CHAPTER 1

INTRODUCTION

1.1 Introduction

Cardiovascular disease is the leading cause of morbidity and mortality worldwide. World Health Organization reported that 31% of global death are due to heart disease (WHO, 2021). The increase in heart problems led to an increase in heart surgery. Heart surgery is a major surgery that may rises many complications. Common complications include stroke, renal failure, arrhythmias, postoperative cognitive dysfunction and worst, mortality. Among all heart-related surgery, coronary artery bypass grafts (CABG) are the most common procedure for surgeons up to date (Melly et al., 2018). CABG is a procedure of bypassing a narrowed or clogged major artery to restore blood flow and oxygen supply to the heart. Despite technological advancement during the procedure, these postoperative complications are still unavoidable (Pooria et al., 2020).

Postoperative cognitive dysfunction (POCD) remains as an unsolved problem since the first cardiopulmonary bypass (CPB) was introduced (Glumac et al., 2019). Up to 30-40% of CABG patients were reported to develop early POCD. The percentage reduced to 20% after a few months postoperatively (Nemeth et al., 2017). After years, POCD cases may reduce but possess increased risk of death (Brodier & Cibelli, 2021). The reported incidences of POCD worldwide are high in prevalence and could have a severe effect on affected patients (Zhang et al., 2018). Furthermore, POCD effect on patients vary depends

on their individual factors, which is important to be addressed. Generally, POCD brings many setbacks as prolonged hospital stays and rehabilitation, reduced quality of life, common working disability and early retirement, thereby producing a burden to the healthcare system (Keage et al., 2016).

Besides, CPB imposes risks to organ injury which includes organs such as the brain and kidneys. Despite having cutting-edge technology, postoperative brain injury remains high. One of the detrimental complications is stroke which occurs in 10% of susceptible patients (Tarakji et al., 2011). The possible mechanism of the brain injury may include hypoperfusion, cerebral embolism or brain hyperperfusion (Juliana et al., 2021). Brain injury and POCD were closely related as both were unavoidable postoperative complications. Cutting-edge technology may alleviate the risk of cerebral injury. Continuous monitoring of brain perfusion during surgery is needed to avoid cerebral hypo or hyperperfusion. This will later reduce unwanted complications postoperatively.

1.2 Background of the Study

POCD is characterized by the reduction of cognitive function after an individual undergoes surgery (Rundshagen, 2014). The type of surgery that has been studied is wide, with most studies classifying it as cardiac and non-cardiac surgery. Cardiac surgery shows a higher incidence of POCD with 40% of cases compared to 20% in non-cardiac surgery (Brown & Purdon, 2013). Open heart surgery imposes additional risks to patients due to cardiopulmonary bypass during surgery, together with various other risk factors.

Concerning the occurrence of POCD after CABG, multiple studies have been conducted worldwide to see the prevalence in different anaesthesia types, CPB types and cognitive tests. A study in 2001 in United States by Newman et al. found that 53% of 261 patients had cognitive decline at discharge, and the percentage reduced to 36% and 24% after six weeks and six months post-CABG. After five years, cognitive decline was found in 42% of the patients (Newman et al., 2001). The prevalence was quite high and a similar result was seen in a study in Sweden in 2006 by Vedin et al. where the incidence of cognitive decline at 1 week was 57% for on-pump CABG (Vedin et al., 2006). With the advancement of technology and the usage of sedative that ameliorates cognitive function, the current study shows improvement in the occurrence of POCD. The usage of dexmedetomidine over midazolam has shown a significant reduction in POCD occurrence in a clinical trial in Iran (Rajaei et al., 2019). A similar study in China by Wang et al. (2019) shows POCD occurrence at 26.3% at 5-7 days postoperatively, and the numbers reduced to 12.1% after 3 months. In short, the occurrence of POCD post-CABG ranges about 20-30% in the early stages, and the number lowered to less than 20% after a few months postoperatively. In Malaysia, the incidence of POCD was reported to be at 40% postoperatively, with no further studies following the patients after discharge (Kadiman, 2023).

On the other hand, previous studies suggested that continuous monitoring of cerebral perfusion improves postoperative outcomes. Studies have correlated it with decreased composite outcome of death, prolonged mechanical ventilation >48 hours, stroke, renal failure requiring dialysis, mediastinal re-exploration, myocardial infarction, and deep-sternal wound infection (Murkin, 2011; Juliana et al., 2021). Overall, it helps in reducing

morbidity and mortality of patients' post-cardiac surgery. Since POCD mainly involves brain functions, the monitoring of cerebral perfusion might serve as an alternative to maintain cognitive function postoperatively. Monitoring of cerebral oxygenation intraoperatively was found to lower the incidence of cognitive decline compared to control. It also served as a predictor for early POCD (odds ratio, OR=0.21) (Colak et al., 2015).

POCD is not a disease that is listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (Berger et al., 2015). Hence, to define an individual have POCD, they need to undergo a neuropsychological assessment before and after surgery as part of the research. Since these assessments involve many different tests, the consistency and reliability are questionable (Ramussen et al., 2004). Many other objective ways of diagnosing POCD have been studied such as using biomarkers as predictive value. Biomarkers such as S100B and neuron-specific enolase (NSE) are commonly used to characterize inflammatory responses in patients. There is a correlation between the level of inflammation with the occurrence of POCD (Kok et al., 2017). Current advancements and technology in research have allowed researchers to explore molecular fields. Several studies listed some RNAs that were expressed differently in POCD patients compare to non-POCD patients. They suggested the differently expressed microRNAs involves in the pathway and development of POCD occurrences (Wang et al., 2019; Zhang et al., 2018). With this valuable information and understanding, we can suggest options to reduce the incidence of POCD for better patient quality of life postoperatively.

1.3 Problem Statements

The increase in coronary artery bypass grafts has led to an increase in POCD occurrence. Currently, the standard for diagnosing POCD is by neuropsychological assessments. The diversity in the assessment has caused many problems such as reliability issues, the long time taken to complete the assessment and the floor and ceiling effect of the test. Due to the following issues, we need to have other definitive diagnoses that can help in diagnosing POCD. Diagnosis from blood tests and analysis could give us precise information such as the use of biomarkers. Even though many biomarkers have been studied, there are still conflicting results exist and the pathway of PCOD occurrence are less understood. Hence, it is a wise approach to explore the molecular level in POCD occurrence by performing gene analysis. By doing so, we can understand the pathway and elucidate the mechanism and gene expression involved in the development of POCD. Also, potential proteins involved in the occurrence could be detected. The identification of these proteins are important to prove the clinical intervention that is being done during surgery is manifested in patients' blood. The proteins could also be used as novel biomarkers or assist in POCD management, and could help in diagnosis, prevention and proper intervention during CABG procedure to reduce POCD occurrence.

On the other hand, the utilization of cerebral oximetry is sought to be the future of cardiothoracic surgery. With the advantages of monitoring brain perfusion to mitigate brain injury and overall improve neurological outcome, cerebral oximetry monitoring is opted to be used in each surgery case. However, the technology added more cost to the procedure which eventually increased the financial burden. It is not a standard protocol to use in intraoperative setting despite knowing it benefits to patient's morbidity and mortality as

well as their postoperative outcomes. Randomized control trials have been conducted to intervene the patient's cerebral perfusion, yet we less understand the genes involve and pathway differences in patients benefits from its utilization and those who do not. Deeper understanding in this area will help clinicians to decide the best option for patients to balance the need of cerebral oximetry usage and its financial concern.

1.4 Research Questions

1. What are the gene expressions profiles in high-risk CABG patients with and without POCD?
2. What are the gene expressions profiles in high risk CABG patients utilizing cerebral oximetry with the outcome of POCD?
3. What is the potential immunoregulatory pathway significantly expressed in high-risk CABG patients with POCD?
4. What are the differences of erythroferrone level between POCD and non-POCD?

1.5 Research Hypotheses

Ho: There is no differences in gene expression profiles and the circulating protein level in high-risk CABG patients with POCD.

Ha: there is a difference in gene expression profiles and the circulating protein level in high-risk CABG patients with POCD.

1.6 Research Objectives

General Objective:

To elucidate the gene expression profiles, and the circulating level of protein in high-risk CABG patients with POCD.

Specific Objectives:

1. To elucidate the gene expressions in high-risk CABG patients with and without POCD.
2. To elucidate the gene expressions in high risk CABG patients utilizing cerebral oximetry with the outcome of POCD.
3. To identify the potential immunoregulatory pathway significantly expressed in high-risk CABG patients with POCD.
4. To determine the differences of erythroferrone level between POCD and non-POCD. that correlates with the expressed genes.

1.7 Study Outcome

The outcome of the study will give insight into the pattern of postoperative cognitive dysfunction in Malaysia since Institut Jantung Negara is the national referral center for cardiac surgery. This will give valuable information to evaluate our nation's competitiveness level in providing the best healthcare services, particularly in cardiac surgery. Besides, the analysis of gene expressions allows us to maximise current technology to dig deeper into the molecular mechanism of disease pathology. By understanding the mechanisms, researchers can deploy various preventive ways to reduce

POCD occurrence. For example, the use of anaesthetic agents during surgery, medications to alleviate the symptoms, as well as provides prognostic value to improve a patient's quality of life. Since POCD has no definitive mechanisms up till now, the result of this study will fill to the gap of knowledge for researchers.

1.8 Implication of Study

1. Identification of proteins involved in the pathways to be potentially used as biomarkers in the clinical setting for early prediction and better management of patients with POCD.
2. The usage of cerebral oximetry and its effects on neurological outcomes, particularly in POCD. The study will add in evidence on its usage and POCD occurrence in cardiothoracic patients, which currently become the spotlight to researchers in this field.
3. Elucidating pathway involves with the utilization of cerebral oximetry during cardiothoracic surgery. This will emphasize the importance of cerebral oxygenation monitoring for better brain perfusion and equipoise the need for its usage in the standard protocol. The usage of such technology is uprising nowadays hence promoting better healthcare procedures and management.

1.9 Conceptual Framework

Individuals are predisposed to cognitive decline regardless undergoing surgery or not. The risk of postoperative cognitive dysfunction occurs as the insult of surgery that gives rise to many possibilities of cognitive decline. The pre-existing factors before patients undergo surgery will influence the outcome. However, the insult of surgery increases the risks as intraoperative and postoperative factors determined most of the outcome. Patients that have a significant reduction in cognitive function test postoperatively means they developed early POCD. The development of POCD is complex. Multiple factors throughout the surgery process have led researchers to understand each mechanism in detail. By utilizing current technology, we can explore the gene expression in POCD development. Furthermore, the increased attention in cerebral oximetry usage led us to acknowledge the differential expressions that may involve in POCD. Hence, gene expression analysis will allow us to understand which genes involves, in their up- and downregulation of the genes specifically. By acknowledging the molecular pathway in depth, we can construct an association of the gene expression with the occurrence of POCD. The importance of the study as it will give insights for us to suggest many ways to alleviate the occurrence of POCD. This includes giving drugs or medications, usage of anaesthesia that targets specific pathways, or using the constructed pathway for the prognosis of patients for future rehabilitation and better patient management. Figure 1 shows the conceptual framework of the study.

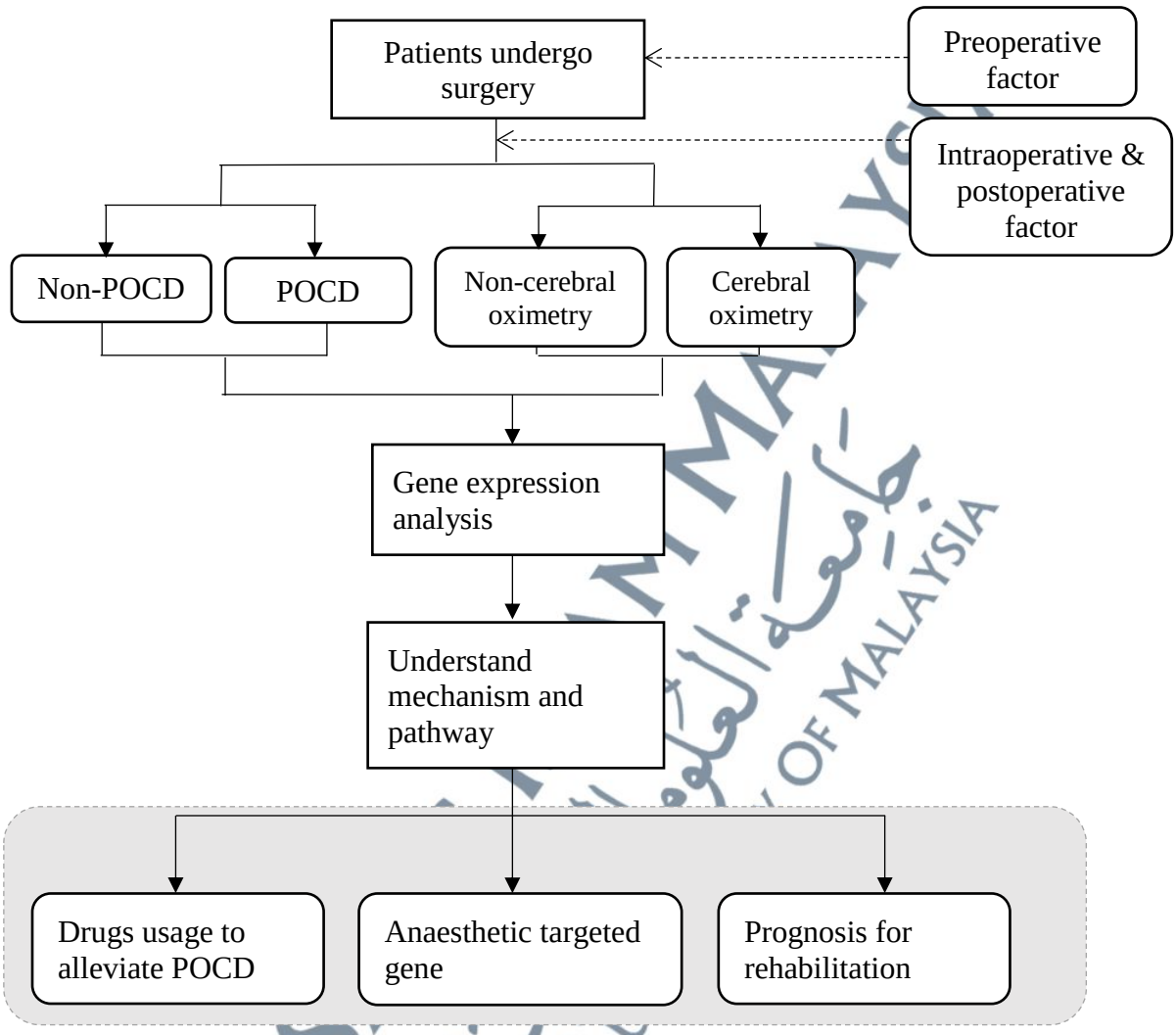

Figure 1.1: Conceptual framework of this study. Patients were predisposed to patients' factors and intraoperative factors when undergoing surgery. They may experience POCD or not, and may or may not utilize cerebral oximetry during surgery. In both cases, the profiling of gene expression is vital to understand the mechanism and pathway related, that later benefits through drugs discovery and usage, anaesthetic targeted genes and prognosis for rehabilitation.