UNIVERSITY of RWANDA

BURDEN AND SHORT TERM OUTCOME OF NEONATAL JAUNDICE AT UNIVERSITY TEACHING HOSPITAL OF KIGALI

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By

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A dissertation submitted in partial fulfillment of the requirements for the degree of MASTER OF MEDICINE IN PEDIATRICS in the college of Medicine and Health Sciences at University of Rwanda

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2019-2020

DECLARATION

This dissertation contains my own work except where it is acknowledged.It has passed in anti-plagiarism system and found to be compliant with University of Rwanda regulations. This is the approved final version of the Thesis.

Dr. Emelyne KARIGIRWA

10103887

Signature……..

Date ……../ …… /2020

Main Supervisor Names: Dr. Faustine AGABA

Signature……..

Date ……/……/2020

DEDICATION

To the Almight God who cares about us;

To my husband TUYISENGE DAVID for your love and encouragement;

To my children INEZA TUYISENGE Emma and AJENEZA TUYISENGE Evan your smile gave me strength and focus;

To my Parents,my mother NYIRAMUZIMA Marie Claire and my late father MUKINDIGIRI Damien, I owe my success to your upbringing;

To my brothers Protogene,Jean Felix,Edmond,Christian and Sister Léopoldine;

To my lovely Teachers;

I dedicate this work .

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May God bless all the above and anyone who contributed,in their own way, in my training.

ABSTACT

Background

Neonatal jaundice is among the most frequent causes of newborns hospitalization in the first week after birth. It is a benign condition if well managed in a timely manner. Without appropriate management, neonatal jaundice can lead to neurological problems like cerebral palsy, auditory disturbance and gaze abnormalities.

Aims: To evaluate prevalence of neonatal jaundice,short term outcome of newborns with jaundice and its associted factors at CHUK Pediatrics department.

Methods: This study was a retrospective cross-sectionalstudy carried out at CHUK pediatric department for newborns admitted during a period two years,from January 2018 to December 2019.Data collection was done using a structured questionnaire,they were entered in Epidata 3.1 and analysed in SPSS 25. Bivariate and multivariate analysis were used for factors associted with short term outcome. Odds ratios were calculated and Significance level was considered at p-value < 0.05.

Results: Newborns admitted were 1745,those with jaundice were 711.The prevalence of neonatal jaundice at CHUK during 2018-2019 was 40.7%; 13.2% died. Severe hyperbilirubinemia was associated with coming from outside CHUK ($p<0.001$). There was a strong association between death and congenital abnormality ($p<0.001$), direct hyperbilirubinemia ($p<0.001$), sepsis ($p<0.001$), weight less than 2500grams ($p<0.001$).

Conclusion: The burden of neonatal jaundice at CHUK was high. The factors associted with outcome were prematurity, congenital abnormality and sepsis. Neonates who were transferred fromoutside CHUK were more likely to present with severe hypebilirubinemia. Maternal education during prenatal visits and postpartum can improve early consultation. Ealy transfer of neonates with congenital abnormalities and neonatal sepsis will improve outcome.

KEY WORDS

Burden, Short term outcome, Neonatal jaundice

LIST OF SYMBOLS AND ACRONYMS

CHUK: Centre Hospitalier Universitaire de Kigali

CI: Confidence interval

CMHS: College of Medicine and Health sciences

HIE: Hypoxic Ischemic Encephalopathy

IRB: Institutional Review Board

NICU: Neonatal Intensive care unit

OR: Odds ratio

TSB: Total Serum bilirubin

UR: University of Rwanda

USA: United States of America

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CHAPTER1. INTRODUCTION

1.1. Background

Neonatal jaundice is among the frequent cause of admission in newborns during the first week after birth(1). It is a benign condition if managed well on time.Without proper treatment, neonatal jaundice can lead to neurological problems such as cerebral palsy, hearing loss and abnormal eyesight (2).Recent global statistics proposed that about 1.1 million babies a year, may possibly develop severe hyperbilirubinemia, the big number of them live in sub-Saharan Africa and South Asia(3).Tana et al revealed the higher incidence of severe neonatal jaundice in Africa at 667.8/10000 live births, the lowest incidence being in European region with 3.7/10000 live births(4).About 60% of newborns suffer jaundice in the first seven days of life, 84% of neonate born before 35 weeks are affected with jaundice (5).African studies have shown a largeprevalence of neonatal jaundice with55.2% in South-Africa and 37.3% in Ethiopia(6,7).

Twenty-four million newborns over 32 weeks' gestational ageare at risk of adverse events associated with hyperbilirubinemia(8).This study on burden of neonatal jaundice will help to educate parents and improve newborns' care.

1.2. Literature review

Neonatal jaundice is yellowish discoloration of the skin, sclera and mucus membranes. In newborns, jaundice occurs when serum total bilirubin exceeds 5mg/dl (86 µmol/l), which is different from adults and older children where normal total bilirubin is less than 1.5mg/dl (26µmol/l) (5).Total serum bilirubin above the 95thpercentile during the first seven days of life is definedas hyperbilirubinemia (high risk zone) (9).Worldwide jaundice is common in term neonates at 60% and 80% in preterm (10).Neonatal jaundice is a benign, self-limiting problem in most cases, only 5-10% of newborns with jaundice require treatment to prevent further complications (11).

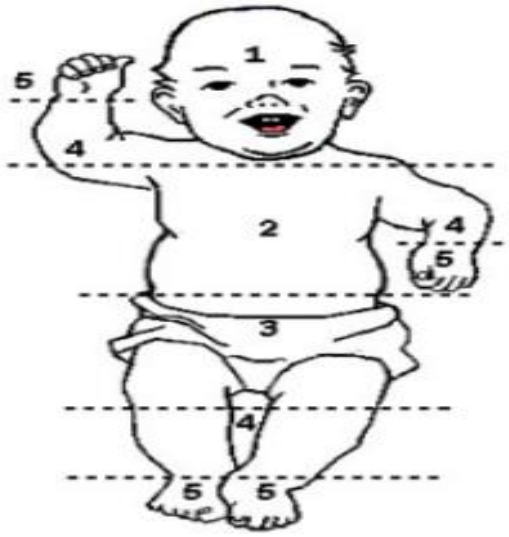
Bilirubin is the result of heme after breakdown of hemoglobin; the heme is converted into bilirubin in reticuloendothelial system (spleen, liver and bone marrow). The heme is initially transformed to biliverdin by heme oxygenase (microsomal enzyme) and then to conjugated bilirubin by biliverdin reductase (sitosolic enzyme). Unconjugated bilirubin binds to serum albumin to be transferred for conjugation in the liver. Unconjugated bilirubin is conjugated under the action of bilirubin uridine diphosphate glucuronosyltransferase and is easily eliminated in bile. This conjugated bilirubin is metabolized by the intestinal flora to urobilinoids and excreted in the faeces. Conjugated bilirubin can be deconjugated by tissue β-

glucuronidase and then reabsorbed in the intestine which is called enterohepatic circulation(12).

Neonatal jaundice is associated with many factors which are: Genetic predisposition, racial disparity, maternal, neonatal, birth history and hematological(13–18).Neonatal jaundiceis difficult to diagnose clinically in black neonates(6).The measurement of total serum bilirubin plotted on bilirubincurve and identifying risk factorsare very important in detecting the neonates(≥35 weeks) who require treatment(19).There is no clear guideline for starting hyperbilirubinemia treatment in preterm less than 35 weeks, it is mainly based on weight or gestational age (20).

Jaundice increases cephalocaudal, Kramer established the rule of visual assessment of neonate with jaundice mainly in centers with limited resources; it has five zone based on the part of the body which are affected by jaundice.(21,22)

Below is attached the image of Kramer‘s rule.



This is the table defining the meaning of five Kramer’s zones

Zone	Definition	TSB in micromole/L
1	Head and neck	100
2	Upper trunk	150
3	Lowe trunk and thighs	200
4	Arms and lower legs	250
5	Palms and sores	>250

The treatment of jaundice in newbornsis mainly phototherapy(12). Exchange transfusion is used for neonates whose total serum bilirubin are in exchange transfusion range, who present

signs of acute bilirubin encephalopathy and those who are not responding to phototherapy (18).Where there are limited resourcesand exchange transfusion is still a challenge, double-sided phototherapy can be used(23). In neonates with bilirubin due to Rhesus or ABO isoimmunization who are at high risk of bilirubin encephalopathy; immunoglobulin can work with good effect and reduce the rate of exchange transfusion (24).

The outcome of neonatal jaundice depends on many factors: causes, risk factors, timeof consultation and management. The acute bilirubin encephalopathy and its complications arehard to reverse even in settings with good facilities (25).Delayed consultation and inappropriate management of neonatal jaundice can lead to permanent sequelae of kernicterus spectrum disorders like hearing loss,choreoathetoticcerebral palsy, delayed mile stones(26).Studies done in Nigeria showed a high prevalence of neonatal jaundice; the associated factors were mainly sepsis and prematurity (27,28). In Rwanda we manage babies with neonatal jaundice,the prevalence and factors associated with neonatal jaundice short term outcome are not well known.

1.3.Study rationale

The burden of neonatal jaundice persists in developing countries (3). Worldwide healthcare personnelknow that severe neonatal jaundice is a "silent" origin of neonatal morbidity and mortality (29). The incidence of severe jaundice in newborns is elevated in Africa (4). Studies done in other African countries have shown that the prevalence of neonatal jaundice remains high(6,7,28). A study done in Kenya by Maalim et al. showed that acute bilirubin encephalopathy was present in 13.8% of the 88 newborns admitted for jaundice(30).Blandina et al. found that neonatal jaundice was the eighth leading cause of admission in northern Tanzania(31). Some unpublished studies done in Rwanda about neonatal jaundice prevalence and risk factors at two district hospital (Ruhengeri and Kabgayi); have shown high prevalence at around 40% in each hospital (32). Rwanda is a low income country with limited data on neonatal jaundiceand itsshort term outcome.

1.4 .Research questions

- What is the prevalence of neonatal jaundice at Centre Hospitalier Universitaire de Kigali (CHUK)?
- What is the short term outcome of neonates with jaundice at CHUK?

1.5. Objectives

1.5.1. General Objectives

To evaluate the prevalence and the short term outcome of neonates with jaundice in CHUK.

1.5.2. Specific objectives

To determinethe prevalenceofneonatal jaundice in neonates admitted at CHUK.

To assess short term outcome of newborns with jaundice at CHUK.

To assess factors associated with short term outcome of newborns with jaundice at CHUK.

CHAPTER2. MATERIALS AND METHODOLOGY

2.1. Study materials

2.1.1. Study site

The survey was conducted in pediatrics department of University Teaching Hospital of Kigali (CHUK), the main public referral hospital in Kigali, Rwanda.

2.1.2. Study design

This study was a retrospective cross sectional descriptive study.

2.1.3. Study period

We collected Data in period of 24 months from January 2018 to December 2019

2.1.4. Study Population

All newborns who were admitted in pediatrics department during study period were included.

2.1.5. Inclusion criteria

All newborns admitted in pediatrics department who developed jaundice during hospitalization.

All newborns whose total serum bilirubin above 85µmol/l and documented in CHUK operating system.

2.1.6. Exclusion criteria

All newborns with missing files in archive and pediatrics department were excluded

All newborns diagnosed with jaundice clinically but their results of total serum bilirubin being not recorded in CHUK operating system.

All newborns whose total serum bilirubin below 85µmol/l

2.2. Study procedures

2.2.1. Procedure at enrollment

To identify all newborns admitted in study period or patients ‘records in archive; neonatology database and admission registries of neonatology unit and pediatrics emergency were used. All newborns meeting the inclusion criteria without any factor allowing them to meet the exclusion criteria were unrolled in the study; with their file reviewed by using a standard questionnaire designed in English.

2.2.2. Measurement of outcomes

2.2.2.1. Questionnaires

A questionnaire was developed by the primary investigator in English from the review of similar studies in other countries (7,27,28,33). It was revised by a neonatologist, a pediatrician and a statistician for validity. The questionnaire had two parts: the first part helped in the collection of independent variables that were selected based on literature; the second part was used for data collection onoutcome and management of neonatal jaundice.

2.2.2.2. Dependent variables

Short term outcome of babies diagnosed with neonatal jaundice

- Severity of hyperbilirubinemia (bilirubin levels requiring exchange transfusion and signs of acute bilirubin encephalopathy)
- Death

2.2.2.3. Independent variables

- Newborn characteristics (sex, origin of neonate, gestational age, birth weight, age at admission, history of poor feeding, direct and total bilirubin, hemoglobin, blood group, Rhesus, mode of delivery).
- Maternal characteristics (Age, parity, blood group, rhesus).
- Birth history (birth trauma, prolonged rupture of membrane,).
- Comorbidities (sepsis, HIE, congenital abnormality, Rhesus incompatibility, ABO incompatibility).

Confounders: in addition to some variables, any condition that interfering with enteral feeding (intestinal occlusion, hirshsprung, atresia, necrotizing enterocolitis).

2.2.3. Sample size

Sampling was done by using single population proportion formula (34).

$n = Z^2 \times P (1-P)/d2$

Using assumption of 95% confidence level, 5% margin of error, and 50% since there is no estimate available of the target population in our settings,

N: Desired sample size

Z: Standard normal deviate at the required confidence interval 1.96 for 95%

P: proportion of new born who has jaundice based on retrospective study done in Nigeria that found 35% (28).

D: The level of statistical significance set.

N= $(1.96)^2$ (0.35) (0.65)/ $(0.05)^2$ =350 participants (the minimum participants)

2.2.4. Data management and statistical analysis

Data entry was done inEpidata version 3.1 then transferred to SPSS version 25 for analysis. Descriptive data analysis was done using frequencies and percentages in tables. The continuous data were outlined using mean and median values depending on their distribution, the difference in median scores among groups was tested using non parametric test where Mann Whitney U test was used as the data were skewed (not normally distributed).ThePearson chi-square test and linear regression (binary logistic regression) were used to determine the relationship between the outcomes and associated factors. The Odds ratios were determined. Statistical significance for associations was considered at the level $p < 0.05$. The statistically significantvariables (p-value ≤ 0.05) in bivariate analysis were the only ones considered in the model of multivariate analysis.

2.3. Ethical considerations and Confidentiality

Ethical approval: The project was approved by University of Rwanda / academic team of pediatrics department on 5th January 2020 and Institutional Review Board (IRB) of CMHS (College of Medicine and Health Science) on 23rd January 2020 (No 013/CMHS IRB 2020). It was approved by CHUK ethics committee.

Confidentiality

Confidentiality was maintained by keeping all data secured in computer with a password .No patients' identification exposed

CHAPTER3. RESULTS

During the study period of 24 months, from January 2018 to December 2019, 1745 newborns were admitted to CHUK pediatrics department. Neonatal jaundice was diagnosed in 40.7% (711/1745) of admitted newborns, 70.6 %of them were in-born babies;the majority were preterm babies at 52.6%. The time of clinical diagnosis was between 24 and 72 hours in many babies, the median weight at admission was 2200 grams, 13.2% of neonates with jaundice died.

3.1. Socio-demographic characteristics of participants

In 711 neonates with jaundice, 396 (55.8%) were male, the rest were female, 443(62.3%).The majority of them were born at CHUK and admitted in first seven day of life summarized in**Table1.**

Table 1: **Social demographic characteristics of participants**

Variable	n	%
Year of admission		
2019	372	52.3
2018	339	47.7
Sex of the neonate		
Male	396	55.8
Female	314	44.2
Origin of the neonate		
CHUK	502	70.6
Outside CHUK	209	29.4
Day of life at admission		
≤7 days	656	92.3
>7 days	55	7.7
Gestational age		
<37 weeks	374	52.6
≥37 weeks	337	47.4
Admission weight		
Median (Q1-Q3) in grams	2200 (1562-3000)	
Category		
<2500 g	396	55.7
≥2500 g	315	44.3
Severity of bilirubin		
Low(<250 micromol/l)	561	78.9
Moderate(250-299 micromol/l)	58	8.2
High(≥300 micromol/l)	89	12.5
Comorbidities		
Congenital abnormality	118	16.6
Sepsis	111	15.6
ABO/Rhesus incompatibility	44	6.2
HIE	15	2.1
Polycythemia	13	1.8

3.2. Maternal characteristics

In this study, 572 (80.9%) mothers were below 35years of age, the median age was 30 years,and most of them were multipara, recorded in **Table 2**.

Table 2: Maternal social demographic characteristics

Characteristic	n	%
Maternal age [Median (IR) = 30(26,34)]		
≤35 years	572	80.9
>35 years	135	19.1
Maternal parity		
Multipara	457	64.3
Primipara	254	35.7
Multiple pregnancy		
No	673	94.7
Yes	38	5.3

3.3. Management and short term outcome of neonatal jaundice

In 711 newborns with jaundice, 54.7% were managed conservatively while 45.3% required phototherapy. Only 2.5% of participants had bilirubin in exchange transfusion range. 13.2 % of participants died, results are illustrated in **Table 3**

Table 3: Management and short term outcome of neonates with jaundice

Variable	n	%
Proposed management meeting exchange transfusion		
Yes	18	2.5
No	693	97.5
Management		
Phototherapy	322	45.3
Observation	389	54.7
Phototherapy duration in days		
Median (Q1-Q3) in days	2 (2-4)	
Outcome		
Transferred	6	0.8
Death	94	13.2
Discharged	611	85.9
Complication with Acute bilirubin encephalopathy		
Yes	1	0.1
No	710	99.9
Follow up plan documented in the file		
Yes	310	43.6
No	401	56.4
Hospital stay		
Median (Q1-Q3) in days	9 (4-21)	

3.4. Factors associated with short term outcome

Our bivariate analysis shows five main predictors of death among babies diagnosed with neonatal jaundice. The factors were as follows: babies with congenital abnormalities and neonatal jaundice had 6.5 times odds of dying compared to those without congenital abnormalities (OR=6.5; 95% CI: 4.0-10.3; p<0.001), direct hyperbilirubinemia (OR=6.0; 95% CI:3.4 – 10.7; p<0.001), those who had sepsis had 4.5 times odds of dying in comparison without sepsis (OR=4.5; 95% CI: 2.7-7.3; p<0.001), neonates coming from outside CHUK had 3.8 times odds of dying compared to neonates from CHUK (OR= 3.8; 95% CI: 2.4-5.9, p<0.001), and neonates admitted with weight <2500grams had 2.2 times odds of dying compared to those admitted with weight >2500grams (OR: 2.2; 95% CI: 1.3-3.5, p<0.001). All the significant factors in the bivariate analysis namely congenital abnormality, direct hyperbilirubinemia, sepsis, admission weight, and origin of the neonate were used in multivariable analysis and all were found to be the real factors of the neonatal outcome, summary in **table 4.**

Table 4: Factors associated with short term outcome (Bivariate and multivariable analysis)

Variables	Short term Outcome		COR (95%CI)	P value	AOR (95%CI)	P value
	Died	Survived				
Origin of the neonate						
CHUK	41 (8.2%)	461 (91.8%)			0.44 (0.2-0.9)	0.025
Outside CHUK	53 (25.4%)	156 (74.6%)	3.8 (2.4-5.9)	<0.001		
Admission weight						
<2500g	67 (16.9%)	329 (83.1%)	2.2 (1.4-3.5)	0.001	7.4 (3.9-14.2)	<0.001
≥2500g	27 (8.6%)	288 (91.4%)				
Gestational age						
<37 weeks	55 (14.7%)	319 (85.3%)	1.3 (0.8-2.0)	0.219	-	
≥37 weeks	39 (11.6%)	298 (88.4%)				
Management						
Phototherapy	36 (11.2%)	286 (88.8%)				
Observation	58 (14.9%)	331 (85.1%)	1.4 (0.9-2.2)	0.145	-	
Direct Hyperbilirubinemia						
Yes	24 (42.1%)	33 (57.9%)	6.0 (3.4-10.7)	<0.001	3.1 (1.5-6.3)	0.002
No	67 (10.8%)	554 (89.2%)				
Exchange transfusion proposed						
Yes	0 (0.0%)	18 (100%)	0.2 (0.01-2.9)	0.219	-	
No	94 (13.6%)	599 (86.4%)				
Sex						
Male	46 (11.6%)	351 (88.4%)				
Female	48 (15.3%)	266 (84.7%)	1.4 (0.9-2.1)	0.149	-	
Sepsis						
Yes	36 (32.4%)	75 (67.6%)	4.5 (2.7-7.2)	<0.001	2.2 (1.2-4.2)	0.009
No	58 (9.7%)	542 (90.3%)				
ABO incompatibility						
Yes	0 (0.0%)	44 (100%)	0.06 (0.004-1.1)	0.059	-	
No	94 (14.1%)	573 (85.9%)				
Congenital abnormality						
Yes	44 (37.3%)	74 (62.7%)	6.5 (4.0-10.3)	<0.001	4.8 (2.4-9.4)	<0.001
No	50 (8.4%)	543 (91.6%)				
Hypoxic Ischemic Encephalopathy						
Yes	1 (6.7%)	14 (93.3%)	0.4 (0.06-3.5)	0.459	-	
No	93 (13.4%)	603 (86.6%)				
Severity of bilirubin						
Low	78 (13.9%)	483 (86.1%)	1.0 (0.5-1.9)	0.915	-	
Moderate	4 (6.9%)	54 (93.1%)	2.2 (0.8-6.2)	0.143	-	
High	12 (13.5%)	77 (86.5%)				

CHAPTER4. DISCUSSION

This was a retrospective cross- sectional descriptive study done at CHUK pediatrics department, in two years. Our aim was to show the burden of neonatal jaundice and short term outcome. This study brought us to these results: the prevalence of neonatal jaundice was 40.7% (711/1745), phototherapy was the main treatment, and death was registered in 13.2% (94/711).

4.1. Neonatal jaundice prevalence

The prevalence of jaundice in newborns was high at 40.7% (711/1745).This prevalence could be due to the fact that CHUK is the main tertiary hospital in Rwanda which receive many transfers from other health facilities; including big number of premature babies transferred in-utero and out-born babies with different pathologies. The age at admission also has played a role because every neonate with age less than 28 days with jaundice meeting inclusion criteria was included in our study.This was different from astudy conducted by Habibur in Bangladesh whichrevealed prevalence of neonatal jaundice at 22%(33). This difference could be due to different rates of admission and referral system as the study was also conducted at tertiary level like CHUK; their inclusion criteria also play a role because neonates above 14 days of age were excluded. Studies conducted in Nigeria from different states showed wide prevalence of neonatal jaundice ranging between 17-35%(27,28,35). Their findings were low in comparison withour findings. This difference could be related to settingsand population which are differentas Nigeria is a middle income country.Our findings were contrary to the study done by Twesigye et al. in Uganda where they found prevalence of 22.7% (55/242)(36). This difference was possibly due to their inclusion criteria because babies treated with intensive phototherapy and exchange transfusion were only considered, they had low number of preterm, and babies with cholestatic jaundice were excluded.

4.2. Bilirubin severity

We found that 2.5% (18/711) of our population had bilirubin in exchange transfusion range, but clinical presentation of acute bilirubin encephalopathy were documented on one baby. As this study was retrospective there might be incomplete documentation of acute bilirubin encephalopathy signs. This was different to the study done in Lagos by Olusegun et al. where acute bilirubin encephalopathy was recorded in 3.2% (28/882)(37). The study done by Maalim et al. in Kenya has showed high prevalence of acute bilirubin encephalopathy 13.8%

(12/88) (30). This difference could be due to the study type, as their study was prospective so they were able to get more complete information about the babies.

We had similarity with the study carried out in Namibia by Shilongo et al. where around one tenth 12.4% (231/1870) of the population developed high bilirubin (critical value), which was considered when total bilirubin was above 291µmol/l (38). Studies done in developed countries like Switzerland and USA showed low incidence of severe hyperbilirubinemia. High level of education in their population and their method of screening could be the main reasons (39,40).

4.3. Management of neonatal jaundice.

The main treatment was phototherapy at 45.3% (322/711), no exchange transfusion done; 54.7% didn't have any specific treatment for jaundice.We had low rate of phototherapy because we have a big number of physiological jaundice and few cases of cholestatic jaundice; exchange transfusion was not being done and all babies with serum total bilirubin in exchange transfusion range have responded well to phototherapy. This study had some similarity with the study conducted by Israel et al. in Benin city where 45% (212/472) of neonate with jaundice were treated with phototherapy, but 35% (166/472) had been treated by exchange transfusion(27). It is also similar to the study carried out by Habibur et al. in Bangladesh where phototherapy was the main treatment at 62.6% (267/426) but exchange transfusion was received by 5.2 % (22/426) of neonates with jaundice, and the main risk for exchange transfusion was rhesus incompatibility(33). The systematic screening of blood group in pregnant women and the use RhoGAM immunoglobulin decrease the rate severe hyperbilirubinemia related to rhesus incompatibility in our population. But we were not able to have access to national data about blood groups among mothers in reproductive age.

4.4.Short term outcome and its associated factors

This study revealed that 13.2% (94/711) of neonates with jaundice died. Our main factors were weight below 2500g, congenital abnormality,direct hyperbilirubinemia andsepsis. This could be explained by the setting we had where neonatal intensive care was under developed and few pediatrics surgeon; that why newborns who had very low birth weight and congenital abnormality were high likely to die.This was different from the study done in Nigeria by Onyearugha et al. where death was registered in 5% (8/160), the main causes were sepsis and kernicterus(28). A studydone by Habibur et al. in Bangladesh revealed mortality of 2.8% (12/426), their main associated factors werekernicterus and exchange transfusion related

complications(33).This difference might be related to characteristics ofsettingsand study population which were different.This outcome has similarityto the study conducted by Israel et al. findings in Nigeria where mortality among newborns with jaundice was 12.7 % (60/472) and the main associated factor was prematurity (27).Folorunso et al. conducted a study in Ibadan college hospital in Nigeria which revealed high mortality at 34.1%, its associated factors were not highlighted(41). While Engida et al. conducted a study on predictor of death in preterm and found that jaundice was the fifth highest predictor of death, which means that preterm with jaundice were more likely to die(42).

4.5. Bias of our study

Our study site is a tertiary hospital which is supposed to receive many transfers of critical babies from districts hospitals, so our result is not generalizable.

4.6. Challenge and limitation of study

During this study, we encountered challenges, the main are: to know the due time of clinical diagnosis of jaundice, lack of maternal knowledge about their blood group and systematic request of blood group in newborn with jaundice. Our study was not able to find the relationship between bilirubin severity and neonatal blood group. As a retrospective study and cross section, it was not possible to identify factors associated with neonatal jaundice. We found one case of acute bilirubin encephalopathy despite eighteen case of neonate with bilirubin in exchange transfusion range; this could be due incomplete documentation in the files.

CHAPTER 5.CONCLUSION AND RECOMMENDATIONS

5.1. Conclusion

The prevalence of neonatal jaundice was high at 40.7%; one fifth of neonate with jaundice had bilirubin which needs attention (serum bilirubin above 250µmol/l).

Low birth weight, congenital abnormality, direct hyperbilirubinemia, sepsis, and origin of neonate are main factors of death among neonates with jaundice.

This study could be a baseline reference on neonatal jaundice, which could help in establishing guideline in investigation, management of neonates with jaundice and follow-up plan.

5.2. Recommendations

To CHUK

To do exchange transfusion for neonates who have serum bilirubin which meet exchange transfusion level**.**

To the health care providers

To do systematic screening of maternal blood group; educate them about its importance and documentin antenatal visit logbook.

To reinforce mother education at discharge about neonatal danger signs like jaundice.

To ealy transfer of neonates with congenital abnormalities and neonatal sepsis to improve outcome.

To further research

We encourage the same study countrywide and to do research on long term outcome of neonates who had severe neonatal hyperbilirubinemia.

BIBLIOGRAPHY

1. Mojtahedi SY, Izadi A, Seirafi G, Khedmat L, Tavakolizadeh R. Risk Factors Associated with Neonatal Jaundice: A Cross-Sectional Study from Iran. Open Access Maced J Med Sci [Internet]. 2018 Aug 11;6(8):1387–93. Available from: https://spiroski.migration.publicknowledgeproject.org/index.php/mjms/article/view/oamjms.2018.319

2. Thielemans L, Trip-Hoving M, Landier J, Turner C, Prins TJ, Wouda EMN, et al. Indirect neonatal hyperbilirubinemia in hospitalized neonates on the Thai-Myanmar border: a review of neonatal medical records from 2009 to 2014. BMC Pediatr [Internet]. 2018 Dec 12;18(1):190. Available from: https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-018-1165-0

3. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. Lancet Child Adolesc Heal [Internet]. 2018;2(8):610–20. Available from: http://dx.doi.org/10.1016/S2352-4642(18)30139-1

4. Slusher TM, Zamora TG, Appiah D, Stanke JU, Strand MA, Lee BW, et al. Burden of severe neonatal jaundice: a systematic review and meta-analysis. BMJ Paediatr Open [Internet]. 2017 Nov 25;1(1):10. Available from: http://bmjpaedsopen.bmj.com/lookup/doi/10.1136/bmjpo-2017-000105

5. Pan DH, Rivas Y. Jaundice: Newborn to Age 2 Months. Pediatr Rev [Internet]. 2017 Nov;38(11):499–510. Available from: http://pedsinreview.aappublications.org/lookup/doi/10.1542/pir.2015-0132

6. Brits H, Adendorff J, Huisamen D, Beukes D, Botha K, Herbst H, et al. The prevalence of neonatal jaundice and risk factors in healthy term neonates at National District Hospital in Bloemfontein. African J Prim Heal Care Fam Med [Internet]. 2018 Apr 12;10(1):1–6. Available from: https://phcfm.org/index.php/phcfm/article/view/1582

7. Lake EA, Abera GB, Azeze GA, Gebeyew NA, Demissie BW. Magnitude of Neonatal Jaundice and Its Associated Factor in Neonatal Intensive Care Units of Mekelle City Public Hospitals, Northern Ethiopia. Int J Pediatr [Internet]. 2019 Apr 10;2019:1–9. Available from: https://www.hindawi.com/journals/ijpedi/2019/1054943/

8. Vinod K. Bhutani1 2, Finn Ebbesen6 JBAZHBRKMS, Tina M. Slusher1 8 Rintaro

Mori7, Fahmy9 N, Praveen Kumar15 SC and JELVKPLDAAOM-F de ABOO. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res [Internet]. 2013 Dec 20;74(S1):86–100. Available from: http://www.nature.com/articles/pr2013208

9. Ullah S, Rahman K, Hedayati M. Hyperbilirubinemia in Neonates: Types, Causes, Clinical Examinations, Preventive Measures and Treatments: A Narrative Review Article. Iran J Public Health [Internet]. 2016 May;45(5):558–68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27398328

10. Adoba P, Ephraim RKD, Kontor KA, Bentsil J-J, Adu P, Anderson M, et al. Knowledge Level and Determinants of Neonatal Jaundice: A Cross-Sectional Study in the Effutu Municipality of Ghana. Int J Pediatr [Internet]. 2018;2018:1–9. Available from: https://www.hindawi.com/journals/ijpedi/2018/3901505/

11. Althomali R, Aloqayli R, Alyafi B, Nono A, Alkhalaf S, Aljomailan A, et al. Neonatal jaundice causes and management. Int J Community Med Public Heal [Internet]. 2018 Oct 25;5(11):4992. Available from: http://www.ijcmph.com/index.php/ijcmph/article/view/3952

12. Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. Br J Hosp Med [Internet]. 2017 Dec 2;78(12):699–704. Available from: http://www.magonlinelibrary.com/doi/10.12968/hmed.2017.78.12.699

13. Tavakolizadeh R, Izadi A, Seirafi G, Khedmat L, Mojtahedi SY. Maternal risk factors for neonatal jaundice: a hospital-based cross-sectional study in Tehran. Eur J Transl Myol [Internet]. 2018 Jul 10;28(3):257–64. Available from: https://www.pagepressjournals.org/index.php/bam/article/view/7618

14. Chen Y-J, Chen W-C, Chen C. Risk factors for hyperbilirubinemia in breastfed term neonates. Eur J Pediatr [Internet]. 2012 Jan 17;171(1):167–71. Available from: http://link.springer.com/10.1007/s00431-011-1512-8

15. Lain SJ, Roberts CL, Bowen JR, Nassar N. Early Discharge of Infants and Risk of Readmission for Jaundice. Pediatrics [Internet]. 2015 Feb 1;135(2):314–21. Available from: http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2014-2388

16. Arnolda G, Nwe HM, Trevisanuto D, Thin AA, Thein AA, Defechereux T, et al. Risk factors for acute bilirubin encephalopathy on admission to two Myanmar national

paediatric hospitals. Matern Heal Neonatol Perinatol [Internet]. 2015 Dec 15;1(1):22. Available from: http://dx.doi.org/10.1186/s40748-015-0024-3

17. Christensen RD, Baer VL, MacQueen BC, O'Brien EA, Ilstrup SJ. ABO hemolytic disease of the fetus and newborn: thirteen years of data after implementing a universal bilirubin screening and management program. J Perinatol [Internet]. 2018 May 6;38(5):517–25. Available from: http://dx.doi.org/10.1038/s41372-018-0048-4

18. Singla D, Sharma S, Sharma M, Chaudhary S. Evaluation of risk factors for exchange range hyperbilirubinemia and neurotoxicity in neonates from hilly terrain of India. Int J Appl Basic Med Res [Internet]. 2017;7(4):228. Available from: http://www.ijabmr.org/text.asp?2017/7/4/228/220364

19. Allen D. Neonatal jaundice. Nurs Child Young People [Internet]. 2016 Jul 8;28(6):11–11. Available from: http://journals.rcni.com/doi/10.7748/ncyp.28.6.11.s15

20. Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol [Internet]. 2012 Sep 7;32(9):660–4. Available from: http://www.nature.com/articles/jp201271

21. Zakaria Z, Abd Jalil J, Sarkawi S, Balkhis I, Abd Rahim MA, Mustafa N, et al. Jaundice Assessement of Newborn Baby: A Short Review on Kramel's Rule and Magnetic Induction Spectroscopy. J Teknol [Internet]. 2015 Apr 13;73(6):103–106. Available from: https://jurnalteknologi.utm.my/index.php/jurnalteknologi/article/view/4426

22. Hakimi A, Bakar A, Hassan NM, Zakaria A, Ashraf A, Halim A. An Overview on Jaundice Assessment in Newborn : Types of Hyperbilirubinaemia , Kramel ' s Rule and Optical Density Method An Overview on Jaundice Assessment in Newborn : Types of Hyperbilirubinaemia , Kramel ' s Rule and Optical Density Method. ARPN J Eng Appl Sci [Internet]. 2016;(January). Available from: www.arpnjournals.com

23. Greco C, Arnolda G, Boo N-Y, Iskander IF, Okolo AA, Rohsiswatmo R, et al. Neonatal Jaundice in Low- and Middle-Income Countries: Lessons and Future Directions from the 2015 Don Ostrow Trieste Yellow Retreat. Neonatology [Internet]. 2016;110(3):172–80. Available from: https://www.karger.com/Article/FullText/445708

24. HANSEN TWR. Prevention of neurodevelopmental sequelae of jaundice in the

newborn. Dev Med Child Neurol [Internet]. 2011 Sep;53:24–8. Available from: http://doi.wiley.com/10.1111/j.1469-8749.2011.04059.x

25. Olusanya BO, Teeple S, Kassebaum NJ. The Contribution of Neonatal Jaundice to Global Child Mortality: Findings From the GBD 2016 Study. Pediatrics [Internet]. 2018 Feb;141(2):e20171471. Available from: http://pediatrics.aappublications.org/lookup/doi/10.1542/peds.2017-1471

26. Kaplan M, Bromiker R, Hammerman C. Severe Neonatal Hyperbilirubinemia and Kernicterus: Are These Still Problems in the Third Millennium? Neonatology [Internet]. 2011;100(4):354–62. Available from: https://www.karger.com/Article/FullText/330055

27. Israel-Aina Y, Omoigberale A. Risk factors for neonatal jaundice in babies presenting at the University of Benin Teaching Hospital, Benin City. Niger J Paediatr [Internet]. 2012 Aug 15;39(4):159–63. Available from: http://www.ajol.info/index.php/njp/article/view/80125

28. Onyearugha CN, Onyire BN, Ugboma HAA. Neonatal jaundice : Prevalence and associated factors as seen in Federal Medical Centre Abakaliki , Southeast Nigeria. Int J Pediatr Child Heal. 2013;1(2):16–20.

29. Slusher TM, Zipursky A, Bhutani VK. A Global Need for Affordable Neonatal Jaundice Technologies. YSPER [Internet]. 2011;35(3):185–91. Available from: http://dx.doi.org/10.1053/j.semperi.2011.02.014

30. Maalim A. Prevalence of Bilirubin Induced Neurological Dysfunction Among Jaundiced Neonates Admitted to Kenyatta National Hospital. [Internet]. UNIVERSITY OF NAIROBI COLLEGE; 2016. Available from: http://erepository.uonbi.ac.ke/handle/11295/101869

31. Mmbaga BT, Lie RT, Olomi R, Mahande MJ, Kvåle G, Daltveit AK. Cause-specific neonatal mortality in a neonatal care unit in Northern Tanzania: a registry based cohort study. BMC Pediatr [Internet]. 2012 Dec 7;12(1):116. Available from: https://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-12-116

32. Caudine M. Jaundice among newborns admitted at a selected district hospital of Rwanda [Internet]. University of Rwanda; 2019. Available from: http://dr.ur.ac.rw/handle/123456789/1018

33. Rasul CH, Hasan MA, Yasmin F. Outcome of neonatal hyperbilirubinemia in a tertiary care hospital in bangladesh. Malays J Med Sci [Internet]. 2010 Apr;17(2):40–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22135536

34. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. Gastroenterol Hepatol [Internet]. 2013;6(1):14–7. Available from: https://pubmed.ncbi.nlm.nih.gov/24834239

35. Omekwe DE, Duke George M, Kennis BT, Fakuma BN, Evidence CC, Destiny EF, et al. Survey and Management Outcome of Neonatal Jaundice from a Developing Tertiary Health Centre, Southern Nigeria. IOSR J Dent Med Sci [Internet]. 2014;13(4):35–9. Available from: http://www.iosrjournals.org/iosr-jdms/papers/Vol13-issue4/Version-1/I013413539.pdf

36. Nyangabyaki-Twesigye C, Mworozi E, Namisi C, Nakibuuka V, Kayiwa J, Ssebunya R, et al. Prevalence, factors associated and treatment outcome of hyperbilirubinaemia in neonates admitted to St Francis Hospital, Nsambya, Uganda: A descriptive study. Afr Health Sci [Internet]. 2020;20(1):397–405. Available from: https://www.ajol.info/index.php/ahs/article/view/195124

37. Adebami O. Factors associated with the incidence of acute bilirubin encephalopathy in Nigerian population. J Pediatr Neurol [Internet]. 2015 Jul 30;09(03):347–53. Available from: http://www.thieme-connect.de/DOI/DOI?10.3233/JPN-2011-0485

38. Sn S, Mukesi M, Gonzo M, Sr M. Prevalence of Critical Bilirubin Results among Neonatal Patients in Windhoek ,Namibia. SM J Fam Med. 2017;1(1):1–5.

39. Christensen RD, Lambert DK, Henry E, Eggert LD, Yaish HM, Reading NS, et al. Unexplained extreme hyperbilirubinemia among neonates in a multihospital healthcare system. Blood Cells, Mol Dis [Internet]. 2013 Feb;50(2):105–9. Available from: http://dx.doi.org/10.1016/j.bcmd.2012.10.004

40. Zoubir S, Mieth RA, Berrut S, Roth-Kleiner M. Incidence of severe hyperbilirubinaemia in Switzerland: a nationwide population-based prospective study. Arch Dis Child - Fetal Neonatal Ed [Internet]. 2011 Jul 1;96(4):F310–1. Available from: http://fn.bmj.com/cgi/doi/10.1136/adc.2010.197616

41. Serifat FA, U CA, &tongo O. Prevalence And Factors Associated With Neonatal Jaundice: A Case Study Of University College Hospital, Ibadan. IOSR J Dent Med Sci [Internet]. 2015;14(4):2279–861. Available from: www.iosrjournals.org

42. Yismaw AE, Gelagay AA, Sisay MM. Survival and predictors among preterm neonates admitted at University of Gondar comprehensive specialized hospital neonatal intensive care unit, Northwest Ethiopia. Ital J Pediatr [Internet]. 2019 Dec 7;45(1):4. Available from: https://ijponline.biomedcentral.com/articles/10.1186/s13052-018-0597-3

APPENDICES

APPENDIX 1: DATA COLLECTION TOOL

Questionnaire on Burden of Neonatal Jaundice

ID: **Number:** **Year of admission:**

Sex	Male Female
Day of life	
Hospital stay in days	
Time of clinical diagnosis of jaundice	In 24hours In 72 hours Above 72 hours
Gestational age in weeks	
Origin	CHUK maternity From District hospital Private Clinic From home
Weight in grs	
Maternal age	
Maternal parity	Primipara Multipara
Multiple pregnancy	Yes No
Mother blood group	A Positive A Negative AB Positive AB Negative O Positive O Negative

	B Positive B Negative Unknown
Birth history	Ruptured membranes Birth trauma Induction of labor Normal labor Unremarkable
Mode of delivery	Vaginal delivery Instrumental vaginal delivery Caesarian delivery
APGAR Score at 5 minute	Value…….. Unknown
Total Bilirubin in Micromol/l	
Direct Bilirubin in Micromol/l	Value……. Unknown
Direct Hyperbilirubinemia	Yes NO
Hemoglobin level g/dl	
CRP	Positive Negative Unknown
Blood culture	Positive Negative Unknown
Fetal blood group	A Positive A Negative B Positive B Negative AB Positive AB Negative O Positive O Negative Unknown

Associated diagnosis	Sepsis Prematurity HIE Congenital abnormality Yes or no If yes which one…… Rhesus incompatibility ABO incompatibility Unknown Polycythemia yes or No Others
Proposed management	Meeting criteria of exchange transfusion Yes No
Management	Phototherapy Observation
Phototherapy duration in days	
Short Outcome	Acute bilirubin encephalopathy Yes No Death Discharged Transferred
Follow up plan documented in the file	Yes No

APPENDIX 2: CHUK ETHIC COMMITTEE

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Quality Health Care Training & Research

Ethics Committee / Comité d'éthique

31.Jan.2020

Ref. EC/CHUK/010/2020

Review Approval Notice

Dear Emelyne KARIGIRWA,

*Your research project: "" **BURDEN AND SHORT TERM OUTCOME OF NEONATAL JAUNDICE AT UNIVERSITY TEACHING HOSPITAL OF KIGALI "***

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 31.Jan.2020 to evaluate your request for ethical approval of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your research project.

You are required to present the results of your study to CHUK Ethics Committee before publication by using this link:www.chuk.rw/research/fulireport/?appid=50&&chuk.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

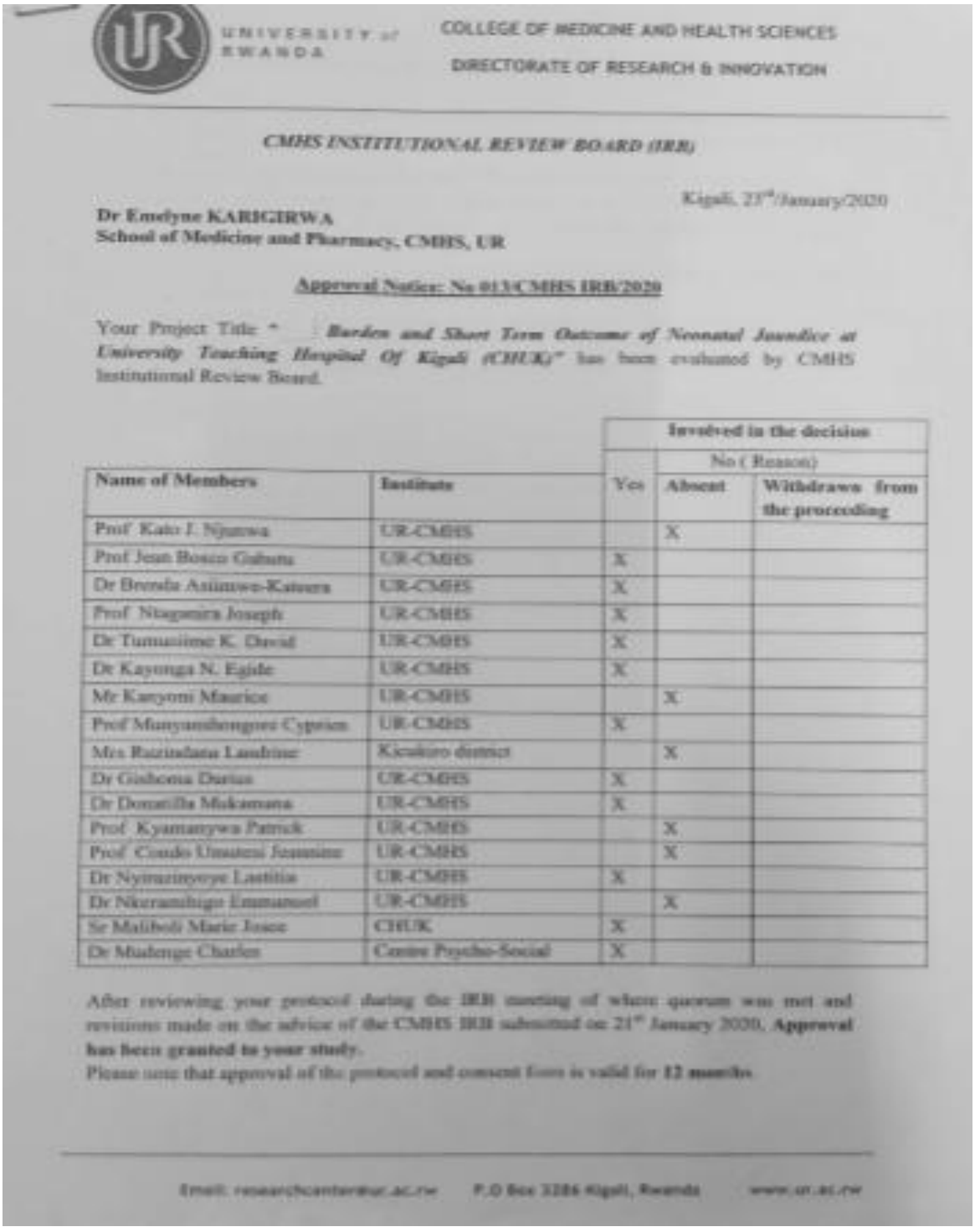
Dr Emmanuel Rusingiza Kamanzi
The Chairperson, Ethics Committee,
University Teaching Hospital of Kigali

ETHICS COMMITTEE
CHUK

Scan code to verify

" University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations "

APPENDIX3:IRB ETHIC CLEARENCE



UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 23rd/January/2020

Dr Emelyne KARIGIRWA
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 013/CMHS IRB/2020

Your Project Title: " ***Burden and Short Term Outcome of Neonatal Jaundice at University Teaching Hospital Of Kigali (CHUK)***" has been evaluated by CMHS Institutional Review Board.

Name of Members	Institute	Involved in the decision		
		Yes	No (Reason)	
			Absent	Withdrawn from the proceeding
Prof Kato J. Njunwa	UR-CMHS		X	
Prof Jean Bosco Gahutu	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyomi Maurice	UR-CMHS		X	
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Rutirindana Laudrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Malibobi Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 21st January 2020, **Approval has been granted to your study.**
Please note that approval of the protocol and consent form is valid for **12 months**

Email: research[illegible] P.O Box 3286 Kigali, Rwanda www.ur.ac.rw

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval.
5. Failure to submit a continuing review application will result in termination of the study.
6. Notify the IRB committee once the study is finished.

Sincerely,

Date of Approval: The 23rd January 2020

Expiration date: The 23rd January 2021

Professor GAHUTU Jean Bosco
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR