



# ASSOCIATION IN NUMBER OF RED BLOOD CELL UNITS TRANSFUSED AND THE OUTCOME OF DISCHARGE AT DIFFERENT HAEMOGLOBIN LEVELS IN ACUTE NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING PATIENTS AT HOSPITAL PUTRAJAYA

BY

# **DR. MOHD FAEIZ BIN YUSOP**

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

# ADVANCED MEDICAL AND DENTAL INSTITUTE (AMDI) UNIVERSITI SAINS MALAYSIA 2019

# 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. Mohd Faeiz bin Yusop

PIPM 0069/15

## ACKNOWLEDGEMENT

Alhamdulillah all praises to Allah SWT, peace and blessings be upon the Prophet Muhammad SAW, his family members and his companions. My highest gratitude goes to the Almighty for giving me the opportunity, good health, courage and strength to continue this dissertation. It is only due to His blessings that I was able to complete my Master programme with the submission of my dissertation.

Especially to my dearest other half, my wife, Dr. Nur Farizah binti Johari, I will not be able to reach this point without your support. Your love and sacrifice gave me the strength to complete this journey.

To my beloved parents Yusop bin Hj Ahmad and Halimatos Saadiah binti Abdullah and to my inlaws Dr. Johari bin Surin and Dr. Latifah binti Abdol Latif, I cannot thank you enough for your endless love, prayer and support throughout this journey. To my other beloved family members, thank you for the advice and constant support. Words cannot express my appreciation and love for all of you.

Special appreciation to my supervisors, Dr. Hasmah binti Hussin and Dr. Sharifah Azdiana binti Tuan Din, Senior Lecturer of Advanced Medical & Dental Institute (AMDI), Universiti Sains Malaysia (USM), Dato' Dr. Faraizah binti Abd Karim, Consultant Haematologist of Hospital Ampang and Honorary Lecturer of AMDI for their supervision and constant advice. Also special thanks to Dr. Suzanna binti Shariff of AMDI USM for the statistical guidance and assistance with data analysis and interpretation.

Very special thanks to the staff of Hospital Putrajaya for cooperation and assistance throughout the study. I would also like to acknowledge the continuous support from my fellow colleagues of Transfusion Medicine who were together with me in completing the master's degree.

Last but not least, I would like to thank to those who helped me directly or indirectly in completing my thesis. Thank you.

# **TABLE OF CONTENTS**

Declaration	ii
Acknowledgement	iii
Table of Contents	v
List of Tables	ix
List of Figures	X
List of Abbreviations	xi
List of Appendices	xiii
Abstrak	xiv
Abstract	xvi

# **CHAPTER 1: INTRODUCTION**

1.1	Overview	1
1.2	Blood Transfusion and NVUGIB	
1.3	Research Justifications and Benefits	
1.4	Research Objectives	6
	1.4.1 General Objective	6
	1.4.2 Specific Objectives	6
1.5	Research Hypothesis	7
1.6	Conceptual Framework	7

# **CHAPTER 2: LITERATURE REVIEW**

2.1	Indication and Predictive Factors of RBC Transfusion	8
2.2	Transfusion Practice in Upper Gastrointestinal Bleeding	11
2.3	Liberal and Restrictive Transfusion Strategy	13
2.4	Outcome of Discharge Haemoglobin in Association with RBC units transfused,	
	Length of Stay and Adverse Events after Discharge	16

# **CHAPTER 3: METHODOLOGY**

3.1	Study Design	18
3.2	Data Collection Method	18
3.3	Study Duration	19
3.4	Sample Size	19
3.5	Inclusion Criteria	20
3.6	Exclusion Criteria	21
3.7	Statistical Analysis	21
3.8	Flow Chart of Study	23
3.9	Definition of the terms used	24
3.10	Ethical Approval	25

# **CHAPTER 4: RESULTS**

4.1	Descript	tive Analysis	26
	4.1.1	Demographic Characteristics	26
	4.1.2	Characteristics of NVUGIB patients	27
	4.1.3	Transfusion Characteristics and Glasgow Blatchford Score	29
4.2 Statist		al Analysis	30
	4.2.1	Association between presenting symptoms and number of RBC units	
		transfused	30
	4.2.2	Association between aetiologies and number of RBC units transfused .	32
	4.2.3	Correlation between GBS and RBC units transfused	33
	4.2.4	Prediction Model for Number of RBC units Transfused in NVUGIB	34
	4.2.5	The Outcome of two discharge Haemoglobin Groups	36
	4.2.6	The association between Adverse Events after discharge with two	
		discharge Haemoglobin groups	37

# **CHAPTER 5: DISCUSSION**

5.1	5.1 Demographic Characteristics of Non-Variceal Upper Gastrointestinal Bleed	
	patients	38
5.2	Characteristics of Non-Variceal Upper Gastrointestinal Bleeding patients	40
5.3	Predictive Factors of RBC Transfusion in NVUGIB patients	43
5.4	Outcome of NVUGIB patients with different level of Hb upon discharge	46

# CHAPTER 6: CONCLUSION, RECOMMENDATION AND LIMITATIONS

APPE	NDICES	75
REFE	RENCES	58
6.3	Limitations	56
6.2	Recommendations	54
6.1	Conclusion	54

