PREVALENCE AND CLINICAL CORRELATES OF PROLONGED NEONATAL JAUNDICE, AMONG NEONATES WITH JAUNDICE, AT KENYATTA NATIONAL HOSPITAL, NAIROBI

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DECLARATION

This dissertation is my original work and has not been presented for the award of a degree in any other university.

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DEDICATION

I would like to dedicate this work to my dear parents Mr Mehboob Ali Hassan and Mrs Hashmatt Mehboob Ali, my loving husband Muntazim Bachani and my loving family. A special thank you to my husband for supporting me and being my pillar in all my ups and downs through this process.

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ABBREVIATIONS:

AAP- American Academy of Pediatrics

ESPGHAN- European Society for Paediatric Gastroenterology, Hepatology and Nutrition

HPE- Hepatic Portoenterostomy

JZS- Jaundice Z-score

KNH- Kenyatta National Hospital

NASPGHAN- North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

NBU- New-born unit

NICU- neonatal intensive care unit

NNJ – neonatal jaundice

NNS- Neonatal sepsis

pNNJ – prolonged neonatal jaundice

TcB – transcutaneous bilirubin levels

TPN – total parenteral nutrition

UTI- Urinary tract infections

DEFINITIONS:

- Neonate – child aged less than 28days of life
- Preterm neonate – baby born before 37 completed weeks of gestation
- Neonatal jaundice – yellow discoloration of skin and mucous membranes
- Prolonged neonatal jaundice – yellow discoloration of skin and mucous membranes for more than 14days in term and more than 21days in preterm babies.
- TORCH screen- Testing for Toxoplasma, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus and Herpes infections.
- TPN – total parenteral nutrition is nutrition given intravenously including lipids, proteins and trace elements.

NB: The above definitions have been derived from NASPGHAN guidelines.

ABSTRACT

Introduction: Prolonged neonatal jaundice (pNNJ) is jaundice persisting beyond fourteen days in term and twenty-one days in pre-term babies. Globally, the incidence of cholestatic neonatal jaundice (NNJ) is one in two thousand five hundred live births, and prolonged neonatal jaundice is reported in up-to 15% of all new-born babies. The most commonly identifiable causes of prolonged neonatal jaundice globally, are biliary atresia, metabolic causes and other inherited syndromes, among others. Nonetheless, several studies in developing countries reveal neonatal infections to be playing a major role in the aetiology. In Kenya, NNJ is a common reason of morbidity and mortality in the neonatal period. Since the differential diagnosis of prolonged NNJ is extensive, a step-wise approach will be useful to identify the underlying pathology, based on the initial history and physical examination. A well-planned protocol can prevent us from having premature and expensive tests to establish cause. Also prevents time wastage and thus worsening clinical condition and outcomes of neonates.

Study objectives:

PRIMARY: To determine the prevalence of prolonged neonatal jaundice among neonates with jaundice admitted to Kenyatta National Hospital.

SECONDARY: To describe the laboratory and radiological investigations done, with results recorded, recorded aetiology and outcomes for babies admitted with prolonged neonatal jaundice in KNH.

Methodology: A retrospective cross-sectional study was carried out, aimed at determining the prevalence of prolonged neonatal jaundice in patients admitted to new born unit and paediatric wards, from 1st January 2016 – 31st December 2018, at Kenyatta National Hospital. A total of 368 files of patients with neonatal jaundice were randomly selected, with most recent files preferred to minimize missing data. 8files were excluded due to neonates reported to have total parenteral nutrition (TPN) administration. 360 files were analyzed manually to collect data as per the paper-based data collection tool. Data was then exported to Stata version 15.1 for statistical analysis. Categorical data was presented as proportions and comparison of patients with or without neonatal jaundice. Continuous data was analyzed using means or medians depending with underlying probability distribution.

Results:

During study period, records from 360 eligible neonates were retrieved and analysed. Sixty-seven (19%) were born preterm while 293 (81%) were term babies. Fifty-six neonates had prolonged jaundice; prevalence of 16%. Fifty-three (95%) had liver function tests done, of which 91% had conjugated hyperbilirubinemia. Fifty-two (93%) had full blood count done and the remaining first tier tests done in less than 50% of patients. The most common

causes were noted to be viral (25%) and bacterial (23%) sepsis. Other causes included biliary atresia (4%), breastfeeding jaundice and cholecystitis among others. 21% had no known diagnosis. As for the outcome, 1 out of 7 pre-terms and 4 out of 44 term neonates died during the first admission, thus, neonates admitted at earlier gestation were more likely to die than near term neonates.

Conclusion:

The prevalence of prolonged neonatal jaundice was noted to be high (16%) among jaundiced neonates admitted to Kenyatta National Hospital with no difference in gestational age at presentation.

Patients with prolonged neonatal jaundice were not fully evaluated even for first tier as per ESPGHAN guidelines, but from the evaluation done, infections noted to top the list of possible aetiology, especially viral hepatitis.

The outcome of neonates with prolonged jaundice could improve as 1 in every 10 admissions would die during the first admission.

Recommendations:

Neonates with prolonged jaundice should be evaluated fully at-least from the first tier of investigations to be done.

We need to come up with a written protocol on evaluation and management of neonates with prolonged neonatal jaundice.

1. BACKGROUND

Jaundice is the yellow discoloration of sclera, mucous membranes, skin and bodily fluids, due to accumulation of bilirubin in the circulation and tissues(1). Hyperbilirubinemia is a state of having elevated levels of bilirubin in blood without necessarily presenting as jaundice(2). Hyperbilirubinemia is divided into conjugated and unconjugated types. Unconjugated hyperbilirubinemia can result from impaired conjugation, increased production, or impaired hepatic uptake of bilirubin. Conjugated hyperbilirubinemia is raised direct bilirubin resulting from impaired excretion of bilirubin(3). Direct bilirubin of greater than 1.0 mg/dL (17.1 micromol/L), or greater than 20 percent of the total serum bilirubin, if the total serum bilirubin is <5.0 mg/dL (85.5 micromol/L), or >5.0 mg/dL (85.5 micromol/L) respectively, is significant(2). Direct bilirubin includes both the conjugated bilirubin and the delta fraction, which represents bilirubin covalently bound to albumin(4).

Neonatal jaundice can be divided in to two broad categories:

- Physiologic neonatal jaundice:

Jaundice caused due to physiological immaturity which usually appears between 1-3 days of age, peaks at 4th and 5th days and disappears by 10-14days in term neonates. In preterm neonates, jaundice peaks at 7^{th} day and disappears by 21 days of life. The predominant form is unconjugated bilirubin and usually its serum level is less than 15 mg/dl (256micromols/l). Bilirubin levels up to 290 – 308micromol/l may be accepted as normal in term healthy newborns(4).

- Pathologic neonatal jaundice:

This is clinical jaundice appearing within 24 hours mainly due to increase in serum bilirubin >85.5micromols/l/day, presence of clinical jaundice more than 2 weeks (prolonged NNJ), peak levels higher than the expected normal range, and conjugated bilirubin(5). Prolonged Neonatal jaundice occurs beyond 14days of life in term babies and 21days in preterm babies(6)(7). Up-to 15% of all new-borns have prolonged jaundice(8), nonetheless, 1 in 2500 live births are reported to have cholestatic liver disease worldwide (excluding those with parenteral nutrition related cholestasis)(6). Cholestatic jaundice defines persisting conjugated hyperbilirubinemia in the new-born with conjugated bilirubin levels exceeding 20% of total bilirubin level(9).

Prognosis of prolonged neonatal jaundice is good, (90% full recovery in idiopathic neonatal hepatitis)(10) and timely management of some of the treatable causes can improve survival(11). The overall 10-year survival rate of infants treated with the Kasai operation and, if necessary, liver transplantation reported to be 72%(10).

2. LITERATURE REVIEW

2.1. Causes of prolonged neonatal jaundice

Aetiology can be divided into Intrahepatic causes and obstructive causes.

Intrahepatic causes mainly present with mixed (direct & indirect) jaundice. Causes are varied and can be categorized as:

- Viral causes e.g. Herpes simplex, cytomegalovirus, parvovirus B19, HIV etc
- Bacterial causes e.g. Neonatal sepsis, UTI, Syphilis etc
- Genetic/metabolic disorders e.g. Alagille syndrome, α-1 antitrypsin deficiency, Tyrosinemia, Galactosemia, Progressive familial intrahepatic cholestasis etc

Obstructive causes of prolonged NNJ include Biliary atresia, choledochal cysts, bile duct paucity, neonatal sclerosing cholangitis, inspissated bile syndrome, gall stones, cystic fibrosis and Caroli disease among others(12).

The differential diagnosis of prolonged NNJ is wide, and a step-wise approach is useful to rapidly identify the underlying aetiology, based on the history and physical examination. Of the many conditions that cause prolonged NNJ, up-to 40% of the affected are benign unconjugated hyperbilirubinemia(13). The remaining have conjugated hyperbilirubinemia and liver disease, of which, the most commonly identifiable in the American population include: biliary atresia (25%–35%), genetic disorders at 25%, metabolic diseases at 20%, and a1-antitrypsin deficiency (10%), as presented in Figure 1 (14).

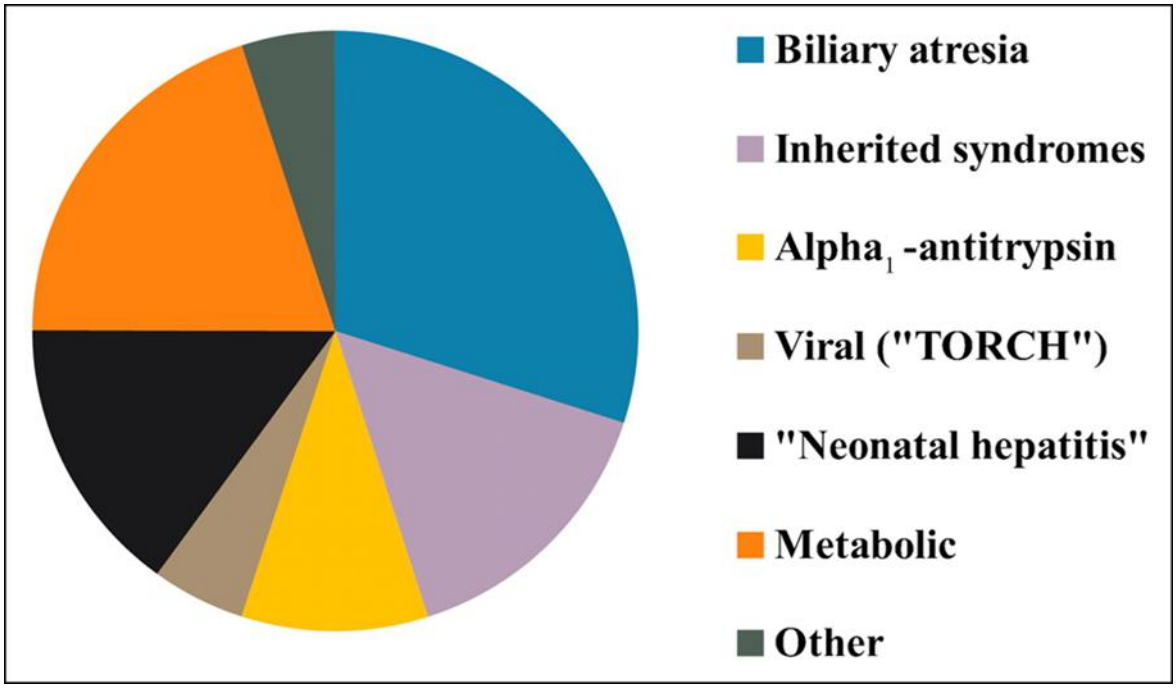


Figure 1 : Causes of prolonged neonatal jaundice

As noted in Figure 1 above, viral infections represent a minimal part of the causes in American population. This included mainly TORCH screen, which involves screening of viral infections associated with congenital anomalies. In developing countries, urinary tract infections (UTI) also reported to be a significant cause.(13)(15)

In a study in South East England, 23.7% of patients with prolonged neonatal jaundice had biliary atresia, 17% had alpha-1-antitrypsin deficiency and the remaining had unidentifiable causes(16).

A study done in Iran in 2018, reported prevalence of UTI in prolonged neonatal jaundice was 11%, E. coli being the main isolated bacteria(13). In yet another study in South of Iran, causes of prolonged neonatal jaundice were biliary atresia (50%), neonatal hepatitis (38%) and bile duct paucity (12%). There were no cases of α-1-anti-trypsin deficiency reported(17).A prospective observational study was carried out in Manipal, India where urine infections was noted in 12.9% of neonates with prolonged NNJ, with 45.45% of UTIs isolated Escherichia coli(18).

In another study undertaken in patients in Nepal, prolonged NNJ was noted in 64.3% of the admitted cases of NNJ. Prematurity (33.3%) and neonatal septicaemia (25.9%) were leading causes of prolonged NNJ(15).

In Africa, a prospective study done in Egypt found that Reovirus type 3 and CMV infections of the neonates are associated with the development of cholestatic disorder. This was due to intrahepatic cholestasis and also because of the production of extrahepatic biliary atresia(19).

2.2. Epidemiology of prolonged neonatal jaundice

The electronic databases searched include Pubmed, Google Scholar, Cochrane reviews, Science direct. A total of fifty-one studies were selected. Three were excluded due to inclusion of patients with TPN and six studies only concentrated on outcomes of specific exposures. Forty-two studies were relevant to the objectives of this study and were therefore included. A summary presented in the Table 1 below.

Key words: pathologic neonatal jaundice, prolonged neonatal jaundice, neonatal hepatitis, idiopathic neonatal jaundice.

Globally, from the database reviewed, no known estimates of prevalence of pNNJ nor any evidence of clinical corelates were found.

Table 1: Summary of included studies on Prevalence/incidence of prolonged neonatal jaundice

SOURCE	STUDY POPULATION AND DESIGN	PREVALENCE/INCIDENCE	CONCLUSIONS
Regionally America Maisels et al 2014 (13)	In North America prospective study on exclusively breastfed babies	Prevalence of prolonged jaundice of 34% at 21days and 21% at 28days of age	Jaundice zone score not a good predictor of level of bilirubin
UK Ekong et al 2017 (20)	Prospective study in South East England carried out between 1971-1973	Incidence of pNNJ 1:2500 live births. Some of the infants were followed up for 10years.	Prognosis of infants with intrahepatic liver disease was good
Asia L. Mullany et al 2013 (15)	In Sarlahi district of South Nepal, retrospective study carried out.	Incidence was 29.3 per 1000 live births	Associated factors noted to be ambient air temperature, mustard oil massage etc
Asia Chaudhary et al 2006 (21)	Hospital based study in Dharan (Eastern Nepal) Retrospective study	They found out 9.2% of admissions to newborn unit had pNNJ. This accounted to 64.3% of neonates with jaundice	Prematurity (33.3%) and neonatal septicemia (25.9%) were the most common causes of pNNJ
Middle East O. Olukman et al 2018 (22)	In Turkey, multicentre prospective study	Incidence was 10.5% term and 25.3% preterm babies with pNNJ	pNNJ is still a major cause of morbidity in Turkey
Developing countries Young Infants Clinical Signs Study Group 2008 (11)	Multicenter cohort study in six developing countries assessing most common reasons of admissions to NBU	Hyperbilirubinemia was a primary diagnosis for severe illness 2-57% of admissions in 7-59days old neonates	A single simple algorithm recommended to identify severe illness in 0 – 2 months old babies
Africa B. Olusanya et al 2009 (23)	In Lagos Nigeria, incidence of pNNJ was calculated	Noted to be 6.7% of newborns in the region.	Severe NNJ is associated with modifiable risk factors
Locally KNH Brigid Cheruiyot 2013 (24)	In a cross-sectional study at KNH for Mmed thesis	Neonatal jaundice accounted for 40.1% of all admissions in NBU	No data available on pNNJ prevalence nor incidence

At specific Country level**,** in North America, a largely white population, reviewed prevalence of prolonged neonatal jaundice between September 2010 and August 2013. Evaluation at 21 ± 3days, 34% were jaundiced with Jaundice Z-score (JZS) >1, 44% had trans-cutaneous bilirubin (TcB) of > 5mg/dl. At 28 ± 3days, 21% were jaundiced and 34% had TcB of >5mg/dl.(25)

A prospective study in South East England carried out between January 1971-December 1973 revealed overall incidence of cholestatic neonatal jaundice of 1:2500 live births. Fifty-four infants with conjugated hyperbilirubinemia were followed for 10years, their survival and outcome recorded. Prognosis for infants with idiopathic intrahepatic liver disease was good (72% four year survival for idiopathic neonatal hepatitis)(26) and every effort should be made to minimise the short-term effects of cholestasis. (6)

In a multi-center study in six developing countries, Bangladesh, Bolivia, Ghana, India, Pakistan, and South Africa, hyperbilirubinemia was a primary diagnosis for severe illness requiring hospital admission, accounting for 12–78% of the admissions in the first 6 days of life and 2–57% of admissions during the next 7–59 days. (11)

In another study from Sarlahi district, South Nepal, the incidence of prolonged neonatal jaundice was 29.3 per 1000 live births. Specific associations reported of jaundice were, ambient air temperature and oil massage. This may be explained by the reduced consideration for phototherapy based on the cultural practices of this study population(15). Research from a hospital-based study in Dharan (Eastern), Nepal found that 9.2% of infants admitted to the neonatal intensive care unit (NICU) had pathologic jaundice, which accounted for 64.3% of the admitted cases of neonatal jaundice(21).

The incidence of pNNJ was calculated to be 10.5% and 25.3% of term and near term new-borns in Turkey(22). The incidence of pNNJ in a recent study in Lagos, Nigeria was 6.7% of all new-borns in 2009(23).

Locally, in a masters dissertation done at University of Nairobi, by Brigid Cheruiyot (2013), neonatal sepsis and neonatal jaundice were the leading causes of admission among the neonates 50(40.2%) and 49 (40.1%) respectively(24) admitted at Kenyatta National Hospital.

2.3. Clinical presentation of prolonged neonatal jaundice

The clinical presentation of pNNJ is varied with signs and symptoms dependent on the underlying cause and features of hepatic failure if present(27). Clinically, patients with cholestatic liver disease have dark urine and pale stools, in addition to jaundice, but otherwise look well. The presence of pale stools is a sensitive marker for cholestatic liver disease (28) but parental reports of the stool colour may be misleading because the stool colour may be influenced by what the parents understand by pale stool and oral intake (29).

Fever, non-specific symptoms like lethargy, sleep disorders, feeding difficulties may be present as part of sepsis presentation. Symptoms of encephalopathy and seizures are far less common and maybe due to hypocalcemia or hypoglycemia. Features of liver failure including easy bruising, itchiness, skin rash, hepatosplenomegaly, bleeding tendencies may also be present(11).

Other signs may depend on underlying cause for instance, dysmorphic facies (Alagille syndrome), congenital heart disease (Alagille, biliary atresia), abdominal mass (choledochal cyst), hepatosplenomegaly, failure to thrive and respiratory symptoms (cystic fibrosis).

Early diagnosis and timely referral for management are key to better prognosis in the neonate(30). Less than 10% survival reported in one of the etiologic factors, extrahepatic biliary atresia, if not treated within the first 30-45days of life(31). Infants who have progressive liver disease, even when treatment is not available or effective, benefit from optimal medical management and nutritional support of the complications of cholestasis and even cirrhosis(1).

2.4. Clinical evaluation of prolonged neonatal jaundice

All neonates who present with jaundice beyond 2weeks of age need to be evaluated. First, to differentiate neonatal cholestasis from unconjugated/mixed hyperbilirubinemia, and, if cholestasis present, to rapidly identify those causes that are amenable to medical or surgical treatment(9). Infants who have pNNJ benefit from early medical management and optimal nutritional support, even when specific treatment is not available or curative, to prevent complications (1)(11).

We then need to evaluate whether prolonged NNJ is benign jaundice or due to a pathology. Any level of elevated conjugated bilirubin is abnormal and warrants further investigation(32). If cholestasis is present, further evaluation should be done urgently because of noted better outcomes if managed within a timely manner.

There were no studies outlining either global or Kenyan recommendations for evaluation of patients with pNNJ from the database searched. WHO gives brief guidelines on ruling out neonatal sepsis in patients with pathologic neonatal jaundice.

The American and European journals have joint recommendations from ESPGHAN and NASPGHAN for a targeted approach to investigate patients with prolonged NNJ according to the common causes in developed countries(20). The recommendation includes all patients with pathologic jaundice to have all tests in TIER 1 done and if no cause found, to be further evaluated as per TIER 2, guided by clinical evaluation. Other developing countries like Nepal and New Zealand, have institutional guidelines for managing pNNJ though not globally recognized(33). We do not have any guidelines in Africa and we happen to use North American and European guidelines as we do not have local evidence on etiology of prolonged NNJ.

Table 2: Targeted investigations of the persistently cholestatic infant according to ESPGHAN and NASPGHAN 2017(20)

TIER 1	**TIER 2**
Complete blood count + differential	Metabolic etiology
International normalized ratio (INR)	Ammonia, lactate, cholesterol
Liver function test + albumin levels	RBC galactose-1-phophate uridyltransferase
Blood glucose	Urine succinyllacetone and Organic acids
α -1- antitrypsin phenotype	Urine bile salt species
Thyroid function tests	DNA-PCR for CMV, HSV
Urine analysis	Sweat chloride tests
Urine culture	Genetic sequencing
Urine reducing substances	CXR
Cultures of blood and other fluids	SPINE XRAY
Fasting ultrasound	ECHO
	Cholangiogram
	Liver biopsy

2.5. Treatment of prolonged neonatal jaundice

The care of these patients is provided by the primary care physician and pediatric gastroenterologist. Specialization, rather than years of experience of professionals, was associated with better skills and practices.(31) Definitive care depends on the underlying cause, if any. Some of the treatable causes and their management have been illustrated in table 3 below. The first aim, in the management of infants with pNNJ, is to recognize diseases responding to specific medical therapy i.e: congenital toxoplasmosis, urinary tract infection, galactosemia, tyrosinemia, hypothyroidism. Also to importantly look for diseases which have better prognosis to early surgical intervention (biliary atresia, choledochal cyst)(34)

Care of patients can be divided into:

- **Supportive care:**

Intensive supportive care is required in managing these patients.

- Nutritional support with 120%-150% of daily caloric intake due to increased metabolic requirements, medium chain triglyceride supplements due to lack of bile flow. Neonates must be followed closely to adjust the caloric intake and supplements as per their growth.(10) Fat-soluble vitamins must also be supplemented with aqueous preparations. Current recommendations include Vitamin E (alphatocopherol) at 25 IU/kg/day and Vitamin K at 1 mg/day to 2 mg/day plus a twice daily dose of a liquid multivitamin supplement. The dose should be titrated based on measurements of serum levels of vitamins A, D and E, and the results of coagulation studies. (29)
- Symptomatic relief: Ursodeoxycholic acid to reduce pruritis and promote bile flow at a dose of 20mg/kg/day. In addition, cholestyramine or rifampin 5-10mg/kg/day to bind intestinal bile acids and further treat pruritis. Phenobarbital enhances bile acid synthesis, stimulates bile acid independent flow, induces hepatic microsomal enzymes, and thus, lowers the circulating bile acid levels. Adverse effects like sedation and behavioral side effects limit its use. The dosage is generally 3–10 mg/kg/d. (35)

- **Definitive care:**

Definitive care depends on the underlying cause. A summary of the common curable causes and their treatment have been tabulated in table 3.

Causes like infections, be it viral or bacterial, need urgent intervention before complications arise. Specific anti-microbial should be initiated as soon as possible. In Kenya, diagnosis of metabolic disorders has remained a challenge due to cost involved, and KNH, being for low resource setting clients, this becomes a major concern in achieving a diagnosis. Surgical cases like biliary atresia should be repaired urgently before complications of liver disease set-in.

Table 3: Treatable causes of prolonged jaundice

Causes of cholestasis	Intervention
Infection (bacterial/viral)	Antibiotics or antiviral medication
Galactosemia	Galactose free diet
Tyrosinemia	Low tyrosine/phenylalanine diet
Hereditary fructose intolerance	Fructose and sucrose free diet
Hypothyroidism	Thyroid hormone replacement
Cystic fibrosis	Ursodeoxycholic acid, pancreatic enzymes
Hypopituitarism	Thyroid, growth hormone and cortisol replacement
Bile acid synthetic defect	Ursodeoxycholic acid replacement
Biliary atresia	Hepatoportoenterostomy
Choledochal cyst	Choledochoenterostomy
Spontaneous perforation of common bile duct	Surgical drainage

2.6. Outcomes of prolonged neonatal jaundice

The outcomes of prolonged neonatal jaundice are good, up-to 90% survival, in patients with timely evaluation and management of underlying cause(10). For prolonged unconjugated jaundice, almost all patients recover by 8weeks of age with no complications(36). Nonetheless, mixed hyperbilirubinemia and conjugated hyperbilirubinemia follow a different course. As noted below, the outcome depends on specific identified aetiology of prolonged jaundice.

Patients with prolonged neonatal jaundice due to adrenal insufficiency or pituitary insufficiency recovered fully with hormonal replacement therapy(37). As for biliary atresia, age at diagnosis is a modifiable risk(38). Patients who have biliary atresia have a fifteen-year survival of almost 90%, if they undergo a Kasai procedure (hepatic portoenterostomy) before 2months of age(39). Other conditions (e.g. hypothyroidism) require prompt treatment to prevent life-long complications(12).

A retrospective analysis done for period of 15years in USA revealed overall outcomes at 2 years of age as: 56% of patients had liver transplants at a median age of 42 weeks, 40% survived with their original liver, and 4% of patients died(38). Patients diagnosed at >100days had universally poor outcomes.

There was no data on short-term outcomes of patients with prolonged neonatal jaundice from the database searched.

3. STUDY JUSTIFICATION

Neonatal jaundice is one of the most common reasons of morbidity and mortality in the neonatal period in Kenya. The prevalence of neonatal jaundice in KNH was 49% of all admissions to our new-born unit. From the evidence of developed countries, incidence is reported to be 1 in 2500 live births for cholestatic liver disease worldwide. Prolonged NNJ is noted to be affecting up-to 40% of all neonates in developing countries in Asia and New Zealand. From the African countries, only Nigeria reports to have incidence of 6.7% of all newborns. In Kenya, neither incidence nor prevalence is currently known.

The aetiology also noted to be varied in developed and developing countries world wide. Developed countries like North America, have higher percentages of congenital anomalies and metabolic disorders, whereas, developing countries like Nepal and Iran, have infections/NNS as a more common cause of pNNJ. Anecdotal evidence from the paediatric wards and new born unit at Kenyatta National Hospital suggest many cases of prolonged neonatal jaundice associated with early onset neonatal sepsis as well as neonatal hepatitis. However, there is no documentation on the prevalence and possible aetiological factors in neonates admitted at the largest public referral hospital in the country.

The prognosis of pNNJ is good and timely management of some of the treatable causes can improve survival to 90% of patients at 15years of age. Thus, there is need to know the causes of disease in order to have timely evaluation and quick referral to specialists.

The differential diagnosis is broad and therefore investigations need to be tailored to the common causes of pNNJ in Kenya. In order to know how to evaluate patients, we need to know what is more common in our setting. Due to our limited resources, it has been very improtant to evaluate only what is very essential. But to get that information, we need to know the aetiology and thus to come up with our own evaluation and management guidelines.

For any disease to be evaluated, we need to know the burden of disease. This study aims to get the burden of disease and thus serve as a start engine towards evaluating the disease in Kenya's main referral centre, Kenyatta National Hospital(KNH).

It also aims to evaluate the short-term outcomes and mortality associated with prolonged neonatal jaundice in KNH.

4. STUDY OBJECTIVES

PRIMARY:

1) To determine the prevalence of prolonged neonatal jaundice among neonates with jaundice admitted to Kenyatta National Hospital during the period January 2016 – December 2018.

SECONDARY:

1) To describe the laboratory and radiological investigations done, with results recorded, for babies admitted with prolonged neonatal jaundice in KNH.
2) To describe the aetiology of prolonged neonatal jaundice, using expert diagnosis in colaboration with results of investigations done, in KNH.
3) To determine the outcomes, in terms of discharge home versus death, of prolonged neonatal jaundice within the admitted period at KNH.

5.METHODOLOGY

5.1 Study design:

This was a hospital based, retrospective cross-sectional study aimed to calculate the period prevalence of prolonged neonatal jaundice in a 3year period at Kenyatta National Hospital (KNH).
It also included a descriptive analysis of laboratory results done and possible aetiology recorded.

5.2 Study population:

new born babies admitted to new born unit, general paediatric wards and paediatric surgical wards in KNH, within the specified 3 year time period with clinical jaundice.

5.3 Study site:

New born unit (NBU) and Paediatric wards at Kenyatta National Hospital (KNH), NAIROBI. Patients enrolled will include those admitted to NBU, general paediatric wards and paediatric surgical wards, fitting the inclusion criteria during the study period. KNH is a tertiary level hospital, serving as the main referral hospital in Kenya. It has highly qualified doctors and nurses to be able to give appropriate expert opinions.

5.4 Study period:

1st January 2016 – 31st December 2018

5.5 Study outcome:

This study aimed to achieve the following:

- Determination of prevalence for prolonged neonatal jaundice in KNH.
- Evaluate the initial laboratory and radiological investigations done, including their results.
- Description of its short-term outcome while within KNH wards and NBU.

5.6 Selection and Enrolment

i. **Inclusion criteria:** each of the participants had to fulfil the following inclusion criteria:

- Neonate (0-28 days) admitted with jaundice at KNH pediatric general/surgical wards and NBU.
- Term neonate admitted with or develops jaundice while in the ward, persisting for more than 14days of life.
- Preterm neonate admitted with or develops jaundice past 21days of life.

ii. **Exclusion criteria:** patients meeting any of the below exclusion criteria were excluded from the study:

- Patients with history of receiving Total Parenteral Nutrition (TPN) i.e. including lipids, as this is a confirmed cause of prolonged jaundice.
- Any patient not fitting into the above criteria.

5.7 Sample Size Determination

The sample size was calculated using Fischer's formula(40). The study used was a retrospective study, done in Dharan, Eastern Nepal. It was in the main referral hospital of the area and it revealed 9.2% of new-born admissions were diagnosed with prolonged neonatal jaundice. It was a hospital-based study done in a developing country and was closest to the aim of this study.

$$n = \frac{z^2\, p(1-p)}{d^2} = \frac{1.96^2 \times\ 0.64 \times 0.36}{0.05^2} = 354$$

- n = Sample Size
- z = Normal Standard Deviation taken with a 95% Confidence Interval; set at 1.96.

- p = Expected Prevalence of prolonged neonatal jaundice in a new born unit in Nepal was 9.2% of all admissions as per Kaini N et al's study done in 2006, accounting for 64.3% of all babies with neonatal jaundice(21).
- d = Study Precision taken as 5%

In view of the above calculation, our estimated minimum required sample size for this study was 354 patient files.

5.8 Patient Sampling Procedure

File numbers of all neonates admitted with neonatal jaundice, in all the paediatric wards in KNH, during the time frame, were recorded from the Hospital management information system (HMIS) at medical records department. The data clerk at medical records randomly selected patient file numbers to obtain files from the store. A total of 368 files retrieved from medical records. I, the principal investigator, went through each file to cross check files and include those that suited the criteria for this dissertation. Eight files were excluded due to administration of TPN during admission phase, and the remaining files were taken for further analysis.

5.9 Data Collection Tool

A stratified data collection tool was used to collect data. It included patient biodata, investigations done with results, diagnoses record from expert consultation and short-term outcomes in each case.

I, being the principal investigator, collected data using this structured, paper-based data abstraction tool. The files were collected from medical records starting from the most recent admissions going backwards, selected randomly. Data to be collected included neonate biodata, age at presentation, investigations done, length of stay and survival.

5.10 Data Management

Completed data abstraction tables were cross checked and any data queries identified resolved by checking the correct values from the neonate hospital file. Data from the completed paper-based tools was entered into a password controlled Epinfo database by trained research assistant. Data was extracted from database and exported to Stata version 15.1(Stata corp, college station, TX, USA) statistical software for statistical analysis. To maintain patient confidentiality, data was stored in lockable and waterproof cabinets accessible only to study team.

5.11 Data Analysis Plan

Categorical data was analyzed as proportions and comparison of neonates with and without prolonged jaundice using chi-square or Fischer's exact test as appropriate.

Continuous data was analyzed using means or medians depending with the underlying probability distribution and differences between neonates with and without prolonged jaundice compared using Z-test or Wilcoxon rank-sum test.

Prevalence of prolonged jaundice was calculated as percentage of neonates meeting criteria of prolonged jaundice with binomial exact 95% confidence interval. Binary logistic regression will be used to determine factors associated with prolonged jaundice.

The main investigations recorded were as per TIER 1 of ESPGHAN guidelines as it is the minimum baseline investigations expected for every patient with prolonged neonatal jaundice to have. For missing data, it was assumed that the test was not done unless it was indicated in doctors' notes in the file and results recorded. The results were further categorized into normal or abnormal as per neonatal cut-offs.

Diagnoses recorded were as per the expert consult made, as all patients are on follow up by a pediatric gastroenterologist. This was recorded and analyzed as percentages of total population of patients with pNNJ.

5.12 Ethical Considerations

Permissions was sought from the Kenyatta Hospital Ethics Research Committee to collect and analyse data collected in the study as part of the Thesis Dissertation. Copies of this Protocol as well as any Subsequent Modifications to either document was presented.

Permission was also be sought from Head of Records Department, KNH to access their files.

No patient names were taken for data analysis so as to maintain patient confidentiality.

No experimental investigations or products were used in this study as this was a retrospective study.

The hospital documentation was maintained strictly under trained medical personnel attached to the study only.

The overall study findings will be availed to the specialists and participating wards for the benefit of patients.

The study findings were also presented to the University of Nairobi (UON), Department of Pediatrics and Child Health Academic Staff and Students in fulfillment of the requirements of the M.Med Program.

5.13 Study Limitations

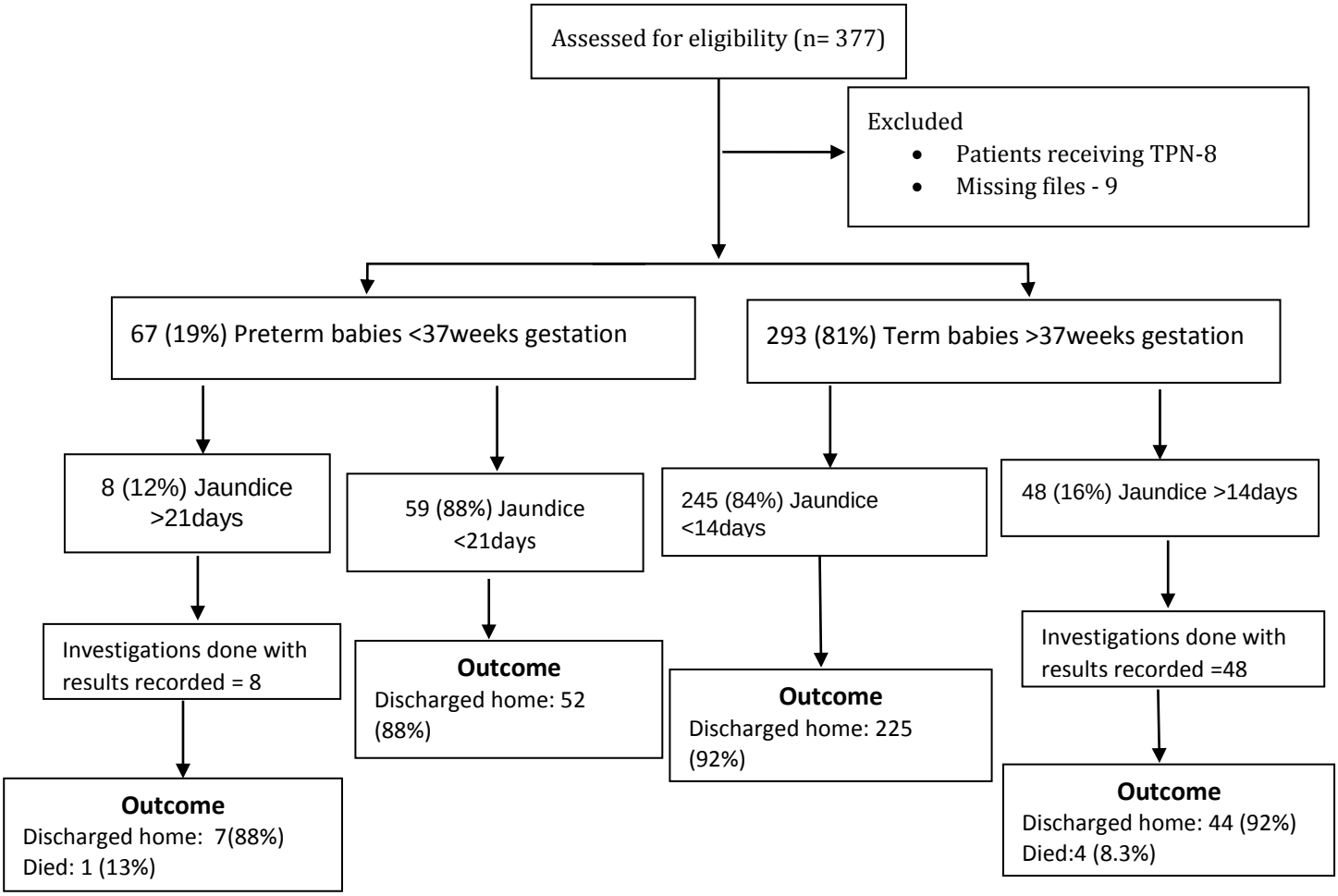
The following study limitations were encountered:

- The study relied on hardcopy manually written medical records so loss of information was noted, which was countered by non-response factor.
- Since the study was carried out in a national referral hospital, its finding may not be generalizable to other hospitals (lower level hospitals)
- The study relied on data from the neonate files that could be non-consistent or missing.
- Being a study at a resource limited centre, it was expected that not all investigations were done for every patient as recommended by international guidelines and this would hinder the results on aetiology.

6 RESULTS

The results were presented into the different sections as per the objectives of the study. 377 patient files numbers were selected for file retrieval. 9 files were missing and from the 368 files available, 8 were excluded due to record of patients receiving TPN. From those, 56 patients were noted to have prolonged jaundice and were taken for further analysis. No much data was noted to be lost as either physical copies or doctors' notes would have a record of all tests done with their results.

Figure 2: Flowchart on Patient Enrolment and Follow-Up.



6.1 Prevalence Of Prolonged Neonatal Jaundice

The total number of patients with neonatal jaundice were 360. The age of onset for all patients with jaundice had median of 3days for all patients, but (IQR = 2 to 6) days for non-prolonged jaundice and (IQR = 2 to 18.5) days for prolonged jaundice.

A total of 56 neonates had prolonged jaundice; period prevalence of 16% (95% CI 12 to 20%). The key subgroups of patients with prolonged neonatal jaundice were according to gestation. Among the 67 neonates born preterm, 8 had prolonged jaundice; a prevalence of 12% (95% CI 5.2% to 22%). While among the 293 neonates born term, 48 had prolonged jaundice; a prevalence of 16% (95% CI 12 to 21%). Males and females had similar prevalence of 51% and 49% respectively.

6.2 Descriptive Characteristics Of Study Participants

During study period, 360 neonates were recruited to the study; 67 (19%) were born preterm while 293 (81%) were term babies (Figure 2). A total of 192 (54%) of the study participants were male, and remaining 166 (46%) were female. The median (IQR) age of jaundice onset was 3 (2 to 4) days in non-prolonged and 3 (2 to 6) days among neonates with prolonged jaundice. The median (IQR) total duration of time with jaundice was 5 (3 to 7) days among patients with non-prolonged jaundice and 42 (25 to 89) days among neonates with prolonged jaundice (Table 4).

Characteristics	**All neonates (N=360)**	**Type of Jaundice**		
		Prolonged jaundice (N=56)	**Non-prolonged jaundice (N=304)**	**P-value**
Age at presentation in days#	3 (2-6)	7 (2-18.5)	3 (2-5)	<0.001
Gender-Female	166 (46)	27 (49)	139 (46)	0.66
Male	192 (54)	28 (51)	164 (54)	
Gestation in weeks#	38 (37-38)	38 (37-38)	38 (37-38)	0.59
Born preterm	67 (19)	8 (14)	59 (19)	0.37
Born term	293 (81)	48 (86)	245 (81)	
Age in days of Jaundice onset#	3 (2-4)	3 (2-6)	3 (2-4)	0.58
Age in days of Jaundice subsided#	10 (7-13)	49 (30-120)	8.5 (6-11)	<0.001
Time with jaundice in days#	6 (4-9)	42 (25-89)	5 (3-7)	<0.001
#-results presented as median (IQR), P-values of variables with median are from Wilcoxon ranksum test, the rest are from chi-square test.				

Table 4: Descriptive characteristics of study participants

6.3 Laboratory Investigations Done and Results Recorded

From the patients selected, none of them had a full profile of investigations done as per ESPGHAN guidelines (Figure 3). Some patients had some tier 2 tests included. The laboratory evaluation done in each case are summarized below and have been sub-divided according to neonatal cut-offs for each result.

Among the 56 neonates with prolonged jaundice, evaluation of neonatal sepsis was as follows: 52(93%) had total blood count done. From those, 7(14%) had low WBC count, 11(21%) had leucocytosis and the remaining 34(65%) had normal WBC count. Haemoglobin levels were normal in 50% of patients enrolled. Of the remaining, 24(46%) had moderate anemia and 3.9% had severe anemia at presentation. Urinalysis

and urine culture were done for 17 (30%) and 14 (25%) respectively. There were six bacterial isolates from the urine culture; two E.coli, two Klebsiella pneumonia and two Enterococcus (Figure 4). Blood culture were done for 19 (34%) neonates and four staphylococcal species were isolated. These included; staph epidermidis, staph haemolyticus, staph lantus, coagulase negative staph (Figure 5).

Liver function tests were done for 53 (95%) neonates. All the participants had hyperbilirubinemia of which 91% had cholestatic jaundice and remaining 9.4% had indirect/mixed hyperbilirubinemia. There were 27 (48%) INR test done of which 17 (63%) were normal and 10 (37%) were abnormal. Albumin levels test were done for 48 (86%), of which 26 (54%) were normal and 22 (46%) were abnormal (Table 5 and Figure 3).

For associated endocrine/metabolic disorders, the following evaluation was noted to have been done: Blood glucose was done for 17 (30%) neonates, and no abnormality was noted. Thyroid function test was done for 28 (50%) neonates. There were no cases of hypothyroidism reported and only 1(2%) case of hyperthyroidism. Urine reducing sugars were done for 9 (16%) neonates, of which 7 (78%) were normal and 2 (22%) were abnormal.

