UNIVERSITI PUTRA MALAYSIA

RETROSPECTIVE REVIEW OF RISK FACTORS AND CAUSES OF NEONATAL JAUNDICE IN NEONATAL INTENSIVE CARE UNIT (NICU), HOSPITAL SERDANG FROM 2015-2019

GROUP 10

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FPSK1 2020 10

CERTIFICATION

It is hereby certified that we have read the project dissertation entitled "Retrospective Review of Risk Factors and Causes of Neonatal Jaundice in Neonatal Intensive Care Unit (NICU), Hospital Serdang from 2015-2019" by Chang Chen Yue, Mohamad Ikmal Che Hat and Maisarah Kamaruzzaman. In our opinion, it is satisfactory in terms of scope, quality, and the presentation as required by Package 11.

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ABSTRACT

Abstract of this research project is presented to the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia for the fulfilment for the degree in Doctor of Medicine (MD)

RETROSPECTIVE REVIEW OF RISK FACTORS AND CAUSES OF NEONATAL JAUNDICE IN NEONATAL INTENSIVE CARE UNIT (NICU), HOSPITAL SERDANG FROM 2015-2019

BY

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OCTOBER 2020

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Introduction: Neonatal jaundice (NNJ) is a phenomenon characterized by the yellowish pigments appearing on the skin, mucous membrane and sclera of the newborns. It happens when there is an elevation of unconjugated bilirubin in blood, so called hyperbilirubinaemia. When blood bilirubin levels reach above 85 μmol/L, jaundice is clinically visible.

Objectives: The aim of this study is to determine the prevalence of neonatal jaundice and the association of the maternal and neonatal risk factors with the presence of severe neonatal jaundice among neonates in Neonatal Intensive Care Unit (NICU) of Hospital Serdang.

Method: A retrospective study was conducted in NICU of Hospital Serdang by reviewing all the medical records from 2015-2019. 647 patient's medical records have been chosen based on convenience sampling method. All the inborn and outborn neonates with neonatal jaundice who were admitted to NICU of Hospital Serdang with gestational age up to 42 weeks were included in this study.

Results: The prevalence of neonatal jaundice in this study was 36.5 %. Risk of haemolysis was not a significant risk factor among the premature neonates and mothers aged below 30 years old. Neonatal jaundice is more likely to occur in male babies that was born via normal vaginal delivery and within 38 to 40 weeks age, under exclusive breastfeeding, with mothers aged between 25 to 29 years, multiparity, and blood group O.

Keywords: Neonatal jaundice, Hospital Serdang, risk factor, causes, NICU

ABSTRAK

Abstrak projek penyelidikan yang dikemukakan kepada Fakulti Perubatan dan Sains Kesihatan, Universiti Putra Malaysia sebagai keperluan untuk ijazah Sarjana Muda Doktor Perubatan (MD)

TINJAUAN RETROSPEKTIF FAKTOR RISIKO DAN PENYEBAB JAUNDIS NEONATAL DI NICU (NEONATAL INTENSIVE CARE UNIT), SERDANG HOSPITAL DARI 2015-2019

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Pengenalan: Jaundis neonatal (NNJ) merupakan fenomena yang berlaku oleh perubahan warna kekuningan pada kulit dan '*sclera'* (bahagian putih pada mata) bayi yang baru lahir. Ia berlaku apabila terdapat pe ningkatan tahap bilirubin tidak terkonjugasi dalam darah, iaitu keadaan yang juga dikenali sebagai *hyperbilirubinemia*. Apabila tahap bilirubin darah mencapai melebihi 85 μmol / L, jaundis dapat dilihat secara klinikal.

Objektif: Tujuan kajian ini adalah untuk menentukan kadar jaundis neonatal dan perkaitan faktor risiko ibu dan bayi dengan kehadiran jaundis neonatal yang teruk di kalangan bayi di NICU *(Neonatal Intensive Care Unit)* Hospital Serdang.

Kaedah: Kajian retrospektif dilakukan di NICU Hospital Serdang dengan menyemak semua rekod perubatan dari 2015-2019. 647 rekod perubatan pesakit telah dipilih berdasarkan kaedah '*convenience sampling'*. Semua bayi yang baru lahir dan dilahirkan dengan jaundis neonatal dan dimasukkan ke NICU Hospital Serdang dengan usia kehamilan hingga 42 minggu dimasukkan dalam kajian ini.

Keputusan: Kadar jaundis neonatal dalam kajian ini adalah 36.5%. Risiko hemolisis bukan faktor risiko yang signifikan dalam kalangan bayi prematur dan ibu yang berumur 30 tahun ke bawah. Jaundis neonatal lebih cenderung berlaku pada bayi lelaki yang dilahirkan melalui faraj secara normal dan dalam usia 38 hingga 40 minggu, di bawah penyusuan eksklusif, dengan ibu berusia antara 25 hingga 29 tahun, '*multiparity'*, dan kumpulan darah O.

Kata kunci: Penyakit kuning neonatal, Hospital Serdang, faktor risiko, punca, NICU

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We would like to express our profound gratitude to God for giving us the wisdom, health, well-being and knowledge necessary to complete this research.

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We would also like to show our gratitude to Dr Zurina Zainuddin and Dr Faizah Bt. Mohamed Jamli as our co-supervisor, for sharing their pearls of wisdom with us during this research. This research would have never been accomplished without their assistance and dedicated involvement.

We acknowledge the Medical Research for Ethics and Committee (MREC) for giving us the ethical approval to conduct this study. We thank the Clinical Research Centre (CRC) of Hospital Serdang for giving us the permission to conduct our study in Hospital Serdang and the doctors and staffs of Hospital Serdang for helping us during the data collection period.

Not to forget our beloved family and friends for their motivation and encouragement which were extremely important and valuable for us to complete this research

DECLARATION

We hereby acknowledge that this Research Project is the result of our original work except the excerpts and quotations that have been explained. We also acknowledge that this project has never been developed before by others at Universiti Putra Malaysia.

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CHANG CHEN YUE (196932)

Date: 15 October 2020

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LIST OF ABBREVIATIONS

NNJ	Neonatal jaundice
NICU	Neonatal Intensive Care Unit
%	Percent
G6PD deficiency	Glucose-6-Phosphate deficiency
Rh	Rhesus
UGT	Uridine Diphosphoglucoronate Glucuronosyltransferase
DM	Diabetes Mellitus
>	More than
<	Less than
g	Grams
kg	Kilograms

CHAPTER 1: INTRODUCTION

1.1 Background

Neonatal jaundice (NNJ) is a phenomenon characterized by the yellowish pigments appearing on the skin, mucous membrane and sclera of the newborns. It happens when there is an elevation of unconjugated bilirubin in blood, so called hyperbilirubinaemia. When blood bilirubin levels reach above 85 μmol/L, jaundice is clinically visible (Brits et al., 2018). NNJ can be caused by a variety of factors, for example, incomplete development of liver function in newborns that lead to physiologic jaundice also a few pathological factors such as sepsis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, ABO incompatibility etc (Najib et al., 2013).

The liver acts as a metabolic organ which metabolizes the substances that are circulating in our body, including bilirubin. Pathophysiology of jaundice starts when the heme in haemoglobin is broken down by spleen and conjugated in the liver. Conjugated bilirubin will be secreted into bile, which later will be reduced by normal gut flora in the small intestine. Most of the conjugated bilirubin will be excreted, and part of it will return into enterohepatic circulation (Kevin, 2018).

Causes and risk factors of NNJ can be divided by mechanisms which are: overproduction of bilirubin, failure of elimination of bilirubin and increased enterohepatic circulation, and by maternal and neonatal factors. Neonatal factors such as gestational age, gender and birth weight, method of delivery, family history of severe neonatal jaundice, erythrocyte enzymatic deficiency, inherited red cell membrane defects, defects in uridine diphosphoglucoronate glucuronosyltransferase, biliary atresia, sepsis, and prematurity play a significant role in the development of neonatal

jaundice. Apart from that, a few maternal factors, which are maternal age, race, socioeconomic class, blood group, infection, prolonged labour, primiparity, maternal comorbid and obstetric illness, and absence of breastfeeding will be studied in this study.

1.2 Problem Statement

NNJ is very common and is present in 60% of term babies and up to 80% of premature babies (Brits et al., 2018). Neonatal jaundice may cause harmful consequences and sequelae to the newborns if therapeutic interventions are not initiated. Addressing this topic highlights the potential causes and risk factors that need to be sought after to ensure NNJ is detected and treated in a timely manner. This knowledge will help to reduce morbidity to the newborns as well as improve the advice given to parents in the care of their newborn infants.

Many studies have done research on the causes or risk factors of neonatal jaundice, but most of those studies are conducted with a relatively narrow perspective, which the studies only consist either of neonatal factors or maternal factors. The lack of papers that focus on an overview of causes and risk factors of neonatal jaundice which includes both neonatal and maternal factors has driven us to conduct this study.

1.3 Significance of the Study

The findings of this study will determine the causes and risk factors of jaundice among newborns admitted to the Neonatal Care Intensive Unit of Hospital Serdang. We aim to highlight the risk factors of neonatal jaundice among our Malaysian patient cohort for early detection in order to prevent complications. This study will provide a guide

when revisiting the screening questions and investigations of mother and child. It will also aid us in the ability to provide appropriate advice for parents-to-be for earlier detection of neonatal jaundice in order to avoid complications resulting from severe neonatal jaundice.

1.4 Research Questions

1. What is the prevalence of neonatal jaundice in the neonates admitted to the Neonatal Care Intensive Unit of Hospital Serdang?
2. What is the association between maternal factors (e.g.: age, race, ethnicity socioeconomic class, ABO or Rhesus (Rh) incompatibility, infection, prolonged labour, primiparity, maternal comorbid and obstetric illness, absence of breastfeeding) with the presence of severe neonatal jaundice in the Neonatal Care Intensive Unit of Hospital Serdang?
3. What are the associations between neonatal factors (e.g.: gestational age/prematurity, gender and birth weight, method of delivery, family history of severe neonatal jaundice, erythrocyte enzymatic deficiency, inherited red cell membrane defects, defects in uridine diphosphoglucoronate glucuronosyltransferase, biliary atresia, sepsis, prematurity) with the presence of severe neonatal jaundice in the Neonatal Intensive Care Unit of Hospital Serdang?

1.5 Research Objectives

1.5.1 General Objective

To identify the prevalence of neonatal jaundice in the neonates admitted to the Neonatal Intensive Care Unit of Hospital Serdang.

1.5.2 Specific Objectives

I. To determine the association between maternal factors (e.g.: age, race, ethnicity, socioeconomic class, ABO or Rh incompatibility, infection, prolonged labour, primiparity, maternal comorbid and obstetric illness, absence of breastfeeding) with the presence of severe neonatal jaundice among neonates in the Neonatal Care Intensive Unit of Hospital Serdang.

II. To determine the association between neonatal factors (e.g.: gestational age/prematurity, gender and birth weight, method of delivery, family history of severe neonatal jaundice, erythrocyte enzymatic deficiency, inherited red cell membrane defects, defects in uridine diphosphoglucoronate glucuronosyltransferase, biliary atresia, sepsis, prematurity) with the presence of severe neonatal jaundice among neonates in the Neonatal Intensive Care Unit of Hospital Serdang.

1.6 Research Hypothesis

1.6.1 Null hypothesis

There is no significant association between maternal and neonatal factors with the presence of severe neonatal jaundice in the Neonatal Intensive Care Unit of Hospital Serdang.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Neonatal jaundice is clinically presented as the appearance of yellowish pigmentation on skin, mucous membrane and sclera of neonates. When neonates' serum unconjugated bilirubin is elevated to 85μmol/L and above, it is clinically diagnosed as neonatal jaundice (Brits et al., 2018). Physiological jaundice usually happens as it is due to incomplete development of neonates' liver function. Apart from this, neonates are predisposed to neonatal jaundice when factors like sepsis, G6PD deficiency or ABO incompatibility are present (Najib et al., 2013).

2.2 Background Introduction

2.2.1 Pathophysiology

Liver as a metabolic organ, functions to process and metabolise the substances in the body. Heme in haemoglobin will usually breakdown by spleen into biliverdin then unconjugated bilirubin. Unconjugated bilirubin will be transported to the liver, conjugated with glucuronic acid and become conjugated bilirubin catalyse by enzyme glucuronosyltransferase. Conjugated bilirubin will be secreted into bile, then the small intestine. In the small intestine, normal gut flora will reduce the conjugated bilirubin to urobilinogen and stercobilinogen, then excreted via urine and faeces respectively. Part of the conjugated bilirubin will be unconjugated and reabsorbed back into enterohepatic circulation (Kevin, 2018).

Any factors that disrupt the balance of production and elimination of bilirubin will cause jaundice.

In neonates, since their liver function is not fully developed yet, they have relatively low activity of the enzyme glucuronosyltransferase. Apart from that, their erythrocytes have a shorter life span, being approximately 80 to 90 days in a full-term infant, compared to 100 to 120 days in adults, which shows rapid breakdown of red cells during neonatal period. In infants, the conversion of bilirubin to urobilinogen by the intestinal flora is relatively low, resulting in relatively high absorption of bilirubin back into the enterohepatic circulation. All of these reasons lead to accumulation of bilirubin in the body and causes jaundice in neonates around 24 hours after birth. This is called physiological neonatal jaundice, which is common in infants (Thor et al., 2017).

2.2.2 Causes

Identification of underlying causes are crucial to determine the most appropriate and effective therapeutic interventions. Three basic mechanisms of neonatal jaundice are either increased bilirubin production, decreased bilirubin clearance or increased enterohepatic circulation. In a study done by Guaran, Drew and Watmins (1992), they suggested that the most common aetiological factor was prematurity (20.3%), followed by ABO erythroblastosis (5.5%), sepsis (1.8%), Rh erythroblastosis (1.8%), bruising (1.3%), multifactorial (1.0%) and glucose-6-phosphate dehydrogenase deficiency (0.5%).

2.3.2.1 Increased bilirubin production

Increased bilirubin production happened in various haemolysis due to ABO or Rh incompatibility, erythrocytes enzymatic defects for instants G6PD deficiency and pyruvate kinase deficiency and inherited red cell membrane defects such as hereditary spherocytosis and elliptocytosis, which cause neonatal jaundice immediately after birth.

A study done by Abolghasemi, Mehrani, & Amid (2004) suggest that neonates with G6PD deficiency have approximately 3 times higher risk (51% vs 31%) to experience neonatal jaundice compared to G6PD-normal neonates.

2.3.2.2 Decreased bilirubin clearance

The second mechanism, which the clearance of bilirubin is decreased due to inherited defects in uridine diphosphoglucuronate glucuronosyltransferase (UGT) for example Crigler-Najjar syndrome and Gilbert's syndrome. UGT as the enzyme to catalyse the conjugation of unconjugated bilirubin to glucuronic acid to form conjugated bilirubin is in deficit state. Thus, the elimination of bilirubin is greatly affected which leads to hyperbilirubinaemia and then jaundice. Fevery, Blanckaert, & Heirwegh (1977) discovered that there is a striking increase of bilirubin monoconjugates in the bile from patients with Gilbert's syndrome (48.6±9.8% of total conjugates) compare to that in normal bile (27.2±7.8%). This increase was even more significant in children with Crigler-Najjar disease, where glucuronide could always be demonstrated in the bile in more severe cases. Another cause of decreased bilirubin clearance is any obstruction occurred along the bilirubin excretion pathway, specifically biliary atresia (Simkiss & Martin, 2012).

2.3.2.3 Increased enterohepatic circulation

Next, an increase in enterohepatic circulation causes neonatal jaundice (Simkiss & Martin, 2012). Failure of breastfeeding or inadequate establishment of breastfeeding leads to hyperbilirubinaemia in newborns. According to Harris, Bernbaum, Polin, Zimmerman and Polin, 5 of 6 infants presented with hyperbilirubinaemia (>30 mg/dL)

associated with abnormal neurologic signs. All were exclusively breastfed or fed a combination of breast and bottle feedings.

2.3.2.4 Other causes

Apart from the three main mechanisms related to bilirubin, other common factors of neonatal jaundice are premature infants and sepsis. Neonatal jaundice is common among babies delivered <37 weeks of gestation ($p<0.0001$). Babies born at 38 to 39 weeks' gestation have higher risk for developing severe jaundice compared with babies of ≥40 weeks' gestation (OR=3.12, 95% CI 1.21 to 8.03) (Ministry of Health Malaysia, 2014). Sepsis or septicaemia directly causes hepatic insufficiency and obstruction of extrahepatic biliary duct and indirectly causes haemolysis which all of these will lead to neonatal jaundice. One study by Israel-Aina, & Omoigberale (2012) found that the diagnosis of sepsis was made in 212 (45.0%) babies with neonatal jaundice. This result made sepsis one of the major factors of neonatal jaundice.

2.3 Demographic Factors

Demographic factors play a crucial determinant in the development of neonatal jaundice in early life. Aspects to be discussed further would be: (1) maternal factors and (2) infant factors.

2.3.1 Maternal Factors

There have been several studies which have highlighted several maternal factors that are closely related with the development of neonatal jaundice.

2.3.1.1 Maternal age

Maternal age has been proven to be significantly associated with neonatal jaundice. According to a study conducted in Jerusalem by Gale, Seidman, Dollberg, Stevenson (1990), who found that younger mothers (≤ 19 years old) had a lower risk for having neonates with hyperbilirubinaemia compared to the older mother (> 35 years old). These results, however, was not confirmed by Srivastav, et al. (1999), who found that neonates with younger mothers (below 30 years old) had higher serum bilirubin levels and risk in developing jaundice compared to neonates with mothers above 30 years old.

2.3.1.2 Maternal race

Maternal race has been implicated as important risk factors that can contribute to development of jaundice in newborn children. A study done in South Africa by Brits, et al. (2018) showed that no significant difference between race groups was found (p=0.60). This finding was supported by the Neonatal Jaundice: Clinical Guideline 2010 from the National Collaborating Centre for Women's and Children's which concluded that race groups do not contribute to hyperbilirubinaemia in infants. But, notwithstanding this, a study specifically on East and Southeast Asian races associated with jaundice readmission by Bentz et al. (2018) had proved that Southeast Asian or Far East Asian had an increased incident of readmission due to hyperbilirubinaemia, with the odd ratio of 3.17. In addition, a study in Malaysia done by Wong, Boo and Othman reported that races had a significant association with neonatal jaundice, such that Malay races are more predisposed to neonatal jaundice (p=0.007). These outcomes lead to a discussion of the effect of races on neonatal jaundice.

2.3.1.3 Maternal ethnicity

Maternal ethnicity has been suggested as a factor that can contribute to high levels of serum bilirubin. Study conducted by Seidman, et al. (1999) concluded that maternal ethnic origin has no significant association with development of jaundice in healthy newborns and the incidence of neonatal jaundice in relation to all mother's ethnicity showed a lower result. On the other hand, a study conducted in Nepal by Scrafford, et al. (2013) states that there is a high association between Pahadi ethnicity ([RR = 0.21 (95% CI:0.18–0.25)], $p<0.001$) and the occurrence of jaundice compared to Madhesi ethnicity.

2.3.1.4 Maternal socioeconomic class

Socioeconomic class can be assessed by looking into 3 important variables which are income, education and occupation. Based on these variables, people's social status can be classified and determined. There are 5 groups of socioeconomic class. The highest class is Class I and the lowest class is Class V.

Some studies have found that patients from low socioeconomic class tend to develop neonatal jaundice. This is attributed to the lack of knowledge regarding children's illness and poor health seeking behaviour (Ogunlesi & Olanrewaju, 2010).

Adebami (2011) found that infants with mothers from low socioeconomic class showed a significant association ($p<0.05$) with neonatal jaundice as they are more likely to expose their infants towards icterogenic factors such as infection due to poor hygiene. His study has also been supported by a study in Nigeria conducted by Ogunlesi, Ogunfowora (2011). They stated that the prevalence of neonatal jaundice is higher in mothers from low socioeconomic class (80%) compared to higher class (11%) with the

significant value, p< 0.001 due to most of them being lacking knowledge regarding neonatal jaundice as the educational qualification and the occupation of both parents are aken into account.

2.3.1.5 Maternal blood group

Maternal blood groups can be divided into type A, B, O and AB. Pregnant mothers “O” blood group found to have higher risk in developing jaundice in their newborns. This has been proven by a study done by Seidman, et al. (1999) stated that mothers with “O” blood group showed a significant association (OR =2.9 [95 % CI:1.5 to 5.8]) with the presence of jaundice in healthy newborns. This outcome has been supported by a study done by Lake, et al. (2011), stated that infants whose mother had “O" blood group have 5 times higher risk of developing hyperbilirubinaemia compared to infants whose mother had “A "blood group. Their result of the study also showed a significant association (p=0.023) between mothers with “O” blood group with presence of jaundice in newborns.

2.3.1.6 Maternal infection

During a mother's pregnancy, infection which involves the genitourinary tract can occur and is an important risk factor in the development of neonatal jaundice. One study conducted in Croatia by Mesić, Milas, Međimurec, & Rimar (2014) found that neonates whose mother had infection during pregnancy showed a statistically significant risk (p< 0.05) of developing jaundice in neonates when compared to those without maternal infection. They also stated that the infection is caused by a few causative agents such as *S. urealyticum, M. hominis and E. coli*.

2.3.1.7 Prolonged labour

Prolonged labour or longer time taken during delivery also has been counted as a factor that contributes to neonatal jaundice. One study done by Tavakolizadeh, et al. (2018) stated that prolonged delivery had significant association ($p=0.03$) with high levels of serum bilirubin in neonates. This study has been supported by other two studies conducted by Scrafford, et al. (2018) and Lake, et al. (2019), stated that prolonged delivery showed significant result ($p< 0.001$) in relation to levels of serum bilirubin after multivariate analysis and neonates who were born with prolonged time of delivery had multiple higher risk in developing jaundice compared to those who had shorter time of delivery respectively.

2.3.1.8 Parity

Primiparity or birth in the first pregnancy has been proven by a few studies to have correlation with jaundice in newborns. Based on a study done by Scrafford, et al. (2013) stated that primiparity showed strong significant association ($p<0.01$) and is one of the most important factors that contributes to development of neonatal jaundice. The result of study has been supported by a study conducted by Tavakolizadeh, et al. (2018) stated that mothers who experienced birth in the first pregnancy showed significant association ($p=0.01$) with high levels of serum bilirubin compared to those who experienced more than one time of pregnancy.

2.3.1.9 Maternal comorbid and obstetric illnesses

Maternal comorbid and obstetric illnesses such as pregnancy-induced hypertension and maternal diabetes may play a significant role in the development of neonatal jaundice. This statement is controversial as there are a few studies that explored different results

on this issue. A study done by Gale, et al. (1990) proposed that high bilirubin levels in neonates were significantly associated with maternal diabetes, either in chronic or gestational form (p=0.004), and pregnancy-induced hypertension (p=0.005). On the other hand, Seidman, Ergaz, Paz, et al. (1999) suggested that neonatal jaundice was not significantly related to maternal comorbid and obstetric illnesses considered in the regression model. This outcome is supported by the study done by Huang, Tai, Wong, Lee and Yong (2009). They detected that neonatal jaundice was not significantly associated with maternal diabetes (p=0.067) and pregnancy-induced hypertension (p=0.607). Thus, this maternal risk factor may be investigated deeper to obtain a definite conclusion.

2.3.2 Neonatal Factors

Aside from maternal factors, there are some neonatal factors that can lead to development of neonatal jaundice.

2.3.2.1 Neonatal gestational age

Several studies have shown that an infant's gestational age has a significant association with high levels of serum bilirubin. According to Paediatrics in Review (2006), neonates with gestational age ranging from 35 to 36 weeks tend to have higher probability to be readmitted due to severe hyperbilirubinemia when compared to neonates with gestational age of 40 weeks. According to the clinical guideline of the National Collaborating Centre for Women's and Children's (2010), development of neonatal jaundice has occurred in about 80 percent of preterm and 60 percent in full term neonates. This is attributed to the infants' immature liver hence unable to clear the bilirubin effectively. A study conducted by Mahmodi, Mahmodi (2016), found that

prematurity (35 to 37 weeks of gestation) was significantly associated with the development of neonatal jaundice ($p<0.05$).

2.3.2.2 Neonatal gender

Gender can contribute to development of neonatal jaundice. These studies discovered that development of jaundice is more common in male compared to female infants. Study conducted in Nepal by Scrafford, et al. (2013) reported male sex is the one of the important factors which can lead to neonatal jaundice. This study has also been supported by studies done by Devi, Vijaykumar (2016) and Lake, et al. (2019), that concluded male gender showed a significant association ($p=0.011$) with the development of jaundice rather than female. But the results of these studies were not supported by a study conducted in Canada by Sgro, Campbell, Shah (2006). They state that male sex did not show a statistically significant association ($p=0.96$) with development of neonatal hyperbilirubinaemia.

2.3.2.3 Neonatal birth weight

Birth weight of newborns have a significant association with development of neonatal jaundice. One study conducted by Narang, Gathwala and Kumar (1997) stated that incidence of neonatal jaundice is about 3 times greater in low birth weight infants compared to infants with weight more than 2500g. This study has also been supported by a study conducted by Devi, Vijaykumar (2016). They discovered that newborns with very low birth weight showed a statistically significant association ($p= 0.0001$) with development of neonatal jaundice. However, the result of these 2 studies show no correlation with a study done in Nepal by Scrafford, et al. (2013). They concluded that

neonates born with weight more than 3000g had strong significant association ($p< 0.01$) with development of jaundice compared to neonates with weight less than 3000g.

2.3.2.4 Method of delivery

There are three common methods of delivery which are oxytocin induced delivery, Caesarean section and normal vaginal delivery. All these methods of delivery have been studied by a few studies around the world in order to show the relationship with high levels of serum bilirubin in neonates. One study conducted by Gupta, Gupta, Ali, Gupta (2016) stated that all three methods of delivery (oxytocin induced delivery, Caesarean section and normal vaginal delivery) showed a significant association ($p<0.001$) with high levels of serum bilirubin on third day of delivery only, but the most significant association of increasing levels of serum bilirubin for first, third and fifth day after delivery can be seen in neonates following oxytocin induced vaginal delivery. Besides that, there are two studies conducted by Najib, et al. (2013) and Brits, et al (2018) stated that normal vaginal delivery had higher risk in contributing to development of neonatal jaundice compared to the other methods with significant value, $p<0.027$ and $p<0.04$ respectively.

2.3.2.5 Family history of severe neonatal jaundice

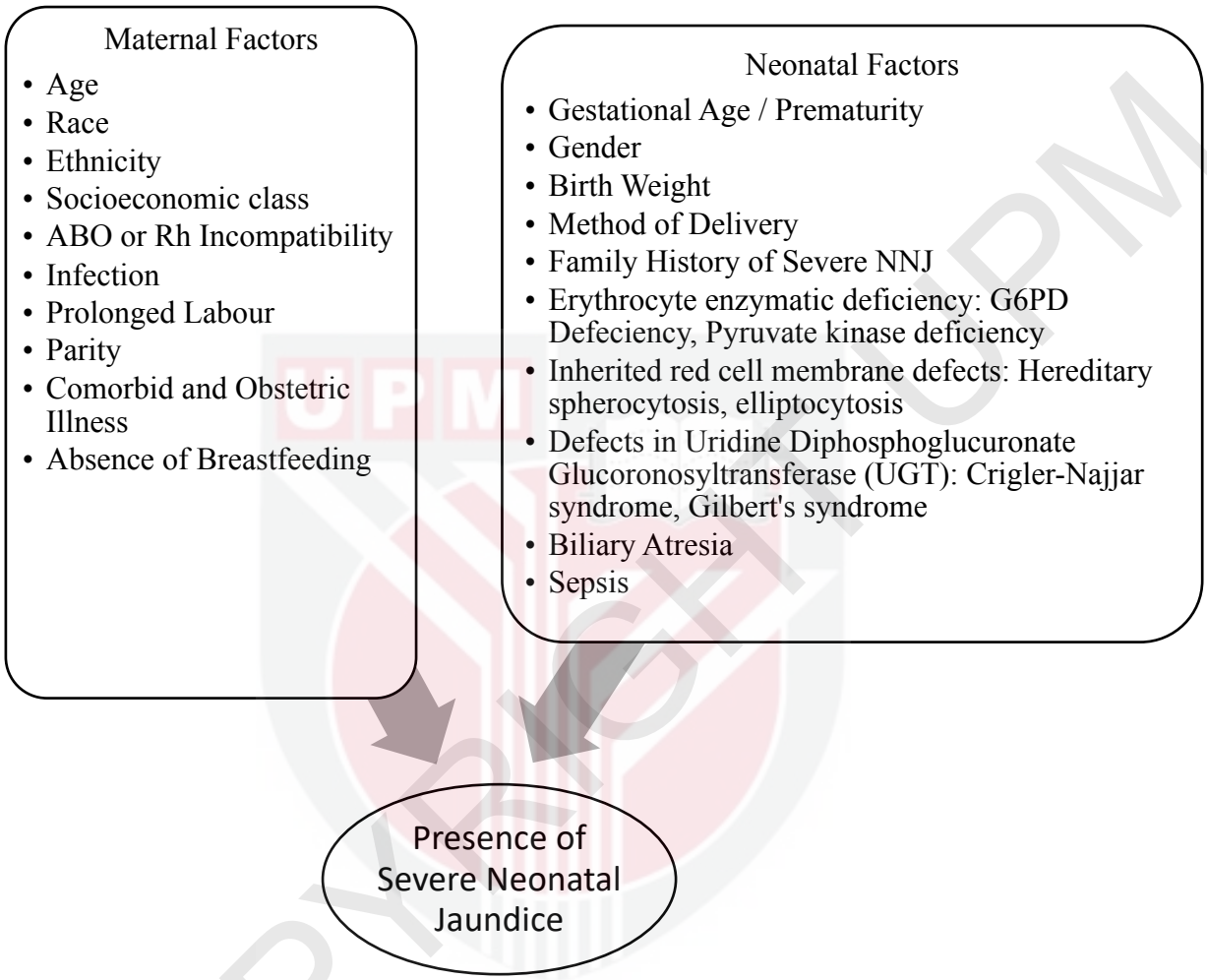
Family history of severe neonatal jaundice has been listed as the important factor in development of neonatal jaundice. Several studies also state that there is a relation between previous siblings who had neonatal jaundice with the levels of serum bilirubin in newborns. Based on a study conducted by Khoury, Calle, and Joesoef (1988), stated that infants who had one or more sibling previous with neonatal hyperbilirubinaemia had greater risk (3.1 times) in developing jaundice compared to without sibling. The

result of study has been supported by several studies conducted by Gale, et al. (1990) and Najib, et al. (2013), stated that there is a strong significant association ($p<0.01$ and $p<0.006$ respectively) between neonates who had previous siblings with neonatal jaundice with high levels of serum bilirubin.

2.4 Complications

Neonatal jaundice caused by hyperbilirubinaemia is a common phenomenon in neonates but should not be underrated as it may lead to more serious complications. Najib, Saki, Hemmati, Inaloo (2013) suggested prolonged hyperbilirubinaemia in neonates will increase the incidence of bilirubin-induced neurologic dysfunction. Acute or chronic bilirubin encephalopathy, also known as kernicterus, at a rate of 0.9 per 100,000 neonates, will cause spasticity, hearing and vision abnormalities and neurodevelopment retardation to newborns. Such neurologic sequelae need appropriate treatment and close monitor as it has a high mortality rate (at least 10 percent) and high morbidity rate (at least 70 percent) (Trikalinos et al., 2018).

2.5 Conceptual Framework



CHAPTER 3: METHODOLOGY

This study was a hospital-based retrospective study. We extracted the data for this study from the medical records concerning neonatal jaundice from the Neonatal Intensive Care Unit (NICU) of the Department of Paediatric of Hospital Serdang ranging from 2015 to 2019. The causes and risk factors of NNJ in newborns were explored. Certain criteria were applied to the data extracted from the above source, which were age distribution, gender, jaundice period, birth weight and etc.

3.1 Study Location

Neonatal Intensive Care Unit (NICU) of the Department of Paediatric of Hospital Serdang.

3.2 Study Design

Retrospective study

3.3 Study Duration

The study will be conducted from 27/4/2020 to 9/10/2020 for a duration of more than 4 months.

3.4 Sampling

3.4.1 Study population

Neonates with NNJ in NICU of the Department of Paediatric of Hospital Serdang from 2015 to 2019.

3.4.2 Sampling population

Inclusion criteria

I. All inborn and outborn neonates who present with severe jaundice and admitted to Neonatal Intensive Care Unit (NICU) of Hospital Serdang

II. All neonates with gestational age up to 42 weeks

Exclusion criteria

I. Incomplete medical records

II. Infants with lethal congenital malformation

3.4.3 Sampling Frame

Medical records of neonates admitted to NICU of the Department of Paediatric of Hospital Serdang with severe NNJ.

3.4.4 Sampling Unit

A newborn with NNJ that has been admitted into NICU of the Department of Paediatric of Hospital Serdang.

3.4.5 Sampling Size Estimation

Two samples proportion formula was used to calculate the sample size estimation. The value of P1 and P2 (estimated proportion of neonatal jaundice with maternal age <20yrs and ≥20yrs) were obtained from a study done by Scrafford (2013).

$$n = \frac{\{[z_{(1-\alpha/2)} * \sqrt{2\bar{P}(1-\bar{P})}] + [z_{(1-\beta)} * \sqrt{P_1(1-P_1) + P_2(1-P_2)}]\}^2}{(P_1-P_2)^2}$$

Where:

P = (P1 + P2)/2 (mean of proportion of two sample)

P1= estimated proportion

P2 = estimated proportion

Z (1-α/2) = level of significance

z (1-β) = power of study

$$n = \frac{[1.96\sqrt{(2(0.320)(1-0.320))} + 0.84\sqrt{(0.270(1-0.270) + 0.370(1-0.370))}]}{(0.270-0.370)^2}$$

n = 359

2n = 718

P = 0.320

P = 0.320

P1= estimated proportion of age ≥ 20 years old (0.270)

P2 = estimated proportion of age <20 years old (0.370)

Z (1-α/2) = 1.96 for 95% CI

z (1-β) = 80% (0.84)

Adjusting for 10% of incomplete data

n = (718 x 10%) + 718

n = 789.8

n = 790

Therefore, the sample size needed for this study is about 790 patients.

3.4.6 Sampling Technique

Convenience sampling method. The first available data source and newborns with neonatal jaundice that fulfilled the inclusion criterions listed above were recruited in this study.

3.5 Data Collection

Data for this study was collected from the medical records concerning severe neonatal jaundice from the Neonatal Intensive Care Unit (NICU) of the Department of Paediatric of Hospital Serdang ranging from 2015 to 2019. The medical records based on NICU admission book which fulfil the inclusion criteria were included in this study.

3.6 Data Analysis

Required data from the medical records were collected and transferred into a case record form that was designed based upon the variables from Hospital Serdang and study objectives.

The data collected were recoded into SPSS version 25 based on the variables and analysed. The statistical tests used in this study were Fisher Exact Test. These tests showed the association between the independent variables (the maternal and neonatal factors) and dependent variable (presence of severe neonatal jaundice).

3.7 Study Ethics

1. The ethical approval from the Medical Research and Ethics Committee (MREC) was obtained.
2. A copy of ethics approval was submitted to JKEUPM (Jawatankuasa Etika Universiti Putra Malaysia Untuk Penyelidikan Melibatkan Manusia) and Clinical Research Centre (CRC) Hospital Serdang after MREC approved this research project.
3. All the medical records from Neonatal intensive Care Unit, Hospital Serdang were accessed by only the research team and the data collection sheets were kept confidential and secure.

3.8 Variables

3.8.1 Dependent variable

The dependent variable is the presence of presence of severe neonatal jaundice.

3.8.2 Independent variables

Independent variables are divided into two groups. The first group is maternal factors, which included age, race, ethnicity, socioeconomic class, ABO or Rh incompatibility, infection, prolonged labour, parity, comorbid and obstetric illnesses, and absence of breastfeeding. As for neonatal factors, it included gestational age/prematurity, gender, birth weight, method of delivery, family history of severe neonatal jaundice, erythrocyte enzymatic deficiency: G6PD deficiency, pyruvate kinase deficiency, inherited red cell membrane defects: Hereditary spherocytosis, elliptocytosis, defects in uridine diphosphoglucuronate glucuronosyltransferase (UGT): Crigler-Najjar syndrome and Gilbert's syndrome, biliary atresia and sepsis.

3.9 Operational definitions

Table 1: Operational definition

No.	Terms	Definitions
1.	Gestational age: Pre-term, full term, post term	I. Pre-term is defined as neonates born with gestational age of less than 37 completed weeks. II. Full-terms neonates are born with gestational age of 38 to 40 weeks. III. Post term neonates are born with gestational age of 40 to 42 weeks.
2.	Inborn and outborn neonates	I. Inborn neonates are born in Hospital Serdang and subsequently admitted for jaundice II. Outborn neonates are neonates that were born in other hospital

		and the admitted into Hospital Serdang for jaundice
3.	Erythrocyte enzymatic defects	Disorders presented with deficiency or functional abnormality of enzyme in red blood cells.
4.	Inherited red cell membrane defects	Presence of hereditary defects in red cells membrane in neonates.
5.	Defects in uridine diphosphoglucuronate glucuronosyltransferase (UGT)	Presence of abnormalities in UGT enzyme.
6.	Biliary atresia	Biliary atresia is a rare disease of the liver and bile ducts that occurs in infants.
7.	Absence of breast feeding	Infants who have not received breastmilk
8.	Sepsis	Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
9.	Age	Year 2020 minus the year of birth of the subject.
10.	Race	Races are distinct populations with specific racial characteristics.
11.	Ethnicity	It is defined as the groups that people identify with measures of cultural affiliation.
12.	Socioeconomic class	It is defined as the combination measure of one's economic and sociological status, that includes income, education and occupation of a person, in total of high, middle and low class.
13.	ABO or Rh incompatibility	Define as the matching of blood groups between neonates and mothers. It is defined as being an "O" blood group or non- "O" blood group.
14.	Infection	It is defined as a mother with infection during pregnancy or without infection.
15.	Prolonged labour	It is defined as time taken for a foetus to be delivered whether it is prolonged or normal delivery.

16.	Parity: Primiparity, Multipara, Grand multipara	I. Primiparity: It is defined as being experienced for the first time of delivery II. Multipara: Have had 2 to 4 deliveries before current pregnancy. III. Grand multipara: Have had 5 or more deliveries.
17.	Comorbid and obstetric illnesses	Can be defined as mother with or without comorbid and obstetric illness during pregnancy.
18.	Gestational age	The length of time from the beginning of the mother's last menstrual period to the day of delivery, in weeks.
19.	Gender	The physical condition of newborns of being male or female.
20.	Birth weight	The body weight of newborns at birth in kilogram (kg).
21.	Mode of delivery	The method of giving birth which includes oxytocin induced delivery, Caesarean section and normal vaginal delivery.
22.	Family history of neonatal jaundice	It is defined as having previous siblings with or without severe neonatal jaundice.

CHAPTER 4: DATA ANALYSIS

4.1 Sample Population

There was a total of 15792 admission to Neonatal Intensive Care Unit (NICU) Hospital Serdang over the 5-year study period. During this time, 5621 were admitted for neonatal jaundice (NNJ) as recorded in the NICU census and admission records. A total of 647 sets of data were collected for data analysis. However, the data collected did not meet the sample size requirement of 790 sets of data due to certain reasons which will be discuss later in this report.

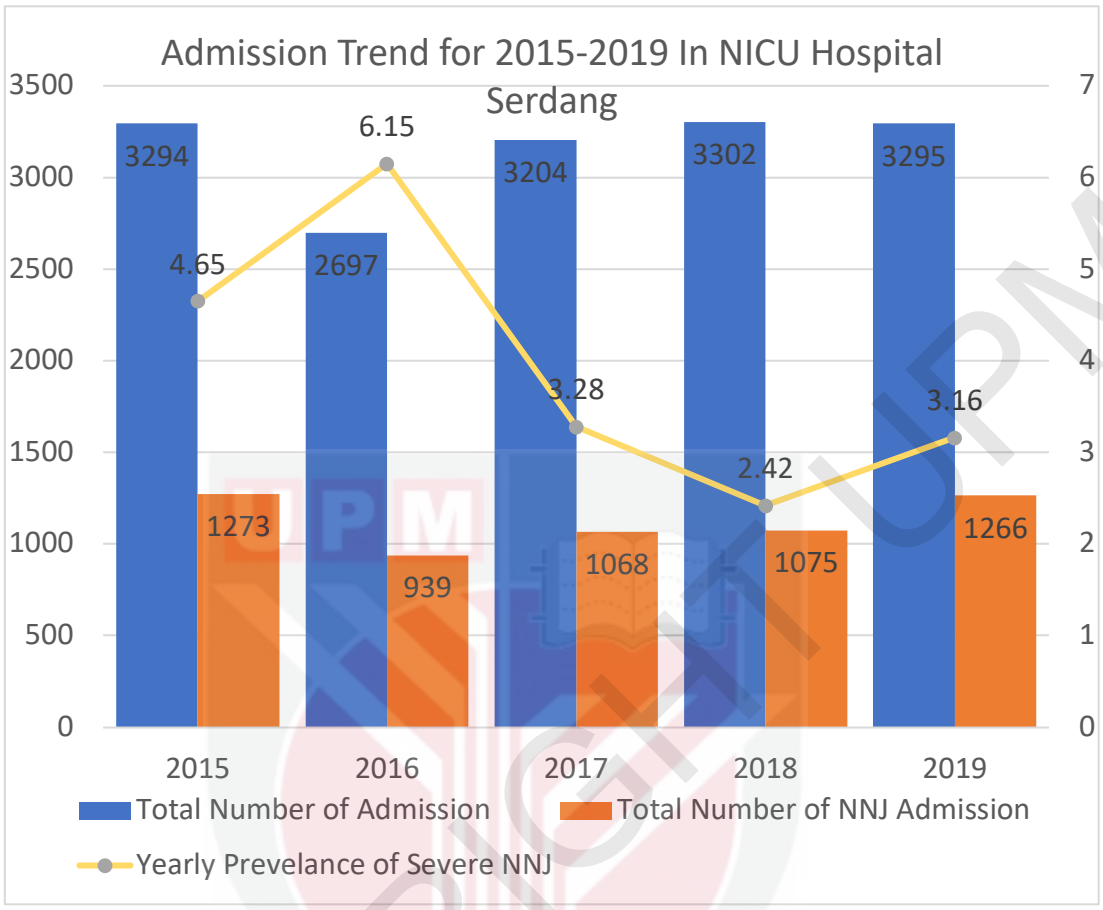
4.2 Prevalence of Neonatal jaundice in Hospital Serdang

A total of 15792 infants were admitted into NICU Hospital Serdang between 2015 to 2019. During the study period, there were 5621 infants who were admitted for NNJ resulting in a prevalence of 35.6%. On the other hand, the prevalence of severe NNJ in NICU Hospital Serdang, which were the NNJ cases with total serum bilirubin level of 340 μmol and above on admission, is 3.85% (608 out of 15972 admission).

Table 2: NICU Admission of Hospital Serdang from 2015-2019

Year	2015	2016	2017	2018	2019
Total Number of Overall Admission	3294	2697	3204	3302	3295
Total Number of NNJ Admission	1273	939	1068	1075	1266
Yearly Prevalence of NNJ	38.65	34.82	33.33	32.56	38.42
Yearly Prevalence Severe NNJ	4.65	6.15	3.28	2.42	3.16

Figure 1: Admission Trend for NICU Hospital Serdang from 2015 - 2019



4.3 Baseline characteristics

As shown in table 3, a large proportion of mothers whose infants had NNJ were aged 25 to 29 years. Most of our patients were Malaysians (95.20%) and from the Malay ethnic group (81.0%), which corresponds to the ethnic distribution in this country. Among 31 non-Malaysians, 11 of them are Indonesian, 5 from Vietnam, each 3 from Burma and Cambodia, and one from Bangladesh, China, Libya, Singapore, Nepal, Myanmar, Filipino and Yemen each and one did not mention. The study also revealed multiparity mothers accounted for a larger part of mothers of infants with NNJ.

Table 3: Baseline Characteristic of Study Population (n=647)

Maternal characteristic	Mothers of Infants with NNJ	
	Frequency (n)	Percentage (%)
Age		
17 – 24	68	10.5
25 – 29	219	33.8
30 – 34	202	31.2
35 and above	153	23.6
Missing*	5	0.8
Nationality		
Malaysian	616	95.2
Non-Malaysian	31	4.8
Ethnicity		
Malay	524	81.0
Chinese	62	9.6
Indian	16	2.5
Others	44	6.8
Missing*	1	0.2
Parity		
Primiparity	26	4.0
Multipara	471	72.8
Grand multipara	135	20.9
Missing*	15	2.3

*Missing data due to gaps of information in clinical notes.

4.4 Maternal factors associated with NNJ

Table 4: Maternal Factors Associated with NNJ (n=647)

Maternal Factors	Mothers of Infants with NNJ	
	Frequency (n)	Percentage (%)
Blood Group		
A+	139	21.5
B+	167	25.8
AB+	49	7.6
O+	283	43.7
B-	2	0.3
Missing*	7	1.1
Infections		
Yes	73	11.3
No	574	88.7
Prolonged Labour		
Yes	5	0.8
No	642	99.2
Parity		
Primiparity	26	4.0
Multipara	471	72.8
Grand multipara	135	20.9
Missing*	15	2.3

Maternal Comorbid and Obstetric Illness:		
Diabetes Mellitus		
Pre-existing DM	6	0.9
Gestational DM	156	24.1
Both Pre-existing DM and Gestational DM	4	0.6
No DM	481	74.3
Pregnancy-induced Hypertension		
Yes	31	4.8
No	616	95.2
Feeding Pattern:		
Exclusive Breastfed	581	89.8
Mixed	64	9.9
Formula Milk	2	0.3
Poor Feeding		
Yes	274	42.3
No	373	57.7

*Missing data due to gaps of information in clinical notes.

The study showed that majority of mothers of infants with NNJ had blood group O positive (43.70%) followed by blood group B positive (25.80%). Only two mothers were blood group B negative. As for infections, only 11.30% of mothers had evidence of infection before or during pregnancy. Urinary tract infection is the most common cause among the mothers with risk of sepsis. In addition, prolonged labour occurs in 0.80% of

the patients, namely 5 out of 647 samples under studied. Majority of mothers with infants with severe NNJ had more than one child. However, there were 15 patients whose mothers' parity was not documented in the clinical notes. From the view of maternal comorbid and obstetric illness, gestational diabetes mellitus appeared the most among the studied subjects, which 24.10% of the samples did diagnosed with the disease during their pregnancies, the number does not include another 0.90% or 6 mothers with pre-existing diabetes mellitus. There were also 4 mothers were associated with pre-existing diabetes mellitus as well as gestational diabetes mellitus during their pregnancies. Apart from that, 4.80% of the individuals were having pregnancy-induced hypertension, with the frequency of 31 cases out of 647. A large portion of neonatal jaundice cases occurred in newborns who were exclusively breastfed which accounted for about 89.80% of the samples. The second highest percentage of breastfeeding pattern was mixed feeding which is 9.90% and followed with formula milk which recorded only 0.3%. In a total of 647 samples collected, 42.30% of subjects were under poor feeding condition and the rest of the cases did not experience poor feeding starting from birth until admission into NICU Hospital Serdang.

4.5 Neonatal factors associated with NNJ

Table 5: Neonatal Factors Associated with NNJ (n=647)

Neonatal Factors	Mothers with infants of NNJ	
	Frequency (n)	Percentage (%)

Gestational Age (Weeks):		
34 and below	9	1.4
35-37	199	30.8
38-40	429	66.3
41-42	7	1.1
Missing*	3	0.5
Prematurity		
Term	436	67.4
Preterm	208	32.1
Missing*	3	0.5
Birth Weight (kg)		
2.49 and below	68	10.5
2.5-2.99	266	41.1
3.0-3.49	226	34.9
3.5 and above	86	13.3
Missing*	1	0.2
Gender		
Male	347	53.6
Female	300	46.4
Method of Delivery		
Normal Vaginal Delivery (NVD)	486	75.1
Caesarean Section (CSC)	153	23.6
Oxytocin-induced	7	1.1

Missing*	1	0.2
Family history of Severe NNJ		
Yes	168	26.0
No	479	74.0
Risk of haemolysis/ ABO incompatibility/ Rhesus incompatibility/ G6PD deficiency		
Yes	87	13.4
No	560	86.6
Sepsis		
Yes	58	9.0
No	589	91.0

*Missing data due to gaps of information in clinical notes.

Table 5 showed the frequency and percentage of mothers with infants of NNJ that presented with certain neonatal factors. Majority of neonates were born male (53.60%) and around 38 to 40 weeks of life (66.30%). Neonates with birth weight around 2.5 to 2.99 were slightly higher compared to neonates weighed between 3.0 to 3.49, with percentage of 41.10% and 34.90% respectively. A large portion of neonates was born via normal vaginal delivery, followed by caesarean section and a few via oxytocin-induced methods. Apart from that, a small group of samples were associated with sepsis and risk of haemolysis due to ABO or Rh incompatibility or G6PD deficiency upon

admission. Among all the subjects studied, 168 of them did have siblings with NNJ, which contributed to the family history of NNJ.

4.6 Statistical Analysis

Table 6: Statistical Analysis between Risk Factors with the Risk of Haemolysis

Risk Factors	Risk of Haemolysis (n=647)		p value
	Yes (n/%)	No (n/%)	
Gestational Age (weeks)			
<38 Weeks	20 (23.0)	188 (33.6)	
≥38 Weeks	67 (77.0)	369 (65.9)	0.113
Missing*	0 (0)	3(0.5)	
Birth Weight (kg)			
<2.50kg	7 (8.0)	61 (10.9)	
≥2.50kg	80 (92.0)	498 (88.9)	0.630
Missing*	0 (0)	1 (0.2)	
Parity			
Primiparity	3 (3.4)	23 (4.1)	
Multiparity and Grand-multiparity	81 (93.1)	525 (93.8)	0.651
Missing*	3 (3.4)	12 (2.1)	
Maternal Age			
<30 years old	41 (47.1)	246 (43.9)	
≥30 years old	45 (51.7)	310 (55.4)	0.522
Missing*	1 (1.1)	4 (0.7)	
Nationality			

Malaysian	83 (95.4)	533 (95.2)	0.594
Non-Malaysian	4 (4.6)	27 (4.8)	
Infections			
Yes	9 (10.3)	64 (11.4)	0.857
No	78 (89.7)	496 (88.6)	
Feeding Pattern			
Exclusive Breastfeeding	73 (83.9)	508 (90.7)	0.058
Mixed + Formula Milk	14 (16.1)	52 (9.3)	

*Missing data due to gaps of information in clinical notes.

Based on the result of Table 6, all risk factors above, namely gestational age and birth weight of neonates, parity, maternal age and nationality, infections and feeding pattern did not show any significant association with the risk of haemolysis. All the p value of the risk factors above was more than 0.05.

CHAPTER 5: DISSCUSSION AND LIMITATIONS

5.1 Discussion

In our study, the prevalence of neonatal jaundice in NICU Hospital Serdang is 35.6%. As a comparison to the Neonatal Jaundice: Clinical Guideline 2010 of the United Kingdom, the finding of this research is lower than the prevalence of neonatal jaundice reported, which is 55.2%. Variation in demographic characteristics and the diverse distribution of this disease may contribute to the difference of prevalence of neonatal jaundice in different countries.

In this study, the frequency and percentage of socio-demographic factors associated with neonatal jaundice such as maternal age, nationality, ethnicity, and parity were determined. Most patients with infants of neonatal jaundice were aged between 25-29 years (33.8%) which comes along with the outcome of previous study done by Srivastav et al. (1999) who suggested younger mothers (in their study stated as below 30 years old) had higher risk of neonatal jaundice babies. As for nationality and ethnicity, the results of this research were as expected outcome that be in line with the socio-demographic distribution of Malaysia, which majority of study samples were Malaysians and from the Malay ethnic group. In contrast with the conclusion of previous studies by Scrafford et al. (2013) and Tavakolizadeh et al. (2018), our study shows that there is a higher frequency (n=469) of neonatal jaundice cases in mothers who were multiparity, with two to four deliveries, compare to primiparity and grand multiparity.

Socioeconomic class were mentioned in the literature review of this study, and it was classified into 5 classes based on the income, education level and occupation of the

mothers. According to the studies done by a few researches, namely Ogunlesi & Olanrewaju (2010), Adebami (2011) and Ogunlesi & Ogunfowora (2011), neonatal jaundice had higher prevalence in mothers from lower socioeconomic class. The main causes are either the lack of knowledge of neonatal jaundice and its relevant causes, insufficient awareness on health seeking behaviour or poor hygiene environment. Unfortunately, we are unable to make a firm conclusion in our study since socioeconomic information of the mothers is not available among the studied population. The scarcity in the information could not be retrieved back as for the reason of the retrospective study nature.

According to the previous research done by Meisić et al. (2014) and Tavakolizadeh et al. (2018), maternal infections and prolonged labour were significant factors that related to the development of jaundice in the newborns. However, these results are opposed by the outcome of our study because only minority of the cases were associated with maternal infections (11.30%) and prolonged labour (0.8%). In addition, our study also reported that there is only 24.10% of the cases with gestational diabetes and 0.90% with pre-existing diabetes. The number does not include 0.60% of total samples who were diagnosed with both pre-existing diabetes mellitus and gestational diabetes mellitus. 5.2% of the subjects were associated with pregnancy-induced hypertension during their pregnancy. These outcomes did not bring a firm conclusion to the controversial issue of the association of maternal comorbid and obstetric illness with the development of neonatal jaundice as there are a few studies with different opinions on this specific maternal factor. Most of the neonatal jaundice cases happened in infants with mothers of blood group O positive (43.70%). This outcome is similar with the conclusions made by Seidman et al. (1999) and Lake et al. (2019) stated that blood group O is one of the

significant risk factors of the presence of neonatal jaundice in newborns. To add on, 90.4% of the samples collected were exclusively breastfed. This result may acknowledge to the long-term promotion of breastfeeding in Malaysia since 1970s.

Apart from maternal factors, we also studied a few neonatal factors. Prematurity or gestational age of 37 weeks and below is a significant risk factor of neonatal jaundice, based on the study done by Maisels (2006), National Collaborating Centre for Women's and Children Health (2010) and Mahmodi & Mahmodi (2016). However, the results of our study indicate that majority of the neonates were born within 38 to 40 weeks (66.30%) and only 31.90% of neonates were born within 37 weeks and below, which do not follow the general outcome on gestational age of newborns. The other two neonatal factors, which are gender and delivery method did correspond to the outcome as stated in previous studies by Gupta et al. (2016), Najib et al. (2013), Brits et al. (2018), Khoury et al. (1998) and Gale et al. (1990). In their studied, they found out that male babies and babies who born via normal vaginal delivery method had higher risk of developing neonatal jaundice few days after birth. Their results are highly correlated with the findings of our study, where 53.60% of the study subjects are male, and 75.10% of them are born via normal vaginal delivery. As for the birth weight, a larger portion of neonates (41.1%) weighed between 2.50 to 2.99 kg. This result proves the outcomes of Narang, Gathwala and Kumar (1997) and Devi & Vijaykumar (2016) where they discovered that neonatal jaundice is more associated with the newborns with lower birth weight.

Among our patients with severe neonatal jaundice, we found that although the majority of our participants had mothers with blood group O+, this risk of haemolysis was not a

significant factor ($p>0.05$) among patients who were born prematurely or small for age. This data is conflicting with a report done by Mahmodi & Mahmodi (2016), who found that prematurity (35 to 37 weeks of gestation) was significantly associated with the development of neonatal jaundice ($p<0.05$). This suggests that risk of haemolysis causes neonatal jaundice and is a risk factor for both the term and premature infants equally. Risk of haemolysis was not significant ($p>0.05$) among participants whose mother was below 30 years of age. This data is not consistent as with data from previous studies by Gale, Seidman, Dollberg, Stevenson (1990) versus study by Srivastav et al. (1999). Both teams reported contrasting data regarding maternal age. This suggests that risk of haemolysis causes severe neonatal jaundice and affects mothers of all ages with newborn infants.

In consideration of the absence of the control group, which are the neonates admitted into NICU Hospital Serdang due to other causes, all risk factors under studied are important risk factors that contributed to neonatal jaundice, especially the one with significant P-value (ABO blood group). To further investigate these risk factors among the community, this study needs to be further expanded and include other newborns that were admitted into NICU Hospital Serdang due to other causes, but not only the admission of newborns due to severe neonatal jaundice.

5.2 Limitations

Due to shortage of time and movement restrictions by the COVID-19 pandemic, we were unable to meet the sample size requirement of 790 sets of data, but only manage to get 647 subjects. This study is more of a pilot study, as there is no control group

(neonates admitted into NICU due to other causes) included in the study. Therefore, the significance of risk factors might not be applied to the general population.

The method we used for data sampling is convenience sampling. We recruited the subjects who were the first available data source and are the newborns with neonatal jaundice that fulfilled the inclusion criterions in this study. As convenience sampling is one of the non-probability sampling methods, it allows us to obtain the basic data and trends regarding our study without the complications of using a randomized sample. However, this sampling method may contribute to certain bias to the study and unable to generalize the study results to the population as a whole.

Apart from that, we had missing data on some of the potential risk factors namely the maternal blood group, parity, ethnicity of the mothers, and the gestational age, birth weight, method of delivery of the newborns. One of the reasons contributing to this fragmented data was incomplete documentation during history taking, which, by nature of this retrospective study, was the source of our data. Apart from that, a portion of subjects under study were outpatient, which the neonates were born at other places that transferred into NICU Hospital Serdang due to neonatal jaundice. This situation precipitated the issue of lack of complete medical records, as maternal information would not be taken as detailed as the inpatient cases. Therefore, some difficulties emerged in the identification of the appropriate exposure factors on the study populations.

Furthermore, certain risk factors (e.g. prolonged labour and pregnancy-induced hypertension) the came with low numbers of study subject, which made it difficult to investigate the association between the risk factors and neonatal jaundice.

In addition, the data collection was done in single centre, which is only in the NICU of Hospital Serdang. Thus, it cannot reflect the distribution of neonatal jaundice and the risk factors associated with neonatal jaundice in the whole country.

CHAPTER 6: CONCLUSION AND RECOMMENDATION

6.1 Conclusion

In short, neonatal jaundice are more likely to be happened in male babies that born via normal vaginal delivery and within 38 to 40 weeks age, under exclusive breastfeeding, with mothers aged between 25 to 29 years, multipartite, and blood group O.

Neonatal jaundice is very common in Malaysia, and if it is left untreated it may lead to fatal complications. Therefore, this study provides a clearer image of the risk factors on both infants and mothers to increase their awareness on such disease, so that they can seek aid from health facilities once they notice any abnormal signs presented by the babies.

6.2 Recommendations

To better elucidate the risk factors, the study needs to be extended to include a control group. All neonates are recommended to check for any possible risk factors, relevant family history and antenatal history of the mothers at every opportunity especially 72 hours after birth. Serum bilirubin level should always be monitored once the neonates were admitted into NICU due to neonatal jaundice. Interventions or therapy such as phototherapy and exchange transfusion should be introduced when the babies presented with specific indications of treatments based on their age, risk factors presented and serum bilirubin level, by following the guidelines in CPG Management of Neonatal Jaundice.

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Appendices

Appendix 1: Ethics Approval

(a) Medical Research Ethics Committee (MREC)

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Kompleks Institut Kesihatan Negara
Blok A, No 1, Jalan Setia Murni U13/52,
Seksyen U13, Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel: 03-3362 8888/8205

Ref : KKM/NIHSEC/ P20-1425 (4)
Date: 03-Aug-2020

DR MELISSA ANNE NUNIS
UNIVERSITY PUTRA MALAYSIA (UPM)

Dear Sir/ Mdm,

ETHICS INITIAL APPROVAL: NMRR-20-1325-55361 (IIR)
RETROSPECTIVE REVIEW OF RISK FACTORS AND CAUSES OF NEONATAL JAUNDICE IN NEONATAL INTENSIVE CARE UNIT (NICU), HOSPITAL SERDANG FROM 2015-2019

This letter is made in reference to the above matter.

2. The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are to be taken to maintain data confidentiality. Permission from the District Health Officer / Hospital Administrator / Hospital Director and all relevant heads of departments / units where the study will be carried out must be obtained prior to the study. You are required to follow and comply with their decision and all other relevant regulations, including the Access to Biological and Benefit Sharing Act 2017.

3. The investigators and study sites involved in this study are:

HOSPITAL SERDANG
Chang Chen Yue
Dr Faizah Mohamed Jamli
Dr Melissa Anne Nunis (Principal Investigator)
Dr. Zurina Bte Zainudin
Maisarah Binti Kamaruzzaman
Mohamad Ikmal Bin Che Hat

4. The following study documents have been received and reviewed with reference to the above study:

Documents received and reviewed with reference to the above study:

1. Study Protocol_Version 04, dated 09-July-2020
2. Study Clinical Report Form/ Data Collection Form_Version 04, dated 09-July-2020
3. Investigator's documents : Declaration of Conflict of Interest (COI), IA-HOD-IA, and CV:
   a) Chang Chen Yue
   b) Dr Faizah Mohamed Jamli
   c) Dr Melissa Anne Nunis (Principal Investigator)
   d) Dr. Zurina Bte Zainudin
   e) Maisarah Binti Kamaruzzaman
   f) Mohamad Ikmal Bin Che Hat

5. Please note that ethical approval is valid until **02-Aug-2021**. The following are to be reported upon receiving ethical approval. Required forms can be obtained from the National Medical Research Regisry (NMRR) website:

Appendix 2: Sample Size Estimation

Variables	Category	Prevalence	Sample size estimation	Reference
Prevalence of neonatal jaundice	-	P: 0.552	380	National Institute for Health and Care Excellence (NICE).
Maternal factors				
Age	P1: ≥20 P2: <20	P1: 0.270 P2: 0.370	**n=718**	Scrafford, C. G. (2013)
Race	P1: non-Malays P2: Malay	P1: 0.089 P2: 0.218	n=270	Feiliang Wong, NemYun Boo, Ainoon Othman (2013)
Ethnicity	No relevant data in previous research.			
Socioeconomic class	P1: Class I & II P2: Class III P3: Class IV & v	P1: 0.110 P2: 0.103 P3: 0.800	20	Ogunlesi TA, Ogunfowora OB. (2011)
Blood group	P1: non-O blood group P2: O blood group	P1: 0.166 P2: 0.270	530	Seidman, D., et al. (1999)
Infection	P1: without infection P2: with infection	P1: 0.231 P2: 0.347	510	Mesić, I., et al. (2014)

Prolonged labour	P1: normal P2: prolonged	P1: 0.054 P2: 0.301	148	Lake, E. A. et al. (2019)
Primiparity	P1: more than one pregnancy P2: first pregnancy	P1: 0.170 P2: 0.290	228	Tavakolizadeh, R. et al. (2018)
Comorbid and obstetric illness	P1: pregnancy not induced hypertension P2: pregnancy induced hypertension	P1: 0.120 P2: 0.200	712	Devi DS, Vijaykumar B. (2016)
Neonatal factors				
Gestational age	P1: full term P2: preterm	P1: 0.060 P2: 0.080	182	Clinical guideline of the National Collaborating Centre for Women's and Children's (2010)
Gender	P1: female P2: male	P1: 0.060 P2: 0.504	78	Lake, E. A., et al. (2019)
Birth weight	P1: ≥2500 g P2: <2500 g	P1: 0.059 P2: 0.150	398	Narang A, Gathwala G and Kumar P. (1997)
Method of delivery	P1: other methods of delivery P2: normal vaginal delivery	P1: 0.476 P2: 0.697	172	Brits, H. et al (2018)

Family history of NNJ	P1: previous sibling without NNJ P2: previous sibling with NNJ	P1: 0.036 P2: 0.103	510	Khoury MJ, Calle EE, and Joesoef RM. (1988)

Appendix 3: Data Collection Sheet

MATERNAL INFORMATION

STUDY ID: ☐ AGE (YEARS): ☐

NATIONALITY: MALAYSIAN ☐

: NON MALAYSIAN, ☐

SPECIFY: _____

OCCUPATION: ☐

HUSBAND'S OCCUPATION: ☐

ETHNICITY: MALAY ☐

: CHINESE ☐

: INDIAN ☐

: OTHERS ☐

SPECIFY: _____

FORMAL EDUCATION: NONE ☐

: PRIMARY ☐

: SECONDARY ☐

: TERTIARY ☐

JOINT HOUSEHOLD INCOME: < RM 3000 ☐

: RM 3000-RM 5000 ☐

: > RM 5000 ☐

ANTENATAL INFORMATION

WEIGHT (KG): _____ HEIGHT (CM): _____ GRAVIDA: _____

PARITY: _____ BLOOD GROUP:_____

PROBLEMS WITH PREVIOUS PREGNANCY

NO: ☐ YES: ☐ SPECIFY:

1) MISCARRIAGE
2) PRETERM (INDICATION: _____)
3) LOW BIRTH WEIGHT/ SMALL GESTATIONAL AGE
4) MICROSOMIA
5) PREVIOUS CHILD WITH NEONATAL JAUNDICE

OTHER MEDICAL CONDITIONS

DIABETES: ☐ HYPERTENSION: ☐ HEART DISEASE: ☐

RVD: ☐ INFECTIONS: ☐ OTHERS: ☐

SPECIFY:_____ SPECIFY: _____

PREGNANCY RELATED COMPLICATIONS

GESTATIONAL DIABETES: ☐ PREMATURITY: ☐

PREGNANCY INDUCED HYPERTENSION: ☐ ANAEMIA: ☐

URINARY TRACT INFECTION: ☐ PROLONGED LABOUR: ☐

BREASTFEEDING PATTERN

EXCLUSIVE BREASTFEEDING: ☐ FORMULA MILK: ☐

MIXED: ☐

NEONATAL OUTCOME

GESTATION (WEEKS & DAYS):_____W _____D GENDER: MALE ☐

: FEMALE ☐

MODE OF DELIVERY: NVD ☐ APGAR SCORE: _____

: CSC ☐

: OXYTOCIN-INDUCED ☐

BIRTH WEIGHT (KG):_____ HEAD CIRCUMFERENCE (CM): _____

LENGTH (CM): _____ LEVEL OF SERUM BILIRUBIN (UMOL/L): _____

SIGNS AND SYMPTOMS ON ADMISSION

PREMATURITY: ☐ BILIARY ATRESIA: ☐

SEPSIS: ☐ POOR FEEDING: ☐

IRRITABILITY: ☐ FEEDING INTOLERANCE: ☐

INHERITED DISEASES: ☐ OTHERS: ☐

SPECIFY:_____ SPECIFY: _____