# LIST OF TABLES

Table 4.1	Demographic Characteristics Distribution of Patients	26
Table 4.2	Characteristics Distribution of the NVUGIB patients	28
Table 4.3	Transfusion Characteristics of the Patients	29
Table 4.4	Presenting symptoms and RBC units transfused	31
Table 4.5	Aetiologies and RBC units transfused	32
Table 4.6	Correlation between GBS and number of RBC units transfused	33
Table 4.7	Prediction model for number of RBC units transfused in NVUGIB	34
Table 4.8	Multiple Linear Regression of number of RBC transfusion factors in	
	NVUGIB patients	35
Table 4.9	Outcome of two discharge Hb groups among NVUGIB patients	36
Table 4.10	The association between AE after discharge with two NVUGIB groups	37
Table 5.1	Comparison of the Forrest Classification findings in NVUGIB patients	42

# LIST OF FIGURES

Figure 1.1	Conceptual Framework	7
Figure 3.1	Flow Chart of Study	23

# LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AE	Adverse Events
CI	Confidence Interval
CPG	Clinical Practice Guideline
FFP	Fresh Frozen Plasma
GBS	Glasgow-Blatchford Score
Hb	Haemoglobin
HKL	Hospital Kuala Lumpur
IHD	Ischaemic Heart Disease
INR	International Normalised Ratio
JEPEM	Jawatankuasa Etika Penyelidikan Manusia
LGIB	Lower Gastrointestinal Bleeding
LOS	Length of Stay
NMRR	National Medical Research Register
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
NVUGIB	Non-Variceal Upper Gastrointestinal Bleeding
OGDS	Oesophagogastroduodenoscopy
OR	Odds Ratio
PBM	Patient Blood Management
PT	Prothrombin Time
RBC	Red Blood Cell

RCT	Randomised Control Trial
SBP	Systolic Blood Pressure
SD	Standard Deviation
UGIB	Upper Gastrointestinal Bleeding
UK	United Kingdom
VUGIB	Variceal Upper Gastrointestinal Bleeding

# LIST OF APPENDICES

Appendix 1	Patient Proforma	75
Appendix 2	Dummy Table	77
Appendix 3	Approval from Medical and Ethics Committee (MREC), Ministry of	
	Health	79
Appendix 4	Approval from Human Research Ethics Committee (HREC), USM	81
Appendix 5	Approval from Hospital Putrajaya	84
Appendix 6	Annual Ethical Renewal from Medical and Ethics Committee (MREC),	
	Ministry of Health	87

## ABSTRAK

Latar belakang: Penyakit pendarahan saluran cerna bahagian atas bukan variseal (NVUGIB) adalah suatu penyakit yang kerap ditemui dan merupakan sebab utama kematian dalam kalangan lebih kurang 5-10% pesakit. Transfusi sel darah merah (RBC) merupakan salah satu kaedah perawatan bagi pesakit yang menghidap NVUGIB. Walau bagaimanapun, transfusi RBC dikaitkan dengan pelbagai morbiditi dan kematian. Kajian in bertujuan untuk mencari perkaitan antara simtom, aetiologi dan Skor Glasgow-Blatchford (GBS) dengan bilangan unit transfusi RBC. Selain daripada itu, kajian ini bertujuan untuk membandingkan kesan terhadap paras discaj Hb yang berbeza dalam kalangan pesakit NVUGIB di Hospital Putrajaya.

**Kaedah:** Kajian kohort retrospektif dilakukan kepada data daripada 180 pesakit NVUGIB yang telah ditransfusi dengan RBC dalam tempoh lima tahun. Data diambil daripada sistem informasi pesakit berkomputer Hospital Putrajaya. Subjek kajian dipilih diisi dalam proforma. Kesemua data demografi dan klinikal termasuk simtom-simtom awal seperti melaena, haematemesis, haematochezia dan anaemia direkodkan. Selain simtom awal tersebut, pembolehubah-pembolehubah lain juga dikaji termasuk aetiologi NVUGIB, GBS, dan bilangan unit RBC yang ditransfusi. Kesan-kesan klinikal terhadap dua kumpulan paras discaj Hb yang berbeza dibandingkan.

**Keputusan**: Dalam kalangan 180 pesakit, 92 (51.1%) mempunyai paras discaj Hb < 10 g/dl manakala 88 (48.9%) mempunyai paras discaj Hb  $\geq$  10 g/dl. Regresi linear pelbagai mendedahkan bahawa hematochezia (p=0.022) dan GBS yang lebih tinggi (p<0.001) merupakan faktor-faktor

yang dikaitkan secara bebas dengan bilangan unit transfusi RBC yang lebih tinggi. Dengan ujian Mann Whitney-U, pesakit dengan paras discaj Hb  $\geq$  10 g/dl menyumbang secara signifikan kepada bilangan unit transfusi RBC yang lebih tinggi (p=0.005) dan tempoh tinggal di hospital (LOS) yang lebih lama (p=0.029).

**Kesimpulan**: Hematochezia dan GBS ialah dua faktor penentu yang penting untuk kebarangkalian bilangan transfusi RBC unit yang lebih banyak dalam kalangan pesakit NVUGIB. Pesakit dengan paras discaj Hb  $\geq$  10 g/dl dikaitkan dengan bilangan transfusi RBC unit yang lebih banyak dan LOS yang lebih lama.

Kata kunci: NVUGIB, Transfusi RBC, Discaj Hb, GBS, Hematochezia

## ABSTRACT

**Background:** Non-Variceal Upper Gastrointestinal Bleeding (NVUGIB) is very common and with considerable 5-10% mortality. RBC transfusion is one of the treatments for NVUGIB patients but it is associated with various morbidity and mortality. This study was to determine the associations between number of RBC units transfused with presenting symptoms, aetiologies and Glasgow-Blatchford Score (GBS). This study also compared the outcomes of discharge at different level of Hb among NVUGIB patients at Hospital Putrajaya.

**Methods:** Retrospective cohort study was performed with data from 180 patients with NVUGIB and were transfused with RBC over a period of five years. Data were retrieved from the computerised patient information system of Hospital Putrajaya. Study subjects selected were filled in the proforma. All demographic and clinical data including presenting symptoms such as melaena, haematemesis, haematochezia, and anaemia were recorded. Besides presenting symptoms, other variables studied include aetiologies of NVUGIB, GBS, and number of RBC units transfused. The clinical outcomes of patients with two different level of discharge Hb were compared.

**Results:** Out of 180 patients, 92 (51.1%) had discharge Hb < 10 g/dl while 88 (48.9%) of them had discharge Hb  $\geq$  10 g/dl. Using multiple linear regression, haematochaezia (p=0.022) and higher GBS (p<0.001) were factors which were independently associated with higher number of RBC units transfused. Using Mann Whitney-U test, patients with discharge Hb  $\geq$  10 g/dl were shown to be significant contributor to higher number of RBC units transfused (p=0.005) and longer length of stay (LOS) (p=0.029).

**Conclusion:** Haematochaezia and GBS were two important determinants for the probability of higher need in RBC unit transfusion for NVUGIB patients. Patients with discharge Hb  $\geq$  10 g/dl will result in higher number of RBC units transfusion and longer LOS.

Key words: NVUGIB, RBC transfusion, Discharge Hb, GBS, Haematochaezia

## **CHAPTER 1: INTRODUCTION**

## 1.1 Overview of Non-Variceal Upper Gastrointestinal Bleeding (NVUGIB)

Gastrointestinal bleeding is a medical emergency which has been illustrated as the most frequent cause of hospitalisation linked to the digestive tracts in most countries (Gralnek *et al.*, 2017; Lanas and Chan, 2017). Upper gastrointestinal bleeding (UGIB) is defined by gastrointestinal bleeding superior to the ligament of Treitz which consists of the stomach, duodenum and oesophagus. UGIB events can be further classified as non-variceal upper gastrointestinal bleeding (NVUGIB) and variceal upper gastrointestinal bleeding (VUGIB) (Sung *et al.*, 2010). NVUGIB presented as haematemesis, melaena, haematochezia or other clinical or laboratory evidence of acute blood loss from the upper gastrointestinal tract confirmed by endoscopy (Lanas *et al.*, 2011).

NVUGIB is most frequently triggered by peptic ulcers which are linked with *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs) therapy including aspirin. By definition, peptic ulcer is a disruption of the mucosal layer that opens up the submucosa to acid secreted in the gastroduodenal lumen. On the contrary, VUGIB is caused after the formation of oesophageal or gastric varices which are commonly linked with chronic liver disease and/or portal hypertension. NVUGIB is five times more likely compared to VUGIB in most countries. NVUGIB is a serious clinical challenge with significant 5-10% mortality to date (Sung *et al.*, 2010).

The United States recorded an incidence of NVUGIB nearly 67 per 100,000 individuals in 2012. The incidence of peptic ulcer bleeding encompasses around 32.1 per 100,000 individuals in 2009 (Lanas and Chan, 2017). In Europe, the incidence of NVUGIB is about 25-35 per 100000 individuals in the early 2000s (van Leerdam *et al.*, 2003). In Malaysia, the incidence is approximately 72 per 100000 for Sabah and Sarawak (Cheng *et al.*, 2001). According to the Clinical Practice Guideline (CPG), bleeding peptic ulcer is the most frequent cause of acute NVUGIB nationally (*MOHM*, 2003).

The risk factors that are associated with NVUGIB are the use of NSAIDs, smoking, alcohol consumption, anti-coagulant, traditional medication and steroids. A study of NVUGIB patients in Europe, revealed that 26.7% of them were smokers, 36.7% consumed alcohol, 34.5% had NSAIDs therapy, and 7.1% used anticoagulants (Garrido *et al.*, 2006). One study of NVUGIB patients conducted in Hospital Kuala Lumpur (HKL) had shown that 50% were smokers, 37.5% consumed alcohol, 17.2% had NSAIDs therapy, 5.5% used traditional medications, 2.3% anti-coagulants and 0.8% steroids (Lakhwani *et al.*, 2000). The most commonly associated risk factor for NVUGIB in the European population was alcohol consumption. Meanwhile in Kuala Lumpur, smoking was the most significant risk factor identified among NVUGIB patients.

The aetiologies of NVUGIB include peptic ulcer, erosive gastritis/duodenitis, Mallory-Weiss tear, neoplasms, angiodysplasia, oesophagitis/oesophageal ulcer, Dieulafoy's lesions (aberrant vessels in the mucosa) and aortoenteric fistulas. The most frequent aetiology of NVUGIB was peptic ulcer disease (Ferguson and Mitchell, 2006). In a local study done in HKL, the aetiologies of NVUGIB include 61.7% peptic ulcer, 21.9% erosive gastritis/duodenitis, 3.9% neoplasms and 1.6% due to other causes (Lakhwani *et al.*, 2000).

Forrest classification which was developed four decades ago classifies acute UGIB patients into low and high-risk categories for mortality. It is most widely used to classify the endoscopic appearance of bleeding peptic ulcers (Forrest *et al.*, 1974). At this point in time, it is generally used to predict the risk of rebleeding as well as mortality (Guglielmi *et al.*, 2002). The Forrest classification classifies ulcers with a spurting haemorrhage (Forrest Ia), an oozing haemorrhage (Forrest Ib), a visible vessel (Forrest IIa), an adherent clot (Forrest IIb), hematin on the ulcer base (Forrest IIc), and a clean ulcer base (Forrest III) (de Groot *et al.*, 2014; Forrest *et al.*, 1974).

# **1.2 Blood Transfusion and NVUGIB**

UGIB is a significant cause of morbidity and mortality. It takes up a significant amount of health resources including the need of blood transfusion specifically packed red blood cells (RBC). Acute and persistent gastrointestinal bleeding will render the patient to have a high mortality rate ranging from 5 to 10%. Transfusion support is vital and one of the essential elements in treating these patients. Thus, it is routinely used in the gastroenterology departments (Garrido *et al.*, 2006). It is a common indication for RBC transfusion because haemodynamic instability can diminish the delivery of oxygen to tissues and also the tissue perfusion. RBC transfusion may be lifesaving in patients who are actively haemorrhaging.

Nonetheless, in patients with stable UGIB, restrictive transfusion strategy could be more beneficial as it would significantly improve patient outcomes. This strategy will help in reducing the risk of rebleeding, the need for rescue interventions and complications. Thus, it improved the survival rate among UGIB patients (Villanueva *et al.*, 2013).

Hospital Putrajaya is one of the tertiary medical centers in Malaysia. Statistics revealed that the number of oesophagogastroduodenoscopies (OGDS) performed in this hospital ranged from 400 to 500 annually between 2010 to 2017. Among the patients who underwent OGDS, 5 to 8% of them received RBC transfusion. (Unpublished data of Hospital Putrajaya, 2017).

## **1.3 Research Justification and Benefits**

This study aimed to evaluate the existing practice on RBC transfusion in NVUGIB patients and to suggest alternative approaches upon the outcomes that turn out not to be favourable to the patients. This study analysed their data profiling with regards to demographic characteristics, risk factors, presenting symptoms, aetiologies, Forrest classification and Glasgow-Blatchford Score (GBS). GBS is a screening tool to assess the likelihood that a patient with an acute UGIB will need to have medical intervention such as a blood transfusion or an endoscopy. Factors such as presenting symptoms, aetiologies and GBS may influence the number of RBC units transfused. Currently, there was no similar research on this subject matter in Malaysia. Hence, this study was done to evaluate the association between number of RBC transfused with these selected variables. Generally, this will improve the availability of local data in Malaysia and the profile of RBC transfusion among NVUGIB patients vary. Identifying patients with higher risk and accelerating their interventions are crucial in reducing their morbidity and mortality rate. One of the tools to assist clinicians in predicting the requirement of blood transfusion is GBS.

Haemoglobin level (Hb) is one of the leading indicators to start RBC transfusion. However, the outcome of the Hb level upon discharge remains controversial. Discharge Hb is essential in clinical practice, and it can be a useful indicator in regulating the appropriateness of RBC transfusion. This study is to investigate discharge Hb level influences the outcome of patients with NVUGIB, hence improving patient blood management (PBM). Apart from that, it also evaluates the outcomes of two different groups of patients with lower and higher discharge Hb level. The evaluated outcomes include the number of RBC units transfused, length of stay (LOS) and adverse events (AE) after discharge.

This study can be of benefit to transfusion services and other tertiary hospitals as these centres would be able to improve the current transfusion practice in NVUGIB patients. It can also enhance the current understanding of the risk-to-benefit profile of RBC transfusion. As a consequence, this study can be used as an instrument to increase the awareness of the potential complications linked with RBC transfusion. This in turn, encourages physicians to be more judicious in blood transfusion practice. In the long run, it could also potentially decrease the rising cost of healthcare services on transfusion services.

# **1.4 Research Objectives**

## **1.4.1** General Objective

To evaluate the RBC transfusion requirement among patients admitted with NVUGIB.

# 1.4.2 Specific Objectives

- i. To identify the demographic characteristics, risk factors, aetiologies and Forrest classification in NVUGIB patients.
- To determine the associations between the number of RBC units transfused in NVUGIB patients with presenting symptoms, aetiologies and GBS.
- iii. To compare the outcomes in two groups of NVUGIB patients (lower discharge Hb and higher discharge Hb) with:
  - a. Number of RBC units transfused
  - b. Length of stay (LOS)
  - c. Adverse events (AE) after discharge (Readmission, Rebleeding and Mortality)

# **1.5 Research Hypothesis**

- i. There is an association between the number of RBC units transfused with presenting symptoms, aetiologies and GBS in NVUGIB patients.
- ii. There is an association between discharge Hb level with the number of RBC units transfused, LOS and AE after discharge.

# **1.6 Conceptual Framework**



Figure 1.1 Conceptual Framework

#### **CHAPTER 2: LITERATURE REVIEW**

#### 2.1 Indication and predictive factors of RBC transfusion in NVUGIB

Gastrointestinal bleeding is the most prevalent cause of hospitalisation due to gastrointestinal disease in the United States. It accounts for more than 507,000 hospitalisations and \$4.85 billion annually (Peery *et al.*, 2015). Acute UGIB is a common emergency condition linked with a high morbidity and mortality (Gralnek *et al.*, 2008). It is also associated with high rate of RBC transfusion which accounts for 11% of all RBC transfused in England (Ferguson and Mitchell, 2006).

The mechanism involved in the development of NVUGIB is not entirely understood. The mucosal layer and submucosal blood vessels must be broken down for the bleeding to occur. *Helicobacter pylori* infection and/or NSAIDs or aspirin are commonly associated with the disruption of the mucosal layer. However, causes such as Mallory-Weis Syndrome, vascular lesions and neoplastic lesions can result in the exposure of blood vessels to the luminal content. Exposure of the underlying blood vessels to the action of acid and pepsin further erodes the vessel wall and interferes with blood coagulation (Lanas and Chan, 2017).

In general, the purpose of RBC transfusion is mainly to improve oxygen delivery to the tissue with the target to correct or prevent hypoxia and intravascular volume replacement. RBC transfusion increases the Hb concentration of patients with acute or chronic anaemia, and this helps maintain the oxygen-carrying capacity of the blood (Murphy *et al.*, 2002). RBC transfusion is a transitory

measure since the deficiency regresses unless the cause of bleeding is treated. Treatment must be individualised depending on factors such as age, symptoms, haemodynamics stability and concomitant illnesses (Murphy *et al.*, 2002).

In a local study, Lakhwani *et al.*, investigated UGIB cases in HKL, involving a sample consisting of 88.3% male and 11.7% females. The mean age was found to be 51.9 years, of which 37.5% was in the > 60 years of age range. With regards to the ethnicity, 49.2% of the patients were Chinese, 25.8% were Malays, 23.4% were Indians and 3.1% of others (Lakhwani *et al.*, 2000). Similar findings were found by Garrido *et al.*, in which 76.41% of the UGIB patients were males while 23.59% were females with a mean age of 60.45 (Garrido *et al.*, 2006).

Acute NVUGIB can present with haematemesis, melaena, haematochaezia or a combination of these symptoms. Haematemesis with bright red vomitus indicates acute haemorrhage while recent haemorrhage appears as "coffee ground" vomitus. The breaking down of haemoglobin in RBC into haematin by gastric acid results in the formation of coffee ground vomitus. Melaena refers to the black, tarry, loose or sticky and foul smelling stool resulting from the breakdown of blood in the intestine (Bouchier and Allan, 1993; Yamada and Alpers, 1995). Occasionally, a brisk UGIB manifests as haematochaezia which is also described as red or maroon stools. Patients presenting with brighter red stool indicates a shorter stool transit time (Laine and Shah, 2010). There is an association between the presenting symptoms and the transfusion risk. Haematemesis carries an Odds Ratio (OR) of 3.12, melaena carries an OR of 1.59 and haematochaezia carries an OR of 33.17 (Garrido *et al.*, 2006).

Studies on the association between aetiologies and the risk or requirement of blood transfusion are limited. However, a study by Garrido *et al.*, found that there was a link between the aetiologies of NVUGIB and transfusion risk. Peptic ulcer carries an OR of 0.5, Mallory-Weis Tear with an OR of 0.34, angiodysplasia with an OR of 0.65, and other causes with an OR of 0.24 (Garrido *et al.*, 2006). In a local study in HKL, it was reported that 21% of peptic ulcer patients and 11% of patients with gastric erosions required RBC transfusion (Lakhwani *et al.*, 2000). In a similar study by Garrido *et al.*, the various aetiologies of UGIB were linked to different transfusion requirements. This is about the number of RBC units required. On average, gastric ulcer requires 2.85 units, Mallory-Weiss tear requires 2.66 units, angiodysplasia requires 2.58 units, and UGIB of unknown origin requires 5.5 units of RBC (Garrido *et al.*, 2006).

Several scoring systems have been designed to establish the risk factors and outcome in UGIB patients. In one of the studies which compare the risk score in UGIB conducted in Glasgow, UK, the Glasgow-Blatchford Score (GBS) was found to be far more accurate in predicting blood transfusion as compared to Rockall Risk Score. The practice of using GBS to predict intervention and outcome following UGIB is becoming more common (Stanley *et al.*, 2011). In another study by Shahrami *et al.*, GBS was found to be a highly accurate scoring system in predicting the probability of rebleeding and the need for blood transfusion (Shahrami *et al.*, 2018). GBS is more superior compared to other different scoring systems, AIMS65 in the detection of high-risk patients and those in need of blood transfusion (Yaka *et al.*, 2015). According to a study by Stanley *et al.*, GBS performs better than other scoring systems in predicting the need for intervention of endoscopic treatment (Stanley *et al.*, 2017). A significant correlation was found between higher

GBS score and the increase in the need for at least one intervention which includes blood transfusion (Shahrami *et al.*, 2018).

#### **2.2 Transfusion Practice in UGIB**

The decision to initiate blood transfusion must be individualised. For most patients, a blood transfusion will be initiated if the Hb is < 7 g/dl with a goal of maintaining Hb of  $\geq 7$  g/dl (Laine and Jensen, 2012). However, the goal is to maintain  $Hb \ge 9 \text{ g/dl}$  if the patients are at increased risk of suffering AE, in particular with unstable coronary artery disease or with evidence of active haemorrhage. This goal is established based on the patient's comorbid condition and is independent of the patient's age group. However, patients with active haemorrhage and hypovolemia may require RBC transfusion despite normal Hb level (Maltz et al., 2000). On the contrary, the current practice in Malaysia is to maintain a Hb level of approximately 10 g/dl according to the CPG. The indications to transfuse RBC in UGIB patients include SBP < 110mmHg, postural hypotension, pulse rate > 110/min, Hb < 8 g/dl, and angina or cardiovascular disease with Hb < 10 g/dl (MOHM, 2003). Our current practice is supported by British Society of Gastroenterology guidelines which recommends RBC transfusion when the Hb is < 10 g/dl (Palmer, 2002). In a cluster randomised trial done in six hospitals in the UK, the indication for RBC transfusion in the restrictive strategy is when their Hb < 8 g/dl. Meanwhile, patients were eligible for RBC transfusion when their Hb is < 10 g/dl in the liberal strategy (Jairath *et al.*, 2013).

Platelet transfusion is also one of the most common blood products used in UGIB patients. In general, patients with active bleeding and thrombocytopenia with a platelet count of  $< 50\ 000\ x\ 10^9/l$  should be transfused with platelets (Ramos *et al.*, 2018). Similarly, based on the Malaysian CPG, platelet transfusion is indicated if the platelet count is  $< 50\ 000\ x\ 10^9/l$  (*MOHM*, 2003). Interventional OGDS is warranted if the platelet count is  $< 20\ 000\ x\ 10^9/l$ . However, patients with active haemorrhage require a platelet count of  $\ge 50\ 000\ x\ 10^9/l$  before endoscopy (Laine, 2018). The benefit of platelet transfusion in patients who are on antiplatelets with UGIB still remains unclear, in fact, it may be potentially harmful. Hence, an individualised approach is necessary based on the complete clinical picture (Zakko *et al.*, 2017).

Patients with coagulopathy as a direct cause of UGIB with prolonged prothrombin time (PT) and INR > 2.0 should generally receive FFP transfusion. OGDS is usually performed once the INR is < 2.5 (Acosta *et al.*, 2016). Urgent OGDS in patients who are haemodynamically stable should not be put on hold until the coagulopathy is corrected and can be done simultaneously with blood product transfusion (Wolf *et al.*, 2007). A unit of FFP should be given after every four units of RBC transfusion as they do not contain coagulation factors (Maltz *et al.*, 2000). PCC infusion is preferred for patients with life-threatening bleeding in which a more rapid reversal of coagulopathy can be achieved. The Malaysian CPG guideline on FFP transfusion in UGIB patients has yet to be updated. FFP transfusion is indicated if the PT is at least 1.5 times higher than the control value (*MOHM*, 2003).

## 2.3 Liberal and restrictive transfusion strategy in NVUGIB

Transfusing RBC for anaemic patients is one of the most extensively utilised medical interventions. It is often driven by anxiety towards any level of anaemia regardless of the aetiology. The basis for RBC transfusion is evident in which low Hb could lead to reduced tissue perfusion, organ failure and mortality. Prevention of anaemia and more liberal RBC transfusion strategies were implemented at one point (*Healthcare Cost and Utilization Project (HCUP)*, 2012). In a 1942 report, the practice of transfusing when Hb level falls lower than 8-10 g/dl was initially suggested (Adams and Lundy, 1942). This was consequently generalised to medical and surgical conditions and incorporated into some guidelines including those for acute UGIB (*Non-variceal upper gastrointestinal haemorrhage: guidelines*, 2002).

Several randomised trials have compared different strategies of transfusing patients with UGIB, specifically the restrictive and the liberal strategy. In the restrictive strategy, the transfusion Hb threshold was 7 g/dl with a target range for the post-transfusion Hb level of 7 to 9 g/dl. On the contrary, in the liberal strategy group, the transfusion Hb threshold was 9 g/dl with a target range for the post-transfusion Hb threshold was 9 g/dl with a target range for the post-transfusion Hb threshold was 9 g/dl with a target range for the post-transfusion Hb threshold was 9 g/dl with a target range for the post-transfusion Hb threshold was 9 g/dl with a target range for the post-transfusion Hb level of 9 to 11 g/dl (Villanueva *et al.*, 2013).

The restrictive strategy appeared to be potentially more advantageous than the liberal strategy in acute UGIB. There are still many uncertainties including the optimal trigger for transfusion, the effects of ongoing haemorrhage, administration of other blood components and patient comorbidities (Jairath *et al.*, 2013; Villanueva *et al.*, 2013). The explanation on why transfusion seems to worsen patients' outcome in certain circumstances remains unclear and requires further

research. It is possible that transfusion could increase the portal and/or systemic blood pressures, hence promoting further haemorrhage (Tsai *et al.*, 2004).

In the following years, there were no less than seven additional large Randomised Control Trials (RCTs) assessing patients with various medical and surgical conditions were published. For all the RCTs, each was comparing restrictive strategy to the liberal strategy. Nonetheless, only two of those RCTs centralised on patients with acute UGIB (Jairath *et al.*, 2013; Villanueva *et al.*, 2013). A multicenter cluster-randomised pilot study of restrictive versus liberal strategy in the UK followed involving 936 patients with UGIB of any aetiology from 6 different hospitals. There were no significant differences regarding 28-day mortality or rebleeding comparing both transfusion strategies. These data are crucial and have contributed to the updated transfusion recommendations in UGIB patients. However, additional studies are required to support this (Barkun *et al.*, 2010; Laine and Jensen, 2012).

A meta-analysis of five RCTs concluded that patients with UGIB who were assigned to a restrictive strategy had a lower risk of mortality and rebleeding as compared to those assigned to a liberal strategy. There was no association between the risk of mortality with the different strategies applied in patients with ischaemic heart disease (IHD). However, in patients without IHD, the risk of mortality was lower when the restrictive strategy was applied. The risk of rebleeding remains similar in both groups of strategies, in patients with or without IHD. There were no significant differences on the risk of myocardial infarction, stroke and acute kidney injury between a restrictive and liberal strategy in the meta-analyses (Ayodele *et al.*, 2017).

Nonetheless, it is essential to avoid the postulation that the liberal strategy is detrimental to the patients. Apparently, in some patients with rapid UGIB haemorrhage, blood transfusion remains a lifesaving intervention (Perel *et al.*, 2014). Massive haemorrhage with haemorrhagic shock could trigger different physiological processes and responses which requires specific treatment (Cannon, 2018). The current guideline for the recommended Hb cut-offs level is reasonable. However, since Hb alone is not an accurate indicator to measure the extent of the tissue oxygenation particularly in the setting of acute blood loss, it should be approached with caution. For this reason, clinicians should not consider absolute Hb values as the only parameter for transfusion decisions (Yen, 2018).

Patient blood transfusion management (PBM) aims to improve patient outcome and to reduce cost related to blood transfusion (Waters and Ness, 2011). PBM involves evidence-based practices primarily to manage anaemia, haemostasis and blood loss and to improve the outcomes of patients (*WHA Resolution 63.12*, 2011). The establishment of PBM programs was mainly to improve blood utilisation since restrictive transfusion strategy results in improved patient safety and reduced costs (Shander and Goodnough, 2010). Over the past half century, PBM has been pointed out as one of the ten critical advances in transfusion medicine (Goodnough and Shander, 2012).

Despite advances in proper blood management, 23% of RBC unit transfusions appear to be inappropriate. This applies most common among younger patients, who underwent surgery with lower comorbidity and those with higher Hb. This study also indicates the absence of awareness among a significant minority of clinicians who are reluctant to accept lower transfusion thresholds. Transfusion practice could be further improved by exploring the obstacles to the implementation

of recommended transfusion threshold and developing guidelines on appropriate post-transfusion Hb level (Barr *et al.*, 2011).

A discharge Hb level of  $\geq 10$  g/dl in a hospitalised patient who was transfused with RBC could indicate unnecessary transfusion. Post-transfusion Hb level of  $\geq 9$  g/dl has not been proven to be associated with an added advantage. Several factors which include comorbidities, LOS, treatments given and transfusion of RBC units could influence the patient's Hb at discharge (Edwards *et al.*, 2012). One of the factors for an appropriate PBM that could be proposed is discharge Hb level of  $\geq 10$  g/dl (Barr *et al.*, 2011). A more stringent target could even be proposed by considering a discharge Hb of  $\geq 9$  g/dl as an indication of overtransfusion (Edwards *et al.*, 2012).

# 2.4 Outcome of discharge Hb in association with RBC units transfused, LOS and AE after discharge

Hb value within 24 hours before discharge is referred to as the "discharge Hb". It is an essential concept in clinical practice that can be a useful indicator in evaluating the suitability of RBC transfusion (Edwards *et al.*, 2012). There is limited study done to evaluate the clinical outcomes based on the discharge Hb level (Lee *et al.*, 2016). The cut-off point for discharge Hb level was taken as 10 g/dl because Hb level should be maintained at a level of approximately 10 g/dl (*MOHM*, 2003). The lower discharge Hb level refers to <10 g/dl while the higher Hb discharge level refers to  $\geq$  10 g/dl. Even though several studies have been conducted on the transfusion strategies in patients with UGIB, there was no specific study on the relationship between discharge Hb and the outcome (Lee *et al.*, 2016).

LOS refers to the length of an inpatient episode of care, calculated from the day of admission to day of discharge, and based on the number of nights spent in a hospital. Patients admitted and discharged on the same day have a length of stay of less than one day (*Segen's Medical Dictionary*, 2012). The average LOS in hospitals is often used as an indicator of efficiency (*Health at a Glance*, 2011). AE is defined as any untoward medical occurrence in a patient or clinical investigation subject who has been administered an intervention. This does not necessarily have a causal relationship with this treatment (*In Guideline for Good Clinical Practice*, 1996).

In a study by Lee *et al.*, comparing the lower and higher discharge Hb group, the former received a lower number of RBC units (Lee *et al.*, 2016). In another study by Villaneuva *et al.*, a similar finding was found in which patients received a lower number of RBC units in the lower Hb group (Villanueva *et al.*, 2013). There were no significant differences in the LOS comparing the two groups of patients (Lee *et al.*, 2016). However, in a study by Villanueva *et al.*, those in the lower Hb group had shorter LOS (Villanueva *et al.*, 2013). The differences in the AE after discharge between both groups were not significant. The AE after discharge in this context refers to readmission, rebleeding and mortality (Lee *et al.*, 2016). However, the risk of rebleeding and mortality was found to be significantly reduced in the lower Hb group (Villanueva *et al.*, 2013).

## **CHAPTER 3: METHODOLOGY**

#### 3.1 Study design

This was a retrospective cohort study composed of data from selected patients who fulfil the inclusion criteria. One hundred eighty patients who underwent OGDS and received at least one unit of RBC over a period of 5 years (2012 to 2017) were selected for this study. Systematic random sampling was used to choose study subjects after the data cleaning process according to the inclusion and exclusion criteria stated in sections 3.5 and 3.6. All demographic and clinical data related to risk factors of NVUGIB, presenting symptoms, aetiologies, Forrest classifications, GBS, AE were captured in Appendix 1. The selected patients were classified according to the level of Hb upon discharge. They were divided into two groups, Hb discharge level of < 10 g/dl and  $\geq$  10 g/dl.

## **3.2 Data Collection Method**

Data of the selected cases were retrieved from computerised patient data system (patient medical record) of Hospital Putrajaya. Patients were chosen using systematic random sampling. Every fifth patient in the medical record arranged in the sequence of dates of the year was chosen. This was done on a clean set of data, starting from the fifth patient in the list. Sample size calculation was as shown in 3.4. The data retrieved were then filled in the proforma.

## **3.3 Study duration**

Study duration period was from 1st January 2017 to 31st December 2018 (24 months).

## 3.4 Sample size

# For objective 1

A computer software PS: Power and Sample Size Calculation version 3.0, 2009, was used to calculate sample size (Dupont and Plummer, 1997). The formula used for sample size calculation was two proportion. The relevant values for sample size estimation were based on a study by Garrido et al., 2006. For the proportion of RBC transfused among NVUGIB, the power of this study was set at 0.8 with CI of 95% ( $\alpha = 0.05$ ). The proportion of non-transfused group among NVUGIB was 0.3 (P<sub>0</sub>), and the proportion of transfused group was 0.7 (P<sub>1</sub>). The ratio of control to experimental subjects was set at 1 (*m*). Therefore, the sample size calculated was 51.

## For objective 2

The sample size was in accordance with objective three as it was calculated as the highest sample size in the particular study.

## For objective 3

A computer software PS: Power and Sample Size Calculation version 3.0, 2009 (Dupont and Plummer, 1997) was used to calculate the sample size. The formula used for sample size calculation was independent T-test in which the estimated sample size was based on the mean difference. The relevant values for sample size estimation were based on a study by Lee *et al.*, 2016. For the correlation between discharge Hb level in NVUGIB patients and the number of RBC units transfused, the power of this study was set at 0.8 with CI of 95% ( $\alpha = 0.05$ ). In a previous study based on Lee *et al.*, 2016, the response within each subject was normally distributed with a standard deviation of 1.8 and a mean difference of 0.8. The largest sample needed was 80 in a single group, and 160 samples were needed for both groups. 10% of additional participants were added to cover the possibility of incomplete data. Therefore, the sample size calculated was 172.

#### 3.5 Inclusion Criteria

- i. Age of 18 years old or more
- ii. Patients admitted to the ward
- iii. Patients transfused with any unit of RBC
- iv. Patients with NVUGIB exclusively

## 3.6 Exclusion criteria

- i. Patients with variceal bleeding
- ii. Patients who were given a follow-up on an outpatient basis
- iii. Patients who had undergone OGDS in daycare.
- iv. Patients with concurrent Lower Gastrointestinal Bleeding (LGIB)
- v. Patients who developed two or more bleeding episodes before discharge.

#### **3.7 Statistical analysis**

SPSS version 24.0 for Windows software (SPSS, Chicago Illinois, USA) was used to perform the statistical analysis to present the descriptive and statistical analysis. Number, percentage, mean and median were used in the descriptive analysis.

## For objective 1

Demographic data were shown using number and percentage for the number of patients, gender, ethnicity, risk factors, aetiologies of NVUGIB and Forrest classification. Meanwhile, for age and LOS, mean and standard deviation were used. The data for age was normally distributed while for LOS, it was not normally distributed. Komolgorov-Smirnov was used for the test for normality. The level of significance was set at a p-value of 0.05.

## For objective 2

The distribution for the number of RBC units transfused for the samples was not parametric. Hence, in order to test the difference of mean for RBC units transfused across groups of presenting symptoms and aetiologies, Mann-Whitney U was used as a non-parametric test. Meanwhile, the Pearson Correlation Coefficient was used to determine the association between GBS with RBC units transfused in NVUGIB patients. Simple linear regression was used to establish the relationship between GBS and the number of RBC units transfused. Multiple linear regression was used to determine the association between presenting symptoms, aetiologies and GBS with RBC units transfused. The level of significance was set at a p-value of 0.05.

# For objective 3

Mann-Whitney test was used to determine the independent impact of discharge Hb group with RBC units transfused and LOS since they were not a normally distributed data. Meanwhile, Pearson Chi-Square test is used to determine the impact of discharge Hb group with the AE after discharge (readmission, rebleeding and mortality). The level of significance was set at a p-value of 0.05

# 3.8 Flow Chart of Study



Figure 3.1 Flow chart of study

## 3.9 Definition of the terms used

- Length of Stay (LOS) is defined as the length of an inpatient episode of care, calculated from the day of admission to day of discharge. However, in this study LOS specifically refers to the time when UGIB symptoms started until the time of discharge from the hospital.
- ii) Adverse Events (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject who has been administered an intervention. However, in this study, AE refers to patients who were readmitted after they have been discharged after the episode of NVUGIB.
- iii) Readmission refers to patient admission to the hospital due to any reasons within 45 days after the episode of NVUGIB.
- iv) Rebleeding refers to patients who were discharged, readmitted, and developed another bleeding episode. This bleeding episode was characterised by haematemesis or fresh melaena associated with haemodynamic instability (pulse rate of > 100 beats per minute, SBP < 100 mmHg, or both) after the episode of NVUGIB.</p>
- v) Mortality refers to patients who were discharged, readmitted and died due to any cause within 45 days after the episode of NVUGIB.

## **3.10 Ethical Approval**

Ethical approval with the reference number of NMRR-17-139-34033 was obtained from Ministry of Health through Jawatankuasa Etika & Penyelidikan Perubatan (Medical Research & Ethics Committee). In addition, ethical approval with the reference number of USM/JEPeM/17020127 was obtained from Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM). All the data were retrieved from patient's medical record and the data were recorded with reference identification. The desired medical record data was recorded in such a way that the respective patients could not be identified either directly or indirectly via linkage codes assigned to the data. Thus, the data that was collected is completely anonymous. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals.