



**RED BLOOD CELL TRANSFUSION
AMONG NEONATAL SEPSIS PATIENTS
AT HOSPITAL USM**

By

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Dissertation submitted in partial fulfilment of
the requirement for the degree of
MASTER OF MEDICINE
(TRANSFUSION MEDICINE)

May 2022

DECLARATION

I declare that this dissertation has been submitted to Universiti Sains Malaysia (USM) for the Master of Medicine (Transfusion Medicine) degree. Furthermore, I certify that I performed the records of the results in this study except for the quotations and summaries, which have been duly acknowledged, and I have no financial interest in the instrument or materials used in this study.

Date: May 2022



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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 could complete my Master programme with the submission of my dissertation. Especially to my parents, Misran bin Sitam, Norreha Binti Munajat and my sisters, Siti Zanariah Binti Misran and Siti Shahreena Binti Misran, for their continuous support for me throughout this programme.

I am deeply grateful to my supervisors, Dr Nur Arzuar bin Abdul Rahim and Dr Rohayu Binti Hami, Senior Lecturer of Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia (USM), Associate Professor Dr Noraida Binti Ramli, Consultant Pediatrician and Neonatologist, Hospital Universiti Sains Malaysia, Kubang Kerian for their supervision and guidance throughout the preparation of this thesis.

Special thanks to Associate Professor Dr Zakuan Zainy bin Deris, Head of Department and Senior Lecturer at Department of Microbiology and Parasitology, the Transfusion Medicine Unit and Record Office, Hospital Universiti Sains Malaysia, Kubang Kerian for cooperation and assistance throughout the study. Last but not least, I would like to acknowledge the support from my colleagues of the Transfusion Medicine master program, who, together with me, completed the master's Degree.

Thank you.

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LIST OF ABBREVIATIONS

HUSM	Hospital Universiti Sains Malaysia
USM	Universiti Sains Malaysia
WHO	World Health Organization
NICU	Neonatal Intensive Care Unit
LSCS	Lower segment caesarean section
PPROM	Premature rupture of membranes
PBM	Patient blood management
JEPeM	Jawatankuasa Etika Penyelidikan (Manusia)
UTI	Urinary tract infection
SPSS	Statistical Package for the Social Sciences
SLR	Simple logistic regression
MLR	Multiple logistic regression
SD	Standard Deviation
IQR	Interquartile range
RBC	Red blood cell
Hb	Haemoglobin
FFP	Fresh frozen plasma
FBC	Full blood count
CRP	C-reactive protein

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ABSTRAK

PENGENALAN: Bilangan sepsis dalam kalangan bayi adalah berbeza mengikut negara dan menjadi salah satu penyebab utama kemasukan bayi di NICU. Sepsis menjadi faktor utama kepada morbiditi dan mortaliti dalam kalangan bayi. Bayi merupakan golongan yang kerap menerima sel darah merah (SDM). Namun begitu, maklumat mengenai transfusi SDM dalam kalangan bayi yang mendapat sepsis di Malaysia amat terhad. Faktor risiko dan potensi reaksi berkaitan dengan transfusi SDM pada bayi juga kurang dijelaskan. Oleh itu, kajian ini bertujuan untuk mengenal pasti faktor klinikal berkaitan bayi yang mendapat sepsis, kesan sampingan berkaitan dengan transfusi SDM dan faktor-faktor yang mempengaruhi mortaliti dalam kalangan bayi yang mendapat sepsis.

KAEDAH: Kajian retrospektif kawalan kes merangkumi 220 orang bayi berusia kurang daripada 28 hari yang dirawat akibat sepsis di NICU Hospital USM dari tahun 2014 hingga 2019. Hubung kait antara demografik pesakit, ciri-ciri klinikal dan transfusi SDM dengan kematian bayi yang mendapat sepsis dianalisis menggunakan kaedah regresi logistik.

KEPUTUSAN: Bayi yang dilahirkan secara pramatang dengan usia kandungan kurang daripada 37 minggu sebanyak 131 orang (59.55%). Bayi yang mempunyai kurang berat badan ketika lahir didapati mempunyai risiko yang lebih tinggi untuk menerima transfusi SDM dengan purata berat badan ialah 2.34 kg. 43 orang (39.1%) daripada jumlah bayi

yang dikesan positif mikroorganisma pada sampel darah, mempunyai sejarah transfusi SDM. Terdapat dua (1.82%) kes reaksi transfusi akut yang dilaporkan dalam kalangan bayi yang memerlukan transfusi SDM. Tempoh purata kemasukan di NICU untuk bayi yang memerlukan transfusi SDM adalah lebih lama, iaitu 15 hari berbanding dengan bayi tanpa transfusi SDM. Bilangan kematian bayi akibat sepsis di NICU ialah 71 orang (32.27%) dan 55 orang (50.0%) daripadanya ialah bayi yang memerlukan transfusi SDM. Faktor-faktor yang berhubung kait secara signifikan bagi kematian bayi sepsis ($p < 0.05$) ialah keputusan sampel darah positif mikroorganisma, berat kelahiran bayi dan jumlah bilangan transfusi SDM, sama ada dua atau lebih daripada dua transfusi SDM.

KESIMPULAN: Kajian kami telah membuktikan sampel darah yang positif mikroorganisma, berat kelahiran bayi dan jumlah bilangan transfusi SDM menunjukkan hubungan yang signifikan dengan kematian bayi yang mendapat sepsis. Hasil kajian ini boleh digunakan sebagai panduan bagi pihak perawat dalam memastikan sebarang keputusan transfusi darah dilakukan secara berhemah khususnya dalam kes bayi yang mendapat sepsis. Audit klinikal berkenaan transfusi darah secara berterusan dan Pengurusan Darah Pesakit (PBM) yang bersesuaian terhadap bayi berupaya untuk mengurangkan morbiditi dan kematian bayi yang mengalami sepsis.

Kata Kunci: sepsis dalam kalangan bayi, tranfusi, reaksi transfusi, mortaliti, kultur darah

ABSTRACT

INTRODUCTION: The prevalence of neonatal sepsis varies in different countries. It is one of the most common reasons for admission to NICU, and it remains a significant cause of neonatal morbidity and mortality. Neonates represent a frequent group of recipients receiving red blood cell (RBC) transfusion. However, there is limited information about the impact of RBC transfusion among neonates with sepsis in Malaysia. The risk and potential adverse associations with RBC transfusions are poorly described in neonates. This study aimed to explore the clinical characteristics of neonatal sepsis, evaluate the outcomes related to RBC transfusion and assess the factors associated with mortality in neonatal sepsis.

METHODS: This case-control retrospective study involved 220 neonates admitted with sepsis in NICU Hospital USM from 2014 until 2019. The association between patients' demographics, clinical characteristics and RBC transfusion with mortality was analysed by logistic regression.

RESULTS: Only half (59.5%) of the neonates were delivered prematurely with a gestational age of fewer than 37 weeks. Low birth weight neonates were found to have a higher risk for RBC transfusion, with a mean birth weight of 2.34 kg. Among 55 (25.0%) neonates who had proven blood culture positive, 43 (39.1%) of them had RBC

transfusion. There were two (1.8%) reported cases of acute transfusion reaction among neonatal sepsis with RBC transfusion. The mean length of stay in NICU for neonatal sepsis with RBC transfusion was prolonged, up to 15 days compared to neonatal sepsis without RBC transfusion, up to 8 days only. About 71 (32.2%) neonates died during hospitalization in the NICU, of which 55 (50.0%) of them were among neonatal sepsis in transfuse group. Mortality among neonatal sepsis was significantly associated with proven positive blood culture, neonatal birth weight and the total number of RBC transfusions, either with two or more than two RBC transfusions ($p < 0.05$).

CONCLUSION: Our study was able to prove that proven positive blood culture, neonatal birth weight and the total number of RBC transfusions were significantly associated with mortality among neonatal sepsis. This information can be utilised by clinicians to ensure that any blood transfusion decision is made judiciously in neonates. Regular clinical audit on blood transfusion and appropriate Patient Blood Management among neonates able to reduce neonatal sepsis morbidity and mortality.

Keywords: neonatal sepsis, transfusion, transfusion reaction, mortality, blood culture

CHAPTER 1

INTRODUCTION

1.1 Title

Red Blood Cell Transfusion Among Neonatal Sepsis Patients at Hospital USM

1.2 Overview

Neonatal sepsis is a systemic infection that develops in neonates under the age of 28 days. It's life-threatening, and any delay in treatment might result in death. The global incidence of neonatal sepsis was estimated to be 2,824 cases per 100,000 live births, accounting for 17.6 % of neonatal mortality. Nonetheless, it is a major cause of morbidity and death in term and preterm neonates (Fleischmann *et al.*, 2021).

Preterm neonates have developmental immaturity in their hepatic, neurological, and immune systems, making them prone to organ injury. As a result, they are at risk of anaemia and need blood transfusions. Term neonates are also vulnerable to sepsis, which can manifest as either early or late-onset sepsis caused by maternal risk factors such as chorioamnionitis or as a result of hospital or community-acquired infections (Tewabe *et al.*, 2017). Transfusion decisions should thus be thoroughly evaluated, with evidence-based guidelines utilised accessible. However, in an attempt to improve the neonate's prognosis, any risk or long-term complications of blood transfusion should be considered.

Although neonates are frequently transfused, they are often under-represented in transfusion trials and many current studies focused mainly on patient blood management among the adult population (Crighton *et al.*, 2018). Furthermore, the RBC transfusion to

neonates is complex and is influenced by many confounding factors. These factors include neonatal birth weight, gestational age, ongoing blood losses, existing comorbidities, clinical signs and symptoms of patients and laboratory parameters (Colombatti, Sainati and Trevisanuto, 2016).

1.3 Literature review

1.3.1 Determinants and predictive factors for RBC transfusion in neonatal sepsis patients

Sepsis continues to be a leading cause of newborn morbidity and death. Preterm and low-birth-weight newborns (less than 2500 g) were susceptible to sepsis, with the causative organism and risk factors varying between many studies, depending on the population, diversity of organisms, and the onset of infection (Guo *et al.*, 2019).

Furthermore, neonates differ physiologically from infants and young children, needing a distinctive set of haemoglobin thresholds (Del Vecchio *et al.*, 2016; Wang *et al.*, 2017; Iskander *et al.*, 2018). Premature infants and critically ill neonates in the NICU with anaemia of prematurity, sepsis, anaemia due to phlebotomy losses or other clinical circumstances frequently require RBC transfusions (Del Vecchio *et al.*, 2016).

Hopewell S and colleagues discovered that neonatal birth weight, gestational age, the presence or absence of sepsis, respiratory issues or the need for assistance, and the severity of the disease were all possible predictors or confounding variables for RBC transfusion in neonates. These confounding variables were chosen with the understanding that the more critically ill the neonates are, the more likely they may require RBC transfusion (Hopewell *et al.*, 2013).

A previous study stated that neonatal hemopoietic systems may malfunction as a result of systemic bacterial infection. For example, anaemia and thrombocytopenia were present in about 73 and 89 cases of newborn sepsis, respectively. These findings show that the hemopoietic system was suppressed in the presence of sepsis. In addition, bacteria toxins and lipopolysaccharide could cause hemopoietic dysfunction. They also found anaemia and thrombocytopenia were common in sepsis caused by *Klebsiella pneumoniae* or *Candida* (Guo *et al.*, 2019).

1.3.2 Practice of RBC transfusion in neonatal sepsis patients

Nevertheless, RBC transfusions are still regularly utilised in neonates patients (Keir *et al.*, 2015). Transfusing a neonate is frequently based on its haematocrit level, clinical condition and severity of the sepsis. Furthermore, RBC transfusions are essential for premature infants and severely ill neonates in the NICU. The extremely preterm neonates have at least one RBC transfusion, and almost 5% of the paediatric patients also receive at least one RBC transfusion during their hospital stay (Goobie *et al.*, 2019). Previous studies had found that preterm neonates of less than 30 weeks gestation and extremely low birth weight (less than 1000 g) receive at least one RBC transfusion during their NICU admission (Bowen *et al.*, 2015). In addition, a multicentre study in China demonstrated that neonates with lower birth weight, diagnosed with pneumonia, or bacterial sepsis had a higher chance of receiving RBC transfusion (Sun *et al.*, 2020). In addition, transfusion practice in the NICU setting remains opinion based rather than evidence-based (Del Vecchio *et al.*, 2016).

Although guidelines have established target haematocrit values for neonates, most of these values are based on expert judgement. However, determining the optimal haematocrit value to utilise for RBC transfusion and whether or not to wait for a sign of insufficient oxygen delivery to prevent any potential short or long-term complication remained a significant challenge (Iskander *et al.*, 2018). There is still lacking evidence regarding optimal volumes, threshold-based vs symptomatic RBC transfusion in neonatal sepsis (H. V. New *et al.*, 2016). Furthermore, the appropriate RBC transfusion threshold in children suffering from severe sepsis or septic shock also remained unknown.

Blood volumes and Hb concentrations among neonates vary with age and weight, whereas newborns and infants have higher blood volumes per weight but a lower tolerance for losses (Goobie *et al.*, 2019). According to worldwide guidelines for neonatal sepsis management, the Hb level should be maintained between 7.0 and 9.0 g/dL until tissue hypoperfusion has been recovered. At the same time, it is recommended for RBC transfusion if haemoglobin decreases to 7.0 g / dL. Most RBC transfusions to neonates are top-up transfusions of small volumes, generally 10-20 ml/kg, typically 15 ml/kg over 4 hours to treat anaemia and maintain Hb as well as haematocrit above a certain threshold while reducing the risk of volume overload (Del Vecchio *et al.*, 2016; H. V New *et al.*, 2016). A previous randomised control trial comparing a transfusion threshold of 7.0 g/dL (restrictive group) and 9.5 g/dL (liberal group) among stabilised critically ill children noted no difference between these two groups in terms of the detrimental outcome of new or progressive multiorgan dysfunction syndrome among neonates. Furthermore, restrictive transfusion practices had reduced exposure to RBC transfusion with no evidence of increased mortality among preterm (Heeger *et al.*, 2019).

While RBC transfusion is one of the conventional treatment options for managing blood loss and anaemia, other effective treatments are available and should be used as an alternative. Although RBC transfusion and other blood components have long been an essential and vital element of global healthcare, they are also associated with a substantial financial and safety burden (Goobie *et al.*, 2019). Hence, implementing three pillars approach of patient blood management (PBM) program in paediatric such as optimising blood volume, minimising blood loss and improving the patient's tolerance of anaemia by optimising their physiological reserve has been shown to minimise blood transfusion, morbidity and mortality and hospital expenses (Crighton *et al.*, 2018; Flores *et al.*, 2020). Besides that, establishing NICU transfusion guidelines has been encouraged as a way of improving practice and avoiding unnecessary transfusions (Del Vecchio *et al.*, 2016).

1.3.3 Benefits and risks of RBC transfusion in neonatal sepsis patients

RBC transfusion is frequently considered a life-saving therapy in critically ill neonates. It immediately enhances tissue oxygenation, providing rapid and effective intervention due to inadequate red blood cell mass, especially in neonatal sepsis with anaemia (Wang *et al.*, 2017; Goobie *et al.*, 2019). Nonetheless, as blood products are considered biological products, any risk of adverse transfusion reactions should be closely monitored. Therefore, in current neonatology practice, the need for transfusion must be balanced against the risks.

When compared to the adult population, the incidence of allergic transfusion reaction, febrile non-hemolytic transfusion reaction, and hypotensive transfusion reaction was higher in the paediatric population. The implicated blood component was mainly platelet followed by RBC and then plasma (Oakley *et al.*, 2015). Transfusion-related acute lung

damage, transfusion-related acute circulatory overload, and hemolytic transfusion response are all associated with 15 to 30% death rates. Furthermore, receiving RBC transfusion in children was associated with an increased risk of 30-day mortality and complication such as post-operative infection (Goobie, DiNardo and Faraoni, 2016; Rajasekaran *et al.*, 2016). Thus, to reduce risks related to the transfusion of blood products, all hospitals and health care providers should avoid unnecessary, inappropriate or over-transfusion (Goobie *et al.*, 2019). According to Meybohm *et al.*, it is crucial to know the baseline transfusion rates, regular monitoring of blood usage, and feedback to physicians for reducing unnecessary blood transfusions (Meybohm *et al.*, 2017).

Unfortunately, the risk and potential adverse complications with RBC transfusion are poorly described and lack information in neonates (Oakley *et al.*, 2015; Keir *et al.*, 2016). Since transfusions to neonates have both benefits and risks thus, specific guidelines must be established to improve practice and prevent unnecessary transfusions (Del Vecchio *et al.*, 2016). This information may be helpful not only to clinicians in balancing the need for transfusion with the risks associated with it but also to patients and their guardians in ensuring that they are well informed before signing a consent form (Oakley *et al.*, 2015).

Several studies have looked into the impact of RBC transfusion on neonatal sepsis outcomes such as length of stay in the intensive care unit, organ dysfunction, the need for oxygen support, nosocomial infection, and neonatal mortality (Muszynski *et al.*, 2018; Karagiannidou *et al.*, 2020). A retrospective cohort study of NICU patients found that RBC transfusion was significantly associated with increased length of stay, resulting in additional medical costs (Kheiry *et al.*, 2019). Other studies identified an association between early-onset neonatal sepsis and types of isolated bacterial culture with the length

of stay in NICU (Ibrahim *et al.*, 2014; Guo *et al.*, 2019). Meanwhile, another study found that neonates infected with *Klebsiella pneumoniae*, *Staphylococcus spp.*, and *Pseudomonas aeruginosa* had longer hospital stays, thus indicating that these pathogens were acquired in the hospital (Al-Matary *et al.*, 2019). However, these studies did not further explore the association between RBC transfusion and length of stay in the NICU.

1.4 Research justification

Clinical decisions for RBC transfusion are frequently made based on recommendations for different paediatric cohorts or expert opinion guidelines. RBC transfusions are given with the expectation that the transfusion will improve oxygen transport to tissues, resulting in a quick and effective intervention. However, studies related to RBC transfusion and other potential risk factors associated with clinical outcomes such as transfusion reaction, length of stay in NICU and mortality were not well explored in neonates.

Although neonates are frequently transfused, they are typically under-represented in transfusion studies and less clinical trial data to support evidence-based transfusion practice in neonates. According to the unpublished data at NICU Hospital USM 2018, it estimated 15-cases of neonatal sepsis were admitted per week and among them might need RBC transfusion. However, as described in the literature review and database in the Hospital USM, there was no local data that specifically described the RBC transfusion and other risk factors that impact the clinical outcomes of neonatal sepsis. These data can be used as a reference to guide the transfusion practice among neonatal sepsis patients. Therefore, this study is mainly to address the research gap. It will provide valuable evidence-based data regarding the demographic, clinical factors and outcomes related to

RBC transfusion such as transfusion reaction, length of stay in NICU and mortality among neonatal sepsis. Therefore, this study may help clinicians in decision making for transfusion after weighing the risk and benefits to improve neonatal outcomes.

1.5 Research questions

- i. What are the patients' demographic, clinical characteristics and RBC transfusion in neonatal sepsis?
- ii. What are the clinical outcomes of RBC transfusion in neonatal sepsis patients?
- iii. Is there any significant association between patients' demographic, clinical characteristics and RBC transfusion with mortality among neonatal sepsis?

CHAPTER 2

OBJECTIVES

2.1 General Objective

To determine the characteristics and clinical outcomes of RBC transfusion in neonatal sepsis at Hospital USM.

2.2 Specific Objectives

- i. To determine the patients' demographic, clinical characteristics and RBC transfusion in neonatal sepsis.
- ii. To determine the clinical outcomes (acute transfusion reaction, length of stay in NICU and in-hospital mortality) of RBC transfusion among neonatal sepsis.
- iii. To determine the association of patients' demographic, clinical characteristics and RBC transfusion with mortality among neonatal sepsis.

2.3 Research Hypothesis

i. Null hypothesis

There is no significant association between patients' demographic, clinical characteristics and RBC transfusion with mortality among neonatal sepsis.

ii. Alternative hypothesis

There is a significant association between patients' demographic, clinical characteristics and RBC transfusion with mortality among neonatal sepsis.

CHAPTER 3

METHODOLOGY

3.1 Study Location

This study was conducted at Neonatal Intensive Care Unit (NICU), Pediatrics Department, Hospital Universiti Sains Malaysia (Hospital USM), a university-based teaching hospital at Kubang Kerian, Kota Bharu, Kelantan. Hospital USM has 65 beds in NICU. It is a tertiary referral centre for neonatology with multiple sub-specialities covering the East Coast of Peninsular Malaysia.

3.2 Study Design

A retrospective case-control study using medical records of neonatal sepsis patients admitted to the Neonatal Intensive Care Unit (NICU) of Hospital Universiti Sains Malaysia (Hospital USM) from 1st January 2014 to 31st December 2019. For each case of neonatal sepsis with RBC transfusion, have a control case selected among the neonatal sepsis without RBC transfusion.

3.3 Study Duration

The study was conducted within 12 months (1st April 2020 to 1st April 2021)

3.4 Study Population

- i. Reference population : Neonates with neonatal sepsis at Kelantan
- ii. Target population : Neonatal sepsis admitted at Hospital USM
- iii. Source population : Neonatal sepsis getting treatment in NICU Hospital USM
from 1st January 2014 until 31st December 2019
- iv. Sampling frame : Registration of neonatal sepsis in NICU Hospital USM

3.5 Subject Criteria

Neonatal sepsis patient that fulfilled the inclusion and exclusion criteria is eligible for the study. The subject details were collected as in research proforma

3.5.1 Inclusion criteria

- Neonates who were born and admitted to NICU, Hospital USM between 1st January 2014 until 31st December 2019
- Neonates who were diagnosed with neonatal sepsis either by clinical diagnosis and/or positive culture
- Neonatal sepsis who had RBC transfusion or no history of RBC transfusion

3.5.2 Exclusion criteria

- Neonates who were diagnosed with chromosomal anomalies, major structural abnormalities, cardiovascular problems or metabolic syndrome that compromise normal physiological function
- Neonates who passed away less than 24 hours of life
- Presumed neonatal sepsis

3.6 Sample size calculation

The sample size in this study was calculated for each objective. The biggest sample size calculation was used as the sample size required in this study.

Objective 1: *To determine the patients' demographic, clinical characteristics and RBC transfusion in neonatal sepsis.*

The estimated sample size for the descriptive study of this objective is based on socio-demographic data (neonatal birth weight) in a study by Tewabe et al., 2017. The calculation uses single proportion formula:

$$\text{Single proportion, } n = \left(\frac{z}{\Delta} \right)^2 p(1 - p)$$

n = sample size

z = the value to estimate the 95% confidence interval (1.96)

p = expected prevalence or proportion

Δ = precision or detectable difference of expected population proportion and true population proportion

Z = 1.96

Δ = 0.05

P = 0.031

n = 46

Considering 10% drop out rate = 51

Objective 2: *To determine the clinical outcome (acute transfusion reaction, length of stay in NICU and in-hospital mortality) of RBC transfusion among neonatal sepsis*

The estimated sample size for this objective's descriptive study is based on the number of deaths in the intensive care unit in a study by Karam et al., 2011. The calculation uses single proportion formula:

$$\text{Single proportion, } n = \left(\frac{z}{\Delta} \right)^2 p(1 - p)$$

n = sample size

z = the value to estimate the 95% confidence interval (1.96)

p = expected prevalence or proportion

Δ = precision or detectable difference of expected population proportion and true population proportion

$$Z = 1.96$$

$$\Delta = 0.035$$

$$P = 0.07$$

$$n = 100$$

Considering 10% drop out rate = 224

Objective 3: *To determine the association of patients' demographic, clinical characteristics and RBC transfusion with mortality among neonatal sepsis.*

The estimated sample size for this objective is based on mortality among neonatal sepsis according to different birth weight categories in a study by Yusuf and Road, 1997.

$$\text{Two proportions, } n = \frac{p_1(1-p_1) + p_2(1-p_2)}{(p_1 - p_2)^2} (z_\alpha + z_\beta)^2$$

n= sample size

P1= proportion of the associated factor among higher risk

P2= proportion of the associated factor among lower risk

Z α = 1.96 for α = 0.05 (two tailed)

Z β = 0.84 for 80% power

P1 = 0.60 (proportion of mortality according to the birthweight \leq 1000 g)

P2 = 0.14 (proportion of mortality according to the birthweight $>$ 2500 g)

Z α = 1.96

Z β = 0.84

n = 13 x 2 = 26

Considering 10% drop out rate = 29, 29 x 2 = 58

Conclusion of Sample Size

Based on the calculations from each objective, the biggest sample size is 224 from the second objective. But in this study, the sample size collected was 220 due to time limitations.

3.7 Sampling method and subject recruitment

There are 1078 neonates admitted to NICU at Hospital USM from 1st January 2014 to 31st December 2019. 446 medical records on neonatal sepsis from 2014 until 2019 were retrospectively reviewed. However, 220 neonates with neonatal sepsis that fulfilled the inclusion and exclusion criteria were included. Purposive sampling was used to select these subjects. The subject was divided into two groups, transfuse (case) and non-transfuse (control) with equal distribution, 110 for each group.

3.8 Research Tool

The research proforma is prepared to ensure the data collection is complete. It was developed based on a studied variable in a literature review and previous studies on neonatal sepsis and blood transfusion. The research proforma was divided into three main components:

i. Demographic profile

- a) *Data related to neonatal history* - gender, nationality, race and confirm neonatal sepsis either clinical and/or positive culture
- b) *Data related to maternal history* - maternal age and relevant maternal antenatal history related to sepsis such as PPROM/ PROM, chorioamnionitis, GBS infection status or history of maternal pyrexia
- c) *Data related to birth history and progress* - date of birth, gestational age, birth weight, method of delivery, Apgar score and admission temperature

ii. Data on transfusion status

Data related to transfusion details were documented, including date of transfusion, indications, volume amount and any reported transfusion reaction. Data regarding neonatal sepsis without red blood cell transfusion and the total number of red cell transfusions episodes, either one, two or more than two was documented.

iii. Data on Patient's Clinical Outcomes

Data regarding the clinical outcomes of neonatal sepsis related to red blood cell transfusion will be documented, including transfusion reaction, the total length of NICU stay and in-hospital mortality. In addition, if the patient passes away, the date, age, time and causes of death were documented.

3.9 Data Collection method

Data collection was started in April 2020. The neonates diagnosed with neonatal sepsis and admitted to NICU Hospital USM were identified using the registration list for NICU admission. A comprehensive patient database was traced and collected from patient's medical records in the medical record office, RBC transfusion and transfusion reaction information from the Lab Information System (LIS) Transfusion Medicine Unit, as well as neonatal sepsis with proven blood culture data, were obtained from the Lab Information System (LIS) Microbiology Department Hospital USM. All of the data was gathered utilising both manual and computerised databases. Data was entered into a research proforma. All information was kept confidential.

3.10 Statistical analysis

Data entry and analysis were performed using IBM SPSS Statistics V26, licensed under IBM Corporation, New York. Descriptive analysis was carried out to analyse the patients' demographic, clinical characteristics and outcomes of RBC transfusion among neonatal sepsis. For descriptive analysis, numerical variables were presented as mean (standard deviation) and median (IQR), while categorical variables were presented as frequency (percentage). The association between patient demographic, clinical characteristics and RBC transfusion with mortality among neonatal sepsis was analysed using simple and multiple logistic regression. For multiple logistic regression, factors with a p-value less than 0.25 from simple logistic regression were selected. A p-value of less than 0.05 was set up as the level statistically significant with a confidence interval of 95%.

3.11 List of variables

Table 3.1 List of variables

Independent variables	Dependent variables
Gender Ethnicity Onset and Diagnosis of Neonatal sepsis Maternal age Risk of sepsis Gestational age Method of delivery Birth weight Total number of RBC transfusions	Mortality

3.12 Ethical Issue

Ethical approval from the Human Research Ethics Committee of Universiti Sains Malaysia (ref no: USM/JEPeM/20010010) was received on 6th March 2020. The data was collected from the patient's medical record and Blood Bank System at Hospital USM. The desired medical record data was recorded using an index number so that the respective patients could not be identified directly or indirectly. As a consequence, the data that has been collected is entirely anonymous. Furthermore, the confidentiality of the patient was strictly protected.

3.13 Conflict of Interest

There was no conflict of interest throughout the study duration by the investigator.

3.14 Community Sensitivities and Benefits

The study will benefit the community by providing evidence-based data on the current practice of red blood cell transfusions in neonatal sepsis infants, morbidities and its relation to in-hospital mortality. Our local data about transfusion, morbidities and mortality among this group of patients is not well established and explored. We seek to get a better understanding of the present practice of RBC transfusion in neonatal sepsis and its potential adverse outcome. It also could help to create awareness among clinicians regarding transfusion practise in neonatal sepsis and their risks. Therefore, there is no issue related to community sensitivities and value in this retrospective study.

3.15 Operational Definition

Table 3.2: Operational definition

	Definition
Neonates	Infants less than 28 days of age and premature infants (<37 weeks' GA) up to 28 days post-term–corrected age (Keir et al., 2016)
Neonatal sepsis	Systemic infection occurs in neonates at 28 days of life. It is categorized into two types: early-onset sepsis which occurs less than 72 hours of life (Kari A. Simonsen et al., 2014) and late-onset sepsis which occurs after 72 hours of life (Dong and Speer, 2014). Neonates with positive blood culture sepsis and clinical sepsis were included.
Clinical sepsis	Neonates that have signs and symptoms include temperature instability, change in behaviour, skin changes, feeding problems, cardiovascular, respiratory and metabolic instability (Paediatric Protocols for Malaysian Hospitals, 4 th edition, 2019).
Clinical outcomes	Clinical outcomes defined as mortality and morbidities that are measured in the study include: <ul style="list-style-type: none"> a) Acute transfusion reaction <p>A transfusion reaction is an undesirable response or effect in a patient temporarily associated with blood or blood component (Transfusion practice guidelines for clinical and laboratory personnel, National Blood</p>

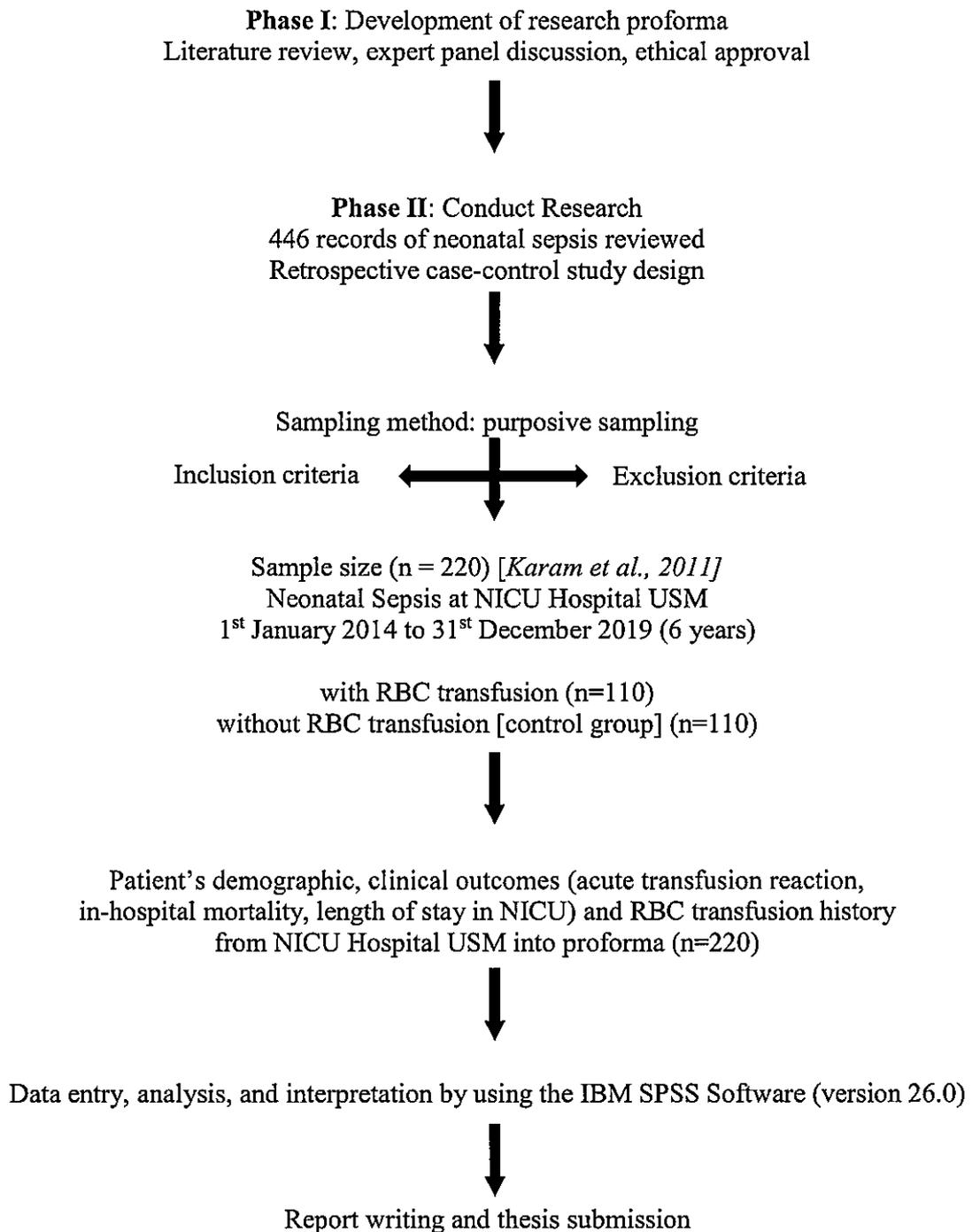
Table 3.2, continued

	<p>Centre, 4th edition 2014). An acute transfusion reaction is a transfusion reaction that occurs within 24 hours of blood transfusion.</p> <p>b) Length of stay in NICU</p> <p>Duration of NICU stay starts from the date of admission until the date of discharge.</p> <p>c) In-hospital mortality</p> <p>Death within hospital stay. Mortality within 24 hours of receiving an RBC transfusion and before discharge from initial hospitalization (Adverse effects of red blood cell transfusions in neonates: a systematic review and meta-analysis, Keir et al., 2016)</p>
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3.16 Study flowchart

This study was divided into two phases: phase 1 was for developing research proforma, and phase 2 was for data collection and report writing. First, a research proforma was designed to collect red blood cell transfusion data and clinical outcomes in neonatal sepsis in NICU Hospital USM. A total of 220 subjects were included in this study. The study flowchart is shown below:

Figure 3.1: Study flowchart



CHAPTER 4
MANUSCRIPT

This section was prepared according to the journal "Malaysian Journal of Medicine and Health Sciences (MJMHS)" Author's guidelines. Instruction to Author is available in Appendix E.