission are older age group, lower ejection fraction, kidney disease and length of stay during index hospitalization.

CHAPTER 2

LITERATURE REVIEW

2.1 Search strategy

Relevant keywords were determined based on the study population and outcome. All related terms or synonyms within similar concept were combined using Boolean operator 'OR'. Then, the concepts (population and outcome) were combined using Boolean operator 'AND'. Search was done using advanced search in PubMed and Scopus. Keywords were searched in the study titles only to improve precision. A total of 749 articles were found in PubMed and 1164 articles in Scopus. Relevant results were added into Mendeley citation manager.

Table 2.1: Keywords used in literature search

Concept	Synonyms
Population	
Heart failure	heart failure OR cardiac failure OR ccf OR poor ef OR hfref OR hfpef OR chf
Outcome	
Readmission	readmission OR rehospitalisation OR readmit OR re-admission

Further search was done using google scholar using simple phrase of "heart failure readmission". Duplicates references were removed manually. Full text articles were retrieved and reviewed. Other relevant articles were also identified using snowball search methods.

2.2 Heart failure

Based on the guideline published by the European Society of Cardiology (ESC) in 2021, HF is described as a clinical syndrome with multiple aetiologies rather than a single disease entity (McDonagh *et al.*, 2021). This latest definition has broadened the scope of HF that can include a multitude of conditions or diseases under it. The clinical syndrome of HF includes some cardinal symptoms like breathlessness, fatigue or leg swelling and they are accompanied by some positive finding on clinical examination such as pulmonary crackles, elevated jugular venous pressure and peripheral oedema (McDonagh *et al.*, 2021). These signs and symptoms are the result of either structural or functional abnormalities of the heart from the underlying disease. Proper identification of the cause of HF is therefore crucial in managing HF patients.

HF is classified according to three different types based on the measurement of left ventricular ejection fraction (LVEF). The classification criteria are defined in Table 2.2 below.

Table 2.2: Classification of HF based on LVEF

Type of HF	**HFrEF[a]**	**HFmrEF[b]**	**HFpEF[c]**
Criteria	LVEF≤40%	LVEF 41-49%	LVEF≥50%

[a] Heart failure with reduced ejection fraction
[b] Heart failure with mildly reduced ejection fraction
[c] Heart failure with preserved ejection fraction

2.3 Readmission

Readmission is generally defined as an event of subsequent admission to hospital within a specified interval after the patient being discharged from initial or index hospitalisation. There have been many published articles that report readmission

rates among HF patients. Majority of these studies identify the all-cause readmission rather than HF related admission. A recent study in Iran reported that readmission rate was 24% within 6-month follow-up period (Naderi *et al.*, 2022). Several studies focus on early readmission within 30 days post discharge. Two studies in USA published in 2020 and 2017 reported readmission rate of 25% and 16.3% within 30-day respectively (Bradford *et al.*, 2017; Regmi *et al.*, 2020). Another study in USA with 1 year follow up found that 60% of HF patients had readmission (Reynolds *et al.*, 2015).

The results from a systematic review that include all relevant articles from Australia were not significantly differ. The pooled estimated of 30-day and 1-year all-cause readmission rates were 20% and 56% (Al-Omary *et al.*, 2018). Another systematic review concluded the pooled 30-day admission rate of 19% based on 11 studies while the pool 1-year readmission rate was 53% from 6 studies (Lan *et al.*, 2021).

There are several local studies that reported 30-day readmission rate of HF. Lim *et al* (2022) reported 18% readmission based on national discharge summary database from 2007 to 2016. However, another two single centre studies in Sarawak General Hospital (SGH) and National Heart Institute (IJN) showed lower readmission rate of 11% and 6.8% (Ling *et al.*, 2020; Mohd Ghazi, Teoh & Abdul Rahim, 2022). The same study in IJN also reported low 1-year readmission rate of 24.7%. This is expected since IJN is a tertiary private hospital with patients from various regions in Malaysia. The finding is in contrast with high 1-year readmission rate of 76.1% from a study in Hospital Sungai Buloh (Raja Shariff *et al.*, 2021).

2.4 Associated factors for readmission

2.4.1 Age

It is a well-known fact that HF is a disease of older age group. However, the trend with younger HF patients is increasing. It is expected that older age group patients will have poorer prognosis in term of morbidity and mortality. This is due to the fact that older patients tend to have multiple comorbidities and physiologically more vulnerable compared to younger patients. This can be seen in a database study from Japan in which those patients aged 75 years old and above had higher risk of admission (Kaneko *et al.*, 2015). The same finding can be seen from a study in USA & Japan for similar age group (Eastwood *et al.*, 2014; Kaneko *et al.*, 2015). Nevertheless, several studies have shown the opposite with the finding that younger HF patients were associated with higher risk of readmission. Naderi *et al.* (2022) found that the mean age of those with readmission was significantly lower compared to those without readmission. The same pattern can be seen in another study that reported patients younger than 65 years old had increased likelihood of readmission (Aranda, Johnson & Conti, 2009).

2.4.2 Ethnicity

Ethnicity may also play important role in predicting readmission. A study in US that focus on HF outcome among different races noted readmission was significantly higher in Hispanic and Black patients compared to white patients (Durstenfeld *et al.*, 2016). In Malaysia, Chinese and Indians had higher readmission rate relative to Malays (Lim *et al.*, 2022). This can be attributed to disparities in term of healthcare access as most Chinese and Indians community reside in urban area. Specific reason for racial differences is most often difficult to tease out since it involves various factors that can

interplay. One need to understand the situation in the local setting before proposing the possible causes.

2.4.3 Socioeconomic status

Socioeconomic status (SES) is one of the important determinants of health outcomes. Markers of socioeconomic status include income level, educational attainment, employment status and environmental factors (Schultz *et al.*, 2018). Individuals living in poverty or near the poverty line were more likely to face difficulties in accessing healthcare, exhibit lower rates of healthcare utilization, and report lower satisfaction with the care they receive compared to those with higher SES scores (Cassedy *et al.*, 2013). Higher readmission among Hispanic and Black patients compared to white patients in US is an example of the consequence of lower SES leading to poorer health outcome (Durstenfeld *et al.*, 2016). Studies have shown a strong association between low SES and an increased risk of cardiovascular disease, including HF, hospitalization, and death (Browder & Rosamond, 2023). A stepwise decrease in the crude frequency of readmission was observed with increasing income among HF patients in New York (Philbin *et al.*, 2001). Low SES was also independently associated with higher mortality and readmission rates in patients with HF with reduced ejection fraction (Mathews *et al.*, 2022).

2.4.4 Chronic kidney disease

Kidney disease is a common comorbidity related to HF. A study in Hospital Sungai Buloh found out that 53.2% of admitted HF patients also had kidney disease (Raja Shariff *et al.*, 2021). Concomitant chronic kidney disease (CKD) consistently showed to be an independent predictor for readmission in several articles. For example, a large study in Canada which is based on hospital discharge data identified history of renal disease as significant risk factor for both 7-day and 30-day all-cause readmission

(Eastwood *et al.*, 2014). Another study with similar follow-up period revealed similar finding and among the subgroup of CKD, stage III was significant in multivariable analysis (Regmi *et al.*, 2020). These findings are in parallel with articles that highlighted higher urea/creatinine level and lower eGFR as the important factors for readmission (Habib & Shaath, 2022; Mohd Ghazi, Teoh & Abdul Rahim, 2022; Naderi et al., 2022). The coexistence of HF and CKD can be explained by the spectrum of cardiorenal syndrome with complicated pathophysiological explanation (Regmi et al., 2020).

2.4.5 Atrial fibrillation

Atrial fibrillation (AF) is the most common cause of arrhythmia related hospitalizations (Munir et al., 2017). Coexisting AF and HF is uncommon. Almost half of HF patients had concomitant AF and HF occurred in more than one third of patients with AF (Gangu et al., 2022). It has been identified as a significant predictor of readmission among heart failure patients (Sherer et al., 2016). In HF patients with normal ejection fraction, presence AF was associated with higher risk of readmission compared to sinus rhythm (Fung et al., 2007). AF causes hemodynamic burden on the heart, leading to worsened symptoms and an increased risk of adverse events (Zoni-Berisso et al., 2014). AF can cause rapid and irregular heartbeats, which may reduce the efficiency of the heart's pumping ability and lead to exacerbation of heart failure symptoms such as fluid retention, dyspnoea, and fatigue. A study in US utilising nationwide readmission database found that among patients hospitalised for AF, most of readmission were associated with AF or heart failure (Munir et al., 2017).

2.4.6 Ischaemic heart disease

IHD remains the leading cause of HF worldwide, characterized by reduced blood flow to the heart muscle due to coronary artery disease (CAD). This condition

often results in acute coronary syndrome (ACS), which impairs cardiac function and contributes to the progression of HF. Habib *et al.* (2022) demonstrated that hospitalized HF patients with clinical presentation of ACS on admission had higher risk of readmission. A study in Europe reported ischaemic cause of HF as predictor of readmission and poor quality of life among HF patients (Di Mauro et al., 2018). Myocardial ischaemia was also found as an independent factor for all-cause readmission within 3 months of follow up (Salamanca-Bautista et al., 2016)

2.4.7 Other comorbidities

There are several other comorbidities that are associated with risk of readmission. Eastwood *et al.* (2014) also reported history of cancer, liver disease and pulmonary disease as the independent predictors. Sherer *et a.l* (2016) on the other hand, identified atrial fibrillation, cardiomyopathy and coronary artery disease as the significant risk factors. Another study in Japan found that DM is one of the independent predictors (Kaneko et al., 2015).

2.4.8 Ejection fraction

Heart failure is classified according to ejection fraction (EF) status. The latest classifications are HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF), HF with preserved ejection fraction (HFpEF) and finally HF with improved ejection fraction (HFimpEF) (Bozkurt et al., 2021). Even though about half of HF patient are HFrEF but the prevalence of HFpEF is increasing (Savarese et al., 2023). Regmi *et al.* (2020) concluded that patients with HFpEF had higher risk of readmission compared to HFrEF. However, another study that included only HFrEF patients found lower EF to be independent predictor (Naderi et al., 2022). This finding is supported by a study in Palestine (Habib & Shaath, 2022). A systematic review

reported the hazard risk for a composite endpoint of death and readmission rate was highest in HFrEF group (Choi, Wiseman & Betihavas, 2021).

2.4.9 Length of stay

Longer length of stay (LOS) or duration of admission for index hospitalisation might increase the risk of admission. Two studies in USA categorised the LOS of more than 5 days and found it to be independent predictor for readmission (Reynolds et al., 2015; Bradford et al., 2017). An older study in 2009 had similar finding for LOS of more than 7 days (Aranda, Johnson & Conti, 2009). Extended LOS often reflects the severity of the patient's condition and the complexity of their treatment needs (Reynolds et al., 2015). Another study reported LOS is associated with increased risk of worsening heart failure during admission and mortality post discharge but not associated with readmission (Davison et al., 2016). Thus, LOS during the index hospitalization serves as a critical marker for identifying patients at high risk for readmission

2.4.10 Medications

Medications remain the mainstay of heart failure management. The four pillars for Guideline-directed medical therapy (GDMT) for HF with reduced ejection fraction consist of angiotensin receptor-neprilysin inhibitors (ARNI), β-blockers, mineralocorticoid receptor antagonists (MRA) and sodium glucose cotransporter 2 inhibitors (SGLT2i) (Straw, McGinlay & Witte, 2021). These medications have been extensively studied and proven to contribute better outcome for HF patients in term of mortality and hospitalisation. Utilisation of ARNI in clinical practice is still limited within Malaysia and most HF patients are on the cheaper and more available alternatives such as Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs). A similar situation is observed for SGLT2 inhibitors where their availability is limited within tertiary care centres in Malaysia.

Certain medications prescribed upon discharge are associated with higher risk of readmission. Among non-cardiovascular medications, antigout medications and use on insulin had higher risk of readmission (Kruik-Kollöffel et al., 2022). The use of insulin can be explained by the presence of DM as a possible independent predictor. Kaneko *et al.* (2015) identified the use of loop diuretic increases the risk of readmission. It has been proven that ACEi and Beta-blocker can reduce mortality risk among HF patients. However, their role in reducing the risk of readmission have not been shown in real-world data (Yamaguchi et al., 2018).

2.4.11 Brain natriuretic peptide

Several laboratory values were found to be related to HF readmission. Both BNP and N-terminal pro b-type natriuretic peptide (NT-proBNP) are useful markers for HF. NT-proBNP is more sensitive than BNP due to its longer half-life; however, the clinical differences between them are subtle (Masson et al., 2006). BNP which is a biomarker for heart failure status and severity is indicative of neurohormonal activation and myocardial strain (Di Mauro et al., 2018). It is shown to have some value in predicting readmission (Naderi et al., 2022). Mauro *et al.* (2018) found that NT-proBNP was associated with higher rehospitalisation and poor quality of life post discharge. In another prospective cohort study, BNP level was significantly higher in frequent flyers group at univariable analysis (Feola et al., 2016). NT-proBNP was found to be predictor for both hospitalisation and mortality in a separate multivariable analysis (González-Costello et al., 2018). Similar result was obtained for BNP in predicting composite endpoint of mortality and readmission (Mutlak et al., 2018). In the two aforementioned studies, BNP/ NT-proBNP values were log-transformed for analysis.

2.4.12 Biochemistry

Uric acid level is another laboratory values related to adverse outcome post discharge including readmission. Higher uric acid level was associated with readmission and mortality 1-year post discharge (Mohd Ghazi, Teoh & Abdul Rahim, 2022). Naderi *et al.* (2022) also found higher uric acid as independent predictor of readmission. Another study found an association between elevated uric acid levels and both chronic kidney disease (CKD) and pulmonary congestion.(Palazzuoli et al., 2016). A meta-analysis study also concluded that HF patients with higher uric acid levels had a significantly increased risk of all-cause mortality and the combined endpoint of death or readmission, even after adjusting for confounding factors (Huang et al., 2019). Measuring uric acid level may provide useful information for risk stratification upon discharge.

Although it is not frequently reported, hyponatraemia may influence the risk of readmission. Two studies have reported this finding (Habib & Shaath, 2022; Mohd Ghazi, Teoh & Abdul Rahim, 2022). Similar studies also found higher urea and creatinine to predict readmission in relation to CKD being an independent predictor as described above.

2.4.13 Other predictors for readmission

Prior hospitalisation in the previous year is also indicative for higher risk of readmission. Aranda *et al.* (2009) found both HF hospitalisation in the previous year or any hospitalisation within 9 months increased the odd of readmission.

Vital signs upon discharge are also important factor for readmission. Mohd Ghazi *et al*. (2022) concluded that patients with lower systolic & diastolic blood pressure tended to have early readmission. Meanwhile, heart rate upon discharge was

observed as independent predictor from multivariable analysis in another two studies (Di Mauro et al., 2018; González-Costello et al., 2018)

2.5 Summary of literature review

Summary of readmission is displayed in Table 2.3 and summary of important predictors is shown in Table 2.4.

Table 2.3: Summary of readmission rate

Article (Country)	Sample size (n)	Follow-up period	Readmission
Naderi et al., 2022 (Iran)	428	6 months	24%
Eastwood et al., 2014 (Canada)	18 590	30 days	18%
Regmi et al., 2020 (USA)	1916	30 days	25%
Habib & Shaath, 2022 (Palestine)	164	6 months	32.9%
Reynolds et al., 2015 (USA)	19 927	1 year	21% (30 days) 60% (1 year)
Kaneko et al., 2015 (Japan)	282	3 years	17.5% (1 year) 25.5% (3 years)
Al-Omary et al., 2018	Meta-analysis		20% (30-day) 56% (1-year)
Lan et al., 2021	Meta-analysis		19% (30-day) 53% (1-year)
Lim et al., 2022 (Malaysia)	105 399	30 days	18%
Raja Shariff et al., 2021 (Malaysia)	1307	1 year	39.5% (6-month) 76.1% (1-year)
Mohd Ghazi, Teoh & Abdul Rahim, 2022 (Malaysia)	3923	1 year	6.8% (30-day) 24.7% (1-year)

Table 2.4: Summary of important predictors of readmission

Predictors	Authors, year	Finding
Age	(Kaneko et al., 2015)	Higher risk among those ≥ 75 years old
	(Eastwood et al., 2014)	Higher risk among those ≥ 75 years old
	(Aranda, Johnson & Conti, 2009)	Higher risk among those ≥ 65 years old
	(Naderi et al., 2022)	Younger age among those with readmission
Race	(Durstenfeld et al., 2016)	Higher risk among black & Hispanic compare to white
	(Lim et al., 2022)	Higher risk among Chinese and Indians compare to Malay
Kidney disease	(Eastwood et al., 2014)	Higher risk for those with kidney disease
	(Regmi et al., 2020)	Higher risk for those with kidney disease
	(Naderi et al., 2022)	Higher BUN as predictor for readmission
	(Habib & Shaath, 2022)	Higher creatinine associated with higher risk of readmission
Ejection fraction	(Regmi et al., 2020)	Higher risk for HFpEF compare to HFrEF
	(Naderi et al., 2022)	Higher LVEF is associated with lower risk of readmission
	(Habib & Shaath, 2022)	Higher risk for patients with LVEF<30%
Length of Stay (index admission)	(Reynolds et al., 2015)	Higher risk among those LOS >5 days
	(Bradford et al., 2017)	Higher risk among those LOS >5 days
	(Aranda, Johnson & Conti, 2009)	Higher risk among those LOS >7 days

Table 2.4 Continued

Predictors	Authors, year	Finding
Medication	(Kruik-Kollöffel et al., 2022)	Higher risk among those discharge with anti-gout & insulin
	(Kaneko et al., 2015)	Higher risk for those discharge with loop diuretic
Atrial Fibrillation	(Sherer et al., 2016)	Higher risk among those with AF
	(Fung et al., 2007)	Higher risk among those with AF
	(Munir et al., 2017)	Higher risk among those with AF
Laboratory values	(Naderi et al., 2022)	Higher Pro-BNP & higher uric acid were important factor for readmission
	(Mohd Ghazi, Teoh & Abdul Rahim, 2022)	Increase risk for higher uric acid and hyponatraemia
	(Habib & Shaath, 2022)	Higher risk with hyponatraemia
Vital signs	(Mohd Ghazi, Teoh & Abdul Rahim, 2022)	Higher risk with lower systolic and diastolic blood pressure
	(Di Mauro et al., 2018)	Higher risk among those with heart rate >70 bpm
	(González-Costello et al., 2018)	Higher risk among with higher heart rate

2.6 Conceptual framework

The conceptual framework of the study is presented in Figure 2.1 below. Variables in bold text were collected in this study.

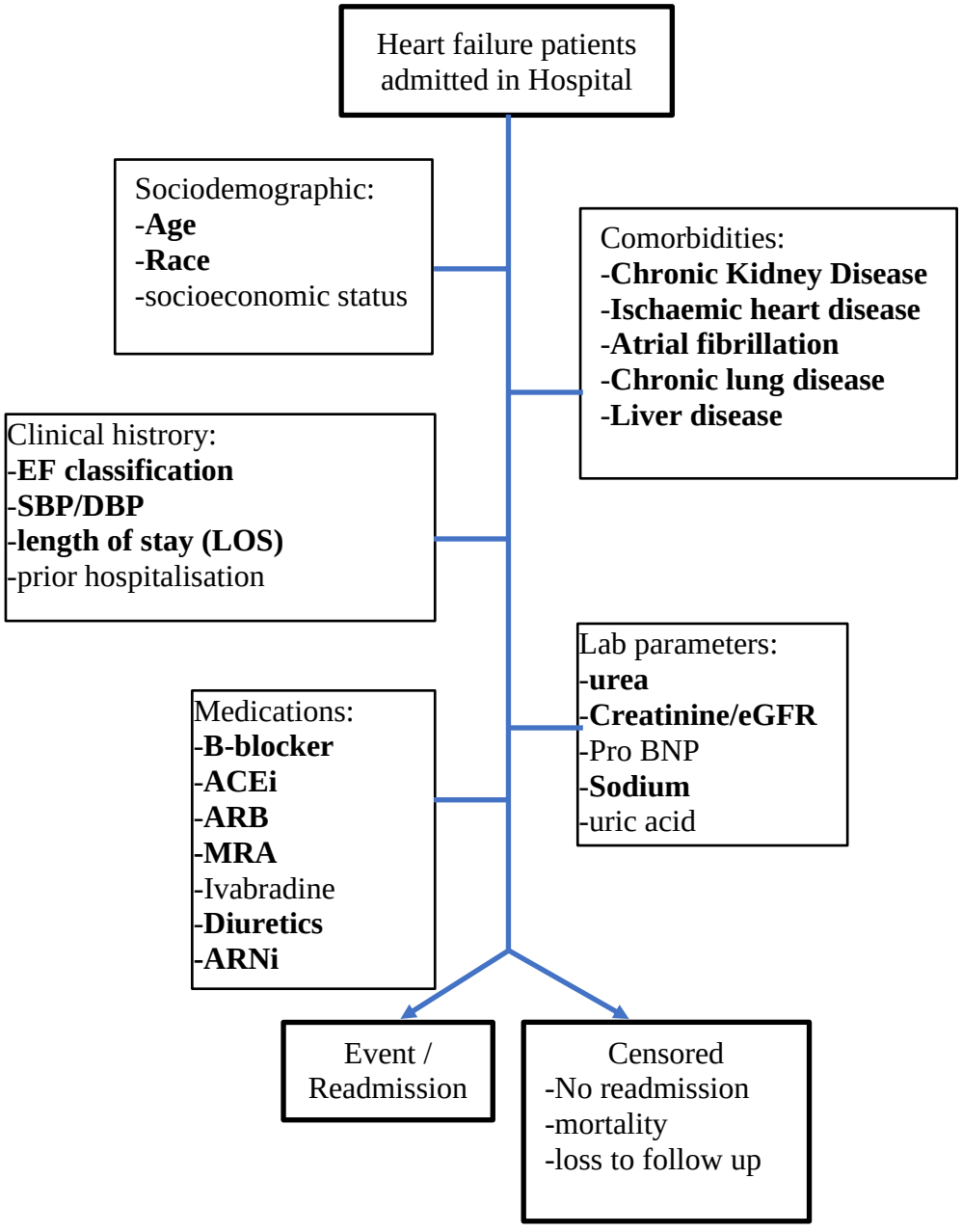

Figure 2.1: Conceptual Framework

CHAPTER 3

METHODS

3.1 Study Design

This was a retrospective cohort study. Study cohort was defined as heart failure patients admitted in HRPZII within the accrual period from Oct 2021 to Dec 2022. The cohort had an additional follow up period for one year (Jan 2023 to Dec 2023) to determine the outcome of readmission.

3.2 Study Duration

The data collection was started in January 2024 and completed in April 2024

3.3 Study Setting

This was a single centre study conducted in Hospital Raja Perempuan Zainab II (HRPZII). HRPZII was selected as it is the main referral centre in Kelantan with complete Cardiology services.

3.4 Study Population & Sample

Table 3.1: Study population and sample

Population & sample	Description
Reference population	All patients admitted in the hospital with a primary diagnosis of heart failure in Kota Bharu, Kelantan
Source population	All patients admitted in HRPZII with a primary diagnosis of heart failure
Sampling frame	All patients admitted in HRPZII with a primary diagnosis of heart failure from Oct 2021 to Dec 2022

3.5 Eligibility Criteria

3.5.1 Inclusion Criteria

- Age 18 years old and above
- Index hospitalization with main diagnosis of heart failure
- Formal echocardiogram finding within one year of index hospitalisation
- Malaysian citizen

3.5.2 Exclusion Criteria

- In-patient mortality during index hospitalisation
- Patients transferred to another facility upon discharge
- Patients discharged with At Own Risk (AOR) consent
- Active malignancy
- Pregnancy

3.6 Sample Size Determination

Objective 1

sample size was calculated based on single proportion formula using online sample size calculator (Arifin, 2023)

Proportion of readmission at **6-month** post discharge: 24% (Naderi et al., 2022)

Precision: 6%

Confidence level: 95%

Expected drop-out rate: 10%

Sample size: 217

Proportion of readmission at **1-year** post discharge: 76.1% (Mohd Ghazi, Teoh & Abdul Rahim, 2022)

Precision: 6%

Confidence level: 95%

Expected drop-out rate: 10%

Sample size: 217

Objective 2

Sample size calculation was not performed for estimation of median survival in view of no readily available software or equation than can be used. Calculation is based on Cox regression analysis as shown in objective 3 below.

Objective 3

For specific objective 3, sample size was calculated using PS power and sample size calculation version 3.0 Jan 2009.

survival -> sample size -> hazard ratio or relative risk

α: 0.05, power: 0.8

Hazard ratio, R = Expected hazard ratio based on researcher decision

Accrual time, A= 15 months (Oct 2021 – Dec 2022)

Follow up period, F= 12 months (Jan 2022 – Dec 2023)

Median survival of control, m1= 6 months, this is based on Kaplan Myer analysis reported in Lee *et al* (2004)

Ratio case to control, m: 1

Table 3.2: Sample size calculation

Variable	Hazard ratio, R[a]	Sample size, n (+ 10% drop-out)
Age (>70 years old)	1.80	58x2 = 116 (129)
Lower LVEF	1.50	116x2 = 232 (258)
Kidney disease	1.45	137x2 = 274 (305)
LOS > 5days	1.60	88x2 = 176 (196)

[a]Expected hazard ratio based on researcher's decision

Sample size for specific objective 2 was also calculated based on the rule of thumb suggested by Vittinghoff *et al* (2007), which is an elaboration from the original and influential work of Peduzzi *et al* (1995) . The author suggests that the rule of 10 events per variable (EPV) should not be applied in all situations and in general, bigger samples and more events are preferred. Ogundimu *et al* (2016) recommended higher EPV is needed in the presence of predictors with low prevalence.

The estimated number of predictors in the final model is four, k=4

EPV of 13 is used in this calculation to minimise the risk of bias.

Prevalence of outcome is 24% (Naderi et al., 2022)

The calculated sample size is n= 13x4/0.24 = 217 (242 including 10% drop-out)

Therefore, the minimum required sample size is **305** from specific objective 2.

3.7 Sampling Method

No sampling method was applied since all available samples were selected based on eligibility. This is due to the limited number of unique patients within the accrual period.