ASSOCIATION OF RED BLOOD CELL TRANSFUSION WITH MORBIDITY AND MORTALITY IN POST CARDIAC SURGERY PATIENTS

BY

DR AHMAD ARIF CHE ISMAIL

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER IN MEDICINE (TRANSFUSION MEDICINE)

UNIVERSITI SAINS MALAYSIA

ADVANCED MEDICAL AND DENTAL INSTITUTE (AMDI)

2017

DECLARATION

I hereby declare that this research has been sent to Universiti Sains Malaysia for the degree of Masters of Medicine in Transfusion Medicine. It is not to be sent to any other universities. With that, this research might be used for consultation and can be photocopied as reference.

Dr Ahmad Arif Che Ismail

PIPM 0004/13

ACKNOWLEDGEMENT

Alhamdulillah, all praises to Allah for the blessing and giving me a good health, courage and strength to continue this dissertation.

Special appreciation goes to my supervisors, Dato Dr Yasmin Ayob, Honourary Lecturer of Advanced Medical & Dental Institute (AMDI), Universiti Sains Malaysia, also Visiting Consultant Haematologist of the National Heart Institute (IJN), Dr Abdul Rahim Hussein, Senior Haematology Lecturer of AMDI and Professor Dato Dr Mohamed Hassan Mohamed Arif, senior consultant Anaestesiologist of IJN as site supervisor, for their supervision and constant advice.

To Dr Rohayu Hami, Dr Noor Suzana Shariff, Mr Nizuwan of IPPT USM Bertam, Penang, and Dr Zul Khairul Naim of School of Public Health, Universiti Malaysia Sabah, thank you so much for the statistical guidance and help with data analysis and interpretation.

Very special thanks to the staffs of Research Unit of IJN and Mr Syahrom Mohamad of IJN Blood Bank for giving me such a great cooperation and assistance throughout the study. I would also like to acknowledge the continuous support from my fellow colleagues of Transfusion Medicine 2013/2017, who were together with me along this four years journey.

Last but not least, my beloved family, for constant love and encouragement. Words cannot express my appreciation and love for them and finally, I thank all those who helped me directly or indirectly in making my thesis a success. Thank you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AMDI	Advanced Medical and Dental Institute
BMI	Body Mass Index
BTS	Blood Transfusion Service
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CME	Continuous Medical Education
CVD	Cardiovascular Disease
EF	Ejection Fraction
Hb	Haemoglobin
HCT	Haematocrit
HLOS	Hospital Length of Stay
ICULOS	Intensive Care Unit Length of Stay
IJN	National Heart Institute
PBM	Patient Blood Management
PDN	National Blood Center
RBC	Red Blood Cell
SPSS	Statistical Package for Social Sciences
USM	Universiti Sains Malaysia
WHO	World Health Organization

ABSTRAK

Latar belakang: Penyakit Arteri Koronari (CAD) merupakan penyakit yang kerap ditemui yang merupakan sebab utama kematian dalam kalangan lebih kurang 20-25% pesakit di hospital awam di Malaysia. Pembedahan pintasan cantuman arteri koronari (CABG) merupakan salah satu cara berkesan untuk merawat pesakit yang menghidap CAD. Walau bagaimanapun, pembedahan CABG dikaitkan dengan transfusi sel darah merah yang banyak (RBC) yang mengakibatkan pelbagai morbiditi dan kematian. Kajian ini berhasrat untuk mencari perkaitan antara transfusi RBC dengan morbiditi dan kematian selepas CABG di Insitut Jantung Negara, Kuala Lumpur (IJN).

Kaedah: Kajian Rentas Retrospektif dijalankan dengan data daripada 434 pesakit yang menjalani CABG selama tempoh dua tahun (2013 dan 2014). Data didapati daripada data pesakit berkomputer di IJN. Subjek kajian dipilih secara persampelan rawak sistematik setiap pesakit kelima daripada rekod perubatan dalam urutan tarikh tahun itu, dan selepas pembersihan data dilakukan. Data yang didapati diisi dalam proforma. Kesemua data demografik dan klinikal berkaitan dengan transfusi RBC – morbiditi dan kematian dicatatkan kemudiannya dianalisa.

Keputusan: Seramai 64.3% pesakit CABG (n=279) yang menerima transfusi RBC peribedah manakala 35.5% (n=155), tidak menerima transfusi RBC. Umur, jantina, Indeks Jisim Badan (BMI) dan Fraksi Ejeksi (EF), merupakan 4 faktor penting yang menyumbang kepada transfusi

RBC. Transfusi RBC sebaliknya menjadi penyumbang kepada tempoh tinggal di Unit Rawatan Rapi (ICULOS) dan di hospital (HLOS) yang lebih panjang, tetapi tidak pada faktor jangkitan dan kematian. Regresi logistik pelbagai mendedahkan bahawa 3.5% pesakit cenderung untuk menjalani transfusi setiap 1 tahun peningkatan umur, manakala dalam 1 kg/m^2 BMI dan 1% FE akan merendahkan kemungkinan transfusi RBC sebanyak 13.0% dan 3.0%.

Kesimpulan: Umur, jantina, BMI dan EF merupakan empat faktor penentu penting dalam kebarangkalian untuk transfusi RBC dalam CABG manakala transfusi RBC akan menyebabkan ICULOS, HLOS yang lebih panjang. Kebarangkalian transfusi RBC adalah lebih tinggi dalam kalangan pesakit yang lebih berusia dan kurang dengan peningkatan BMI dan EF.

Kata kunci: Transfusi RBC, morbiditi, kematian, Institut Jantung Negara (IJN), Penyakit Arteri Koronari (CAD), Pembedahan pintasan cantuman arteri koronari (CABG)

ABSTRACT

Background: Coronary Artery Disease (CAD) is very common and remains an important cause of mortality accounting for 20-25% of all mortality in public hospitals in Malaysia. Coronary artery bypass grafting (CABG) is one effective mode of treatment for patients with CAD. However, CABG operation is associated with high red blood cell (RBC) transfusion that in turn associated with various morbidity and mortality. This study aims to find the association of RBC transfusion with morbidity and mortality in post CABG patients in National Heart Centre, Kuala Lumpur (IJN).

Methods: Retrospective Cross Sectional Study was performed with data from 434 patients who underwent CABG over a period of two years (2013 and 2014). Data were retrieved from the computerized patient data system of IJN. Study subjects selected by systematic random sampling every fifth subject of the patient's medical record in the sequence of dates of the year, after data cleansing performed. Data retrieved were filled in the proforma. All demographic and clinical data in regards to outcome of RBC transfusion - mortality and morbidity were captured.

Results: 64.3% of CABG patients (n=279) received RBC transfusion perioperatively while 35.7% (n=155) did not. Age, gender, Body Mass Index (BMI) and Ejection Fraction (EF), were 4 factors that significantly contributed to RBC transfusion. RBC transfusion in turn, shown to be significant contributor for longer ICULOS and HLOS, but not for infection and death risk. Multiple logistic regression revealed that patients were 3.5% more likely to be transfused for

every 1year increase of age, while increase in 1 kg/m^2 of BMI and 1% of EF will reduce the odds of RBC transfusion by 13.0% and 3.0%.

Conclusions. Age, gender, BMI, and EF are four important determinants for probability of RBC transfusion in CABG while RBC transfusion will result in longer ICULOS, HLOS. Probability of RBC transfusion will be higher with those of older age and reduced with increase in BMI and EF.

Key words: CAD, CABG, RBC transfusion, morbidity, mortality, National Heart Centre (IJN)

CHAPTER 1 : INTRODUCTION

1.1 Overview of Cardiovascular Diseases and Coronary Artery Bypass Graft

Cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels. They consist of coronary artery disease (CAD), cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart disease, as well as deep vein thrombosis and pulmonary embolism. CVD are the number 1 cause of death worldwide with more people dying annually from CVD than from any other cause. In 2012, it was estimated 17.5 million people died from CVD, equal to 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to CAD (Organization, 2014).

Heart attacks are usually very sudden and are mainly caused by narrowing of arteries that prevents blood supply to heart. The main reason for this is fatty deposits on the inner walls of the blood vessels. The heart attacks happen as the result of a combination of risk factors, such as cigaratte use, unhealthy diet and obesity, physical inactivity and excessive use of alcohol, hypertension, diabetes and hyperlipidaemia (Organization, 2014).

In Malaysia, CAD remains an important cause of mortality, which contribute about 20% to 25% of all mortality in public hospitals in Malaysia. It is noted that in Malaysia, patients with Acute Coronary Syndrome presents 6 years younger than those in the

Global Registry of Acute Coronary Events (GRACE) which is at mean age of 59 ± 12 years (Zambahari *et al.*, 2014).

Coronary artery bypass grafting (CABG) is one mode of revascularization treatment for patients with CAD. It was reported that CABG offered better outcome as compared to medical therapy for patients with left main or triple vessel disease (Yusuf *et al.*, 1994). CABG also found to be more effective to relieve angina symptoms as compared to medical therapy (Hueb *et al.*, 2004). The indications for CABG based on guideline of American College of Cardiology Foundation/ American Heart Association 2011 are as attached in Appendix 5.

1.2 Blood Transfusion and CABG

Platelet activation, fibrinolysis, haemodilution and usage of heparin anticoagulation are known to be associated with the usage of extracorporeal circuit and deep hypothermia that are routinely practiced in CABG procedure (Estafanous *et al.*, 2001). All these factors lead to higher tendency of the patients who underwent CABG to have excessive bleeding during intraoperative and postoperative period. Therefore, it is not surprising that CABG procedure is generally associated with high usage of blood products (Estafanous *et al.*, 2001). In addition, platelet dysfunction happen very commonly during and after CABG operation as the result of platelet activation, also contributes to bleeding tendency post operatively (Jakobsen *et al., 2012,* Czer *et al.*, 1987).

It was consistently reported that there is very wide variation of usage of blood products in different cardiac centres and different surgeons, as it ranged from 25% to 95% (Stover *et al.*, 1998). Some centres are practicing bloodless surgery which contribute to as low as 5% of RBC transfusion as compared to more than 90% at other centres (Putney, 2007).

National Heart Institute, Kuala Lumpur (IJN) is the leading tertiary cardiac centre in Malaysia that serves as a national heart referral centre. Statistics of IJN for year of 2010 to 2015 revealed that in average, about 1200 to 1400 CABG cases were performed every year with 60.4% to 82% of patients received blood transfusion perioperatively (unpublished data of IJN, 2016).

Internal audit done by the IJN blood bank showed that there was huge discrepancy of the usage pattern of blood products among surgeons. There were surgeons who has higher tendency to transfuse blood products as compared to the other surgeons for the similar type of surgery. Initiatives have been started in 2013. There were 4 monthly surgeons blood usage audit, Continuous Medical Education (CME) about transfusion guideline and good transfusion practice. The initiatives found to be fruitful to reduce transfusion rate among physicians in IJN as the transfusion rate of CABG patients dropped to 65% in 2015, as compared to 82% in 2010.

1.3 Research Justification and Benefits

The goal of this study was to assess the current practice and the outcome of RBC transfusion in post cardiac surgery patient in IJN, as a single reference centre of cardiac surgery in Malaysia.

The data of transfusion practice in IJN were collected in regards to transfusion rate, its associated morbidity and mortality, as well as the clinical factors that can help to predict possibility of RBC transfusion in CABG patients. The result of this study can contribute to IJN blood bank and other cardiac centres to understand the current blood transfusion practice in CABG patients in IJN. As a result, it can be used as a tool to create more awareness of the potential complications associated with blood transfusion and to convince and encourage physician to be more prudent in blood transfusion practice.

The fact that worldwide reports of huge variability of threshold for transfusion tendency among surgeons for similar type of surgery and significant number of RBC transfusion performed unnecessarily made this study relevant. Hopefully the findings would be helpful to boost the implementation of the current global practice of Patient Blood Management (PBM) and encourage judicious use of blood products among physicians.

1.4 Research Objectives

1.4.1 General Objective

To assess the association of red blood cell (RBC) transfusion with morbidity and mortality rate in post coronary artery bypass graft (CABG) patients in IJN.

1.4.2 Specific Objectives

i. To assess proportion of RBC transfusion in CABG procedure.

ii. To compare the outcome (ICULOS, HLOS, infection complication and death) of patients who received and did not receive RBC transfusion

iii. To determine predictive factors (age, gender, BMI, EF) associated with RBC transfusion in CABG

1.5 Research Hypothesis

i . There is significant difference of characteristic of CABG patients who received RBC transfusion with those who did not.

ii. RBC transfusion is associated with increased morbidity and mortality in post cardiac surgery patients.

1.6 Conceptual framework

There are a few factors that may influence possibility of RBC transfusion in patients who undergo CABG operation as shown in Figure 1.1. In this study, age, gender, BMI and EF are factors that were studied.

The outcome of RBC transfusion in CABG may vary from no issue, morbidities (prolonged ICULOS, HLOS, infection complications, delayed extubation, multiorgan failure, re operation) and mortality. However, only factors highlighted in bold were studied.

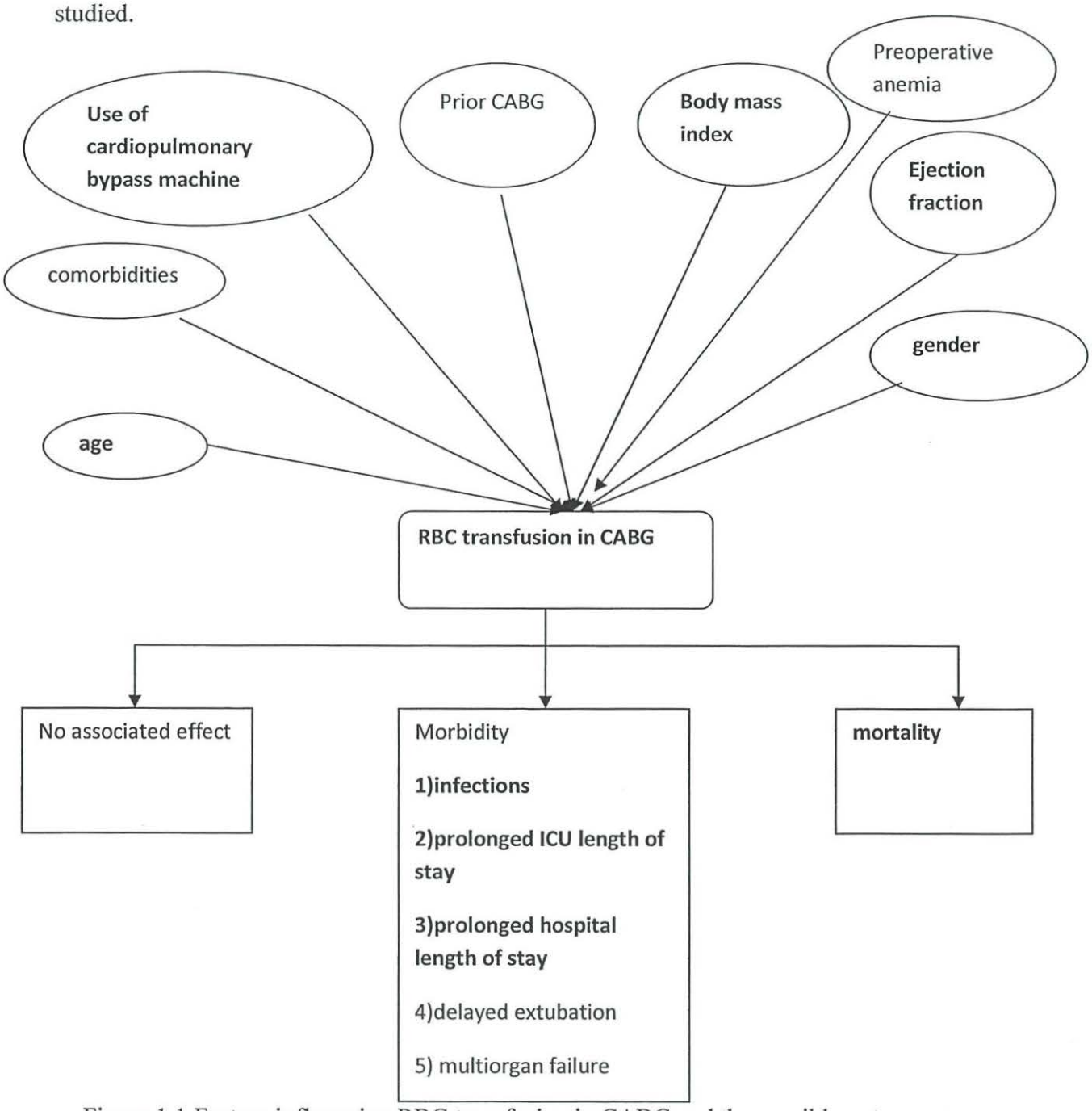

Figure 1.1 Factors influencing RBC transfusion in CABG and the possible outcomes.

CHAPTER 2 : LITERATURE REVIEW

2.1 Introduction

In medical field, cardiac surgery is the largest user of blood products, with data from USA showed that 10% to 15% of total blood supply in the whole USA were consumed by cardiac surgery; while 59.2% of cardiac surgery patients received blood products transfusion (Mehta *et al.*, 2009). Similarly, it was reported that estimated 6% of all RBC transfused in UK happens in cardiac surgery (Wells *et al.*, 2002). Blood usage pattern of every cardiac center are different as the centers that practicing bloodless surgery contributed to as low as 5% of RBC usage, compared to 90% at other conventional centres (Stover *et al.*, 1998).

Moise (2001) reported that as high as 26% of patients in cardiac surgery unit received unnecessary blood transfusion. Other study also supported the fact, that there were elements of excessive administration of allogenic blood products in cardiac surgery (Khanna *et al.*, 2003).

2.2 Indication and predictive factors of RBC transfusion

In general, the main reason for red blood cell (RBC) transfusion performed is to improve oxygen delivery to the tissue, with aim to correct or prevent hypoxia (Murphy *et al.*, 2006; Casutt *et al.*, 2001). Commonly, Haemoglobin (Hb) and Haematocrit (HCT) will be used

as parameters for transfusion threshold since there is no other best and practical way of assessing the oxygen concentration in tissue (Murphy *et al.*, 2001).

However, Hb and HCT values are not the only factors that are weighed in making decision for transfusion. Other important factors that would be considered including the aim to be achieved like for life saving in haemorrhagic shock (Engström *et al.*, 2002), to improve cardiac output by increasing intravascular volume (Pape *et al.*, 2009), to improve haemostasis (Ravn *et al.*, 2011), and to compensate significant surgical bleeding (Jakobsen *et al.*, 2012). In addition, the patient's factors like age, sex, haemodynamic stability, possible presence of mechanisms compensating for the anemia are the points to be considered. Issues like high cost and scarcity of blood products, risk of infection and immunomodulation, potential benefits, conservation strategies available are very important points to be included (Ranucci *et al.*, 2011; Liumbruno *et al.*, 2009).

Galas (2013) and Stone (2012) had reported that predictive factors for blood transfusion in cardiac surgery were female, older age group, lower body weight, underwent complex type of surgeries, had longer Cardiopulmonary Bypass Time (CPB) and surgery duration. Moreover, patients with previous cardiac surgery, renal impairment, preoperative anticoagulant use and underwent emergency cardiac surgery also poses higher risk of bleeding, resulted in higher probability to receive more blood products (Stone *et al.*, 2012). Studies by Khanna (2003), Kulier (2007) and Niranjan (2006) also supported the predictive factors as mentioned earlier. This group of patients, despite being minority, they consumed the most number of blood products supplied to cardiac surgery patients. Society

of Thoracic Surgeon (STS) Workforce report in 2007 revealed that 10% of patients use more than 70% of RBC and Fresh Frozen Plasma (FFP) supplied to cardiac surgery patients. Ravn (2011) had similar finding that 70% of RBC and FFP were administered to less than 12% of total cardiac surgery patients.

2.3 Hemostatic changes and bleeding in cardiac surgery

The coagulation system, endothelium and regulatory proteins, platelets, and fibrinolysis are four pillars of haemostatic systems. These pillars work in harmony to ensure the balance in natural haemostatic process. Major surgery like CABG with usage of cardiopulmonary bypass machine (CPB) contributed to widespread activation and consumption of all haemostatic components. This results in increase platelet activation, coagulation protein activation and fibrinolysis during the procedure. The usage of CPB interferes with normal hemostasis by diluting coagulation proteins after reinfusion of shed blood, and activation of the kallikrein-kinin system, platelet and fibrinolysis (Sniecinski and Chandler, 2011).

It was reported that platelet dysfunction commonly occur during and post CABG operations as the result of platelet activation (Jakobsen *et al.*, 2012; Czer *et al*,. 1987. Uenlue (2007) reported that protein C, protein S and fibrinogen levels were found to be significantly reduced during CPB that further contribute to risk of haemorrhage during intraoperative and post operative period.

The above mechanisms with additional usage of anticoagulant drugs like heparin and deep hypothermia further contribute to excessive bleeding intraoperative and post operatively in CABG (Estafanous *et al.*, 2001; Sniecinski and Chandler, 2011).

Apart from the above mechanisms, the severity of bleeding also depends on the complexity of cardiac surgery in which, extensive surgery that involve thoracic aorta, valve repair and redo cardiac operation were associated with higher risk of bleeding (Ravn *et al.*, 2011). Therefore, cardiac surgeries generally associated with severe bleeding, in which has the potential of causing haemorrhagic shock (Stone *et al.*, 2012), made blood products transfusion during and after cardiac operations common (Santos *et al.*, 2006).

2.4 Transfusion practice in cardiac surgery

There is very wide variation of usage of blood products in different cardiac centres. It was reported to range from 20% to 95% in United Kingdom (Moise *et al.*, 2001) while in Scandinavian cardiac centres, Kytölä (1998) and Øvrum (1995) reported 3% to 88%. In the USA, centres which are practicing bloodless surgery contributed to as low as 5% of RBC usage as compared to more than 90% at other conventional centres (Stover *et al.*, 1998).

In terms of blood products usage in cardiac surgery patients, Stone *et al* reported that allogenic RBC were transfused in 38.2% of patients, while 12.1% and 13.1% for platelet and FFP respectively. Another observational cohort study by Bennett-Guerro (2010) in 798

centres in USA in 2010 revealed that usage of RBC was 7.8% to 92.8%, FFP 0% to 97.5% and platelet 0.4% to 90.4%.

This problem arises from the fact that there is still lack of evidence regarding minimal acceptable level of anemia in patients undergoing cardiac surgery (Corwin *et al.*, 1995; Murphy *et al.*, 2007). In fact, the threshold is not easy to be determined as every physician has different level to what extent they comfortable not to transfuse. Some physician has higher tendency to start transfusion earlier than others. It depends on patient's clinical condition as well as the clinician's experience. To transfuse only when Hb drops to below 7g/dL is deemed unreasonable by most physicians; that explain why most of transfusion started earlier (Brierley *et al.*, 2014). It is difficult to define the exact HCT level which the benefits of transfusion outweigh the risks of anemia in cardiac surgery patients (Murphy *et al.*, 2007).

Blood transfusion guideline would be useful in guiding physician in transfusion practice, however not all cardiac centre has proper blood transfusion guideline. It was noted that even for centre with blood transfusion protocol, not all strictly followed the guideline as there was no proper audit of compliance (Moise *et al.*, 2001). Every physician will definitely claim that they transfuse their patients for a definite reason. However, it were noted that some surgeons has higher tendency to transfuse blood as compared to the other surgeons for a similar type of case (unpublished data of IJN, 2016). It was reported by Moise (2001) that as high as 26% of RBC transfusions in cardiac surgery were unnecessary. Therefore, it is important to assess the real need, versus perceived need for

the transfusion of RBC and other blood products by thoroughly assessing the risk-benefit of blood product transfusion relative to the clinical condition of the patient (Ranucci *et al.,* 2011).

In Malaysia, National Blood Centre (PDN) guideline 2014 suggests RBC transfusion threshold in CABG patients are when Hb less than 7g/dL. However patients can be transfused earlier when clinical conditions like active and massive bleeding happens, or high risk of end organ ischaemia and when other parameters like HCT, SVO2, ECG are deranged, in line with the restrictive transfusion practice.

2.5 Blood transfusion association with morbidity and mortality

Blood transfusion is not without risk that there are many possibilities that can go wrong along the transfusion chain and it can be fatal. However, the awareness of the transfusion reaction seems to be focused on viral, bacteria, prion infection and haemolytic transfusion reaction which are less common (Regan and Taylor, 2002; Spahn and Casutt, 2000). The more frequent transfusion related complications like immunosuppression, lung injury or organ dysfunction however were rarely taken into consideration (Murphy *et al.*, 2006). Lack of awareness of possible serious complications made physician comfortable about blood transfusion and believed that blood transfusion is a very safe procedure (Lee *et al.*, 2003) .

More studies showed that blood transfusion has associated with increased morbidity and mortality (Galas *et al.*, 2013; Horvath *et al.,* 2013; Jakobsen *et al.,* 2012). It was reported

that RBC transfusion in post CABG was associated with high mortality within first year post operation (Kuduvalli *et al.,* 2005), while another journal reported that perioperatively transfused patient had twice risk of 5 years mortality compared with non transfused patients (Engoren *et al.,* 2002). RBC transfusion was identified as an independent risk factor for early mortality post operatively whereas no RBC transfusion improves survival (van Straten *et al.,* 2010).

Crémieux (2000) reported that the cost of a packed RBC tripled to $300/unit as per 2000 price, when compared to 5 years earlier. In addition to direct costs of blood products, intraoperative and postoperative blood transfusions were significantly associated with higher hospitalization fee, $4408 and $10479 respectively (LaPar *et al.*, 2013). Brierley (2014) suggested that RBC transfusion may increase hospital costs by prolonging ICU and hospital stay.

Other studies has shown worse outcomes, that the transfused cardiac surgery patients had increased occurrence of early mortality and morbidity such as renal failure, infection, respiratory, cardiac, and neurologic complications, as compared with non-transfused patients (Murphy *et al.*, 2007; Whitson *et al.*, 2010). Another study also found that infection of the genitourinary system, respiratory tract, blood stream, digestive tract and skin were significant association after allogenic RBC transfusion (Rogers *et al.*, 2009). Another study revealed that the risk of pneumonia is about 13% after Coronary Artery Bypass Surgery (CABG), and with each unit of RBC or platelet transfused, the risk would increase by 5% (Vamvakas and Carven, 2000). In addition, a study in USA concluded that

the CABG patients received blood transfusion had significantly longer time for tracheal extubation, ICU length of stay, postoperative length of stay and higher morbidity and 30-day hospital mortality (Scott *et al.*, 2008).

2.6 Liberal and restrictive transfusion concept

In FOCUS trial, liberal transfusion is defined when blood transfusion indicated when Hb dropped less than 10g/dL, while in restrictive transfusion strategy, transfusion allowed to happen when there is anemia symptoms or once Hb less than 8 g/dL (Carson *et al.*, 2006).

The presumed benefits of blood transfusion are being challenged by the findings of recent studies. The Transfusion Requirements After Cardiac Surgery (TRACS) study suggest that a restrictive transfusion strategy with target HCT of 24% is as safe as a liberal strategy targeting HCT of 30%, with regards to 30-day mortality and inpatient clinical complications. The number of transfused RBC units was an independent risk factor for worse outcomes, including mortality. Furthermore, restrictive strategy also reported as did not produce inferior result of in regards to morbidity (Hajjar *et al.*, 2010).

Murphy (2006) found that there was no benefit from transfusion in patients with HCT as low as 21% (Hb of 7g/dl) and the risk of death within 30 days of surgery was almost 6 times higher for patient who received blood products transfusion (Gavin J. Murphy *et al.*, 2007). Other study also concluded that whether RBC transfusion will affect clinical outcome remains dependent on the individual patient's demand such as dynamics of blood

loss, prevalence of an oxygen debt and choice of transfusion trigger (Pape *et al.*, 2009). It was found that using isolated HCT level as trigger for RBC transfusion is not appropriate, as it is a poor indicator of tisu hypoxia, unless it is too low (Murphy *et al.*, 2007).

2.7 Patient Blood Management (PBM)

Restrictive transfusion strategy cannot be separated with the Jehovah Witness who religiously refuses blood transfusion. Although the outcome of their refusal sometimes can be fatal, but there are a lot of learning points for bloodless medicine and surgery as the result of their non transfusion belief (Shander *et al.*, 2012).

Improvement of preoperative management such as optimization patients Hb level, optimization of haematopoeisis, minimize blood loss and improve oxygen delivery to tissue are part of the practice that being implemented for Jehovah Witness patients (Shander *et al.*,2012). In addition to that, the emphasization of usage of haematinic agents, hemostatic agents, autotransfusion, blood sparing perfusion, minimize diagnostic phlebotomy, usage of smaller cardiopulmonary bypass circuits and improvement of surgical techniques are part of the ways to help these people (Bracey *et al.*, 2015). The knowledge is not just for them, but being implemented for the benefit of non Jehovah Witness patients as well, in line with the PBM.

PBM concept is also evolving with nowadays; the current concept emphasizes more on preventive aspects that will remove the needs of allogenic transfusion, as compared to the

old concept of PBM which focused more on appropriate usage of blood and its derivatives (Shander *et al.*, 2012). It is noted that excellent outcomes of bloodless cardiac surgery in Jehovah Witness patients can be achieved with good early preparation, with comparable mortality to non Jehovah witness patients (Jassar *et al.*, 2012). Other studies also proved that there were no increased risk for the bloodless Jehovah Witness patients post cardiac surgery, with some patients even had shown improved outcome (Guinn *et al.*, 2015; Pattakos *et al.*, 2012).

CHAPTER 3: METHODOLOGY

3.1 Introduction

CABG is a common procedure that performed daily, both as elective and emergency in National Heart Center, Kuala Lumpur (IJN). Between years 2010 to 2015, about 1200 to 1400 of CABG performed annually in IJN, with 60.4% to 82% of patients who underwent CABG there received red blood cell (RBC) transfusion. IJN is the national referral centre for cardiovascular diseases in Malaysia, which is internationally recognized cardiac centre and receives large number of medical tourism patients.

3.2 Study design

This is a Retrospective Cross Sectional Study that composed of data from 434 patients who underwent primary and elective CABG over a period of two years (2013 and 2014). Study subjects were chosen using systematic random sampling after the cleansing process according to inclusion and exclusion criteria stated in section 3.6 and 3.7. All demographic and clinical data in regards to outcome of RBC transfusion - mortality and morbidity were captured as in the Appendix 1.

3.3 Data Collection Method

Data of the cases selected were retrieved from the computerized patient data system (patient medical record) of IJN. Out of all the cases of CABG in IJN in 2013-2014, 434

cases were chosen using systematic random sampling every fifth subject of the patient's medical record in the sequence of dates of the year; after data cleansing process, started from the fifth patient in the list. The sample population consisted of all the patients who underwent CABG surgery in IJN for the year of 2013 and 2014 while the sample frame referred to all patients in the sample population after cleansing of samples done. Sample size calculation is as shown in 3.5. The data retrieved then were filled in the proforma.

3.4 Study duration

Study duration period was from 1 July 2015 till 30 November 2016 (17 months).

3.5 Sample size

For objective 1

Sample size was calculated using one single proportion formula

$n= (Z1-\alpha)^2(P(1-P)/D^2)$,

n: number of sample required

$Z1-\alpha$: 1.96

P : prevalence of blood transfusion in CABG

D : absolute precision required = 5%

Based on **Kuduvalli *et al.* 2004,** prevalence of blood transfusion in CABG were 31.1%

Therefore,

$n = (1.96)^2(0.31(1-0.31)/0.05^2) = 329$

For objective 2

Sample size was calculated using independent t test formula

patients per group = $f(\alpha,\beta) \times 2 \times SD^2 / (d)^2$

$f(\alpha,\beta) = 7.85$ for 80% with 5% significance

Based on **Stone *et al.* 2012**, SD was 2.25days

$d = 1.125$

Therefore

patients per group = $f(\alpha,\beta) \times 2 \times SD^2 / (d)^2$

$= 7.85 \times 2 \times (2.25)^2 / (1.125)^2$

$= 63$

Total patients to be recruited = 63×2

$= 126$

For objective 3

Sample size was calculated using one sample mean

$n = (Z_{\alpha/2}+Z_{\beta})^2 \times 2 \times \sigma^2 / d^2$,

n: number of sample required

$Z_{\alpha/2}$: 1.96

Z_{β} : 0.84,

Based on **Karkouti *et al.* 2001**, SD was 2.25days

d : 0.6

Therefore,

$n = (1.96 + 0.84) \times 2 \times (2.25)^2 / (0.6)^2$

$= 242$

The largest sample needed was 329, 20% of additional sample were required to cover incomplete data; therefore final sample size was 394 samples.

3.6 Inclusion criteria

i. Malaysian citizen

ii. Age 18-70 years old

iii. Patients under IJN follow-up, pre-operation and post-operation

iv. Patient undergoing Elective Coronary Artery Bypass Graft (CABG) procedure only

v. Patient is fit for surgery and must be first time for CABG procedure

vi. Only patients with NYHA class I & II

3.7 Exclusion criteria

i. Patient less than 18 years old and above 70 years old.

ii. Emergency CABG – possibility of inadequate preoperative optimization

iii. Patient with obesity stage III- severe obesity is independently associated with increased mortality

iv. Diabetes mellitus patient with HbA1C > 9% - high HbA1c levels are associated with increased risk of diabetic macrovascular and microvascular complications as well as poor wound healing / infection

v. NYHA > II, higher NYHA classes were associated with higher mortality (majority of patients in IJN are NYHA Class II as the result of optimization pre operatively)

vi. Chronic Kidney Disease on renal replacement therapy – CKD is associated with chronic anaemia

vii. Major haemoglobinopathy eg. Major B thalassemia, severe haemophilia

3.8 Statistical analysis

Statistical analysis was performed using SPSS version 23.0 for window software (SPSS, Chicago Illinois, USA) to present the descriptive, statistical and multivariate analysis. Number, percentage, mean and median were used in descriptive analysis. For statistical analysis, Mann Whitney U-test was used for qualitative data with median.

For objective 1

Demographic data were shown using number and percentage for number of patients gender, and body mass index (BMI), while for age, ejection fraction and cardiopulmonary bypass time, mean was used since the data was normally distributed.

For objective 2

All factors (infection complications, ICU length of stay, hospital length of stay and death) studied were not normally distributed, therefore for infection complication and death, Fisher exact test was used while for ICULOS and HLOS, Man Whitney U test used.

For objective 3

Independent t test was used to analyse age, BMI, ejection fraction and cardiopulmonary bypass time while Pearson chi square was used for gender. The association between the 5 factors (age, gender, BMI, EF, CPB time) with RBC transfusion were analysed individually using simple logistic regression (univariable analysis). Only significant independent variables with p-value < 0.25 were chosen and analysed using multiple logistic regression.

3.9 Flow Chart of Study

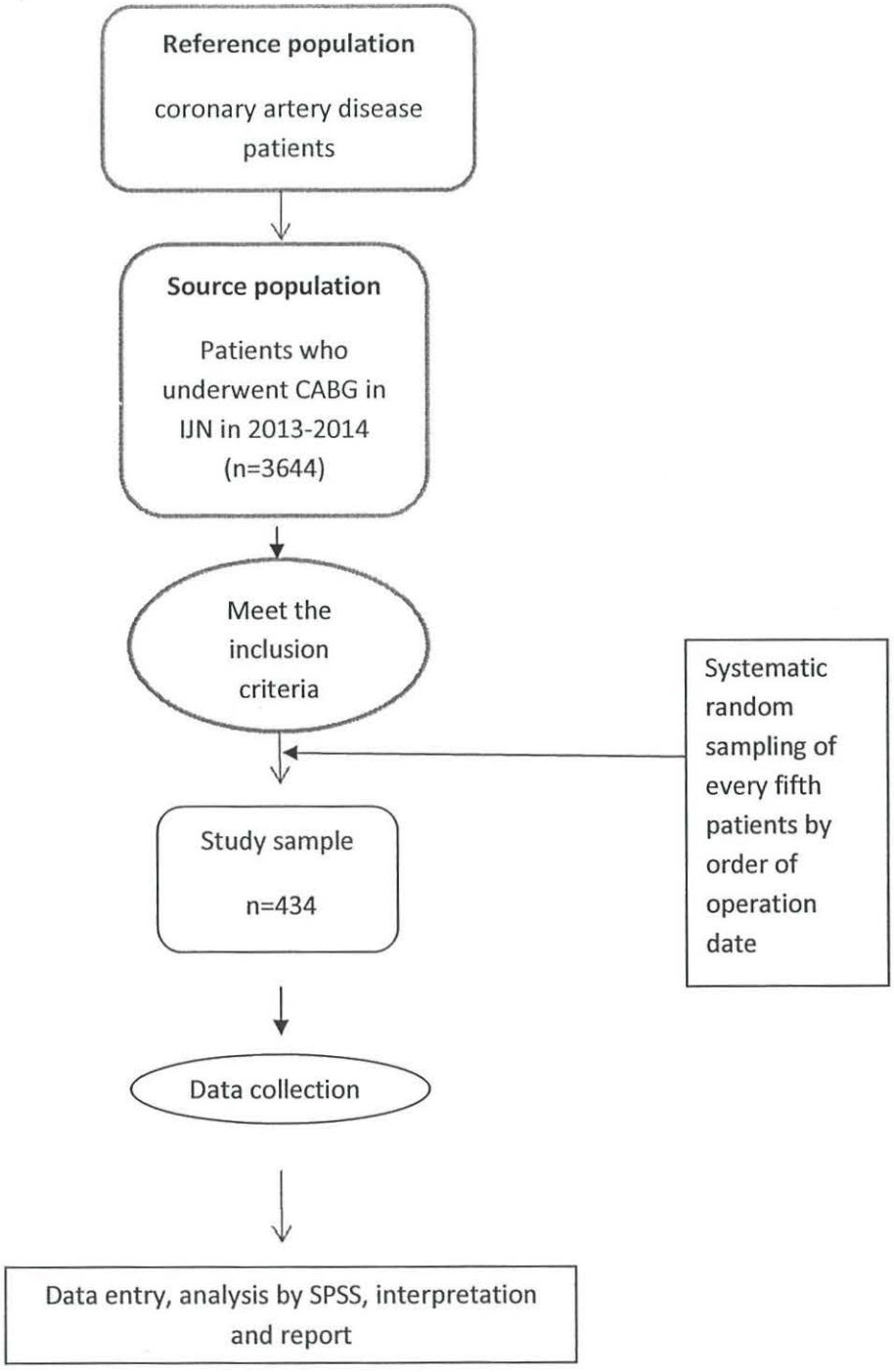

Figure 3.1 Flow chart of study

3.10 Definition of the terms used

i) ICU Length of Stay (ICULOS) is time of admission to the ICU until the time of discharge to the intermediate care or step down unit.

ii) Hospital Length of Stay (HLOS) is time from the day of surgery until the day of discharge from the hospital.

iii) Infection complications are any infection that occurs within 14days after operation. The infection can be diagnosed clinically, imaging or based on blood parameters.

iv) The mortality is death that happen within 30 days after operation

3.11 Ethical approval

Ethical approval from IJN, Jawatankuasa Etika Penyelidikan Manusia USM (JEPEM HUSM) & National Medical Research Register (NMRR) were obtained as all the data were retrieved from patient's medical record. The data were recorded with reference identification so that patients involved cannot be identified directly to the data collected. Therefore the collected data will be anonymous. The use or disclosure of health information of patient would involve no more than a minimal risk to the privacy of the patients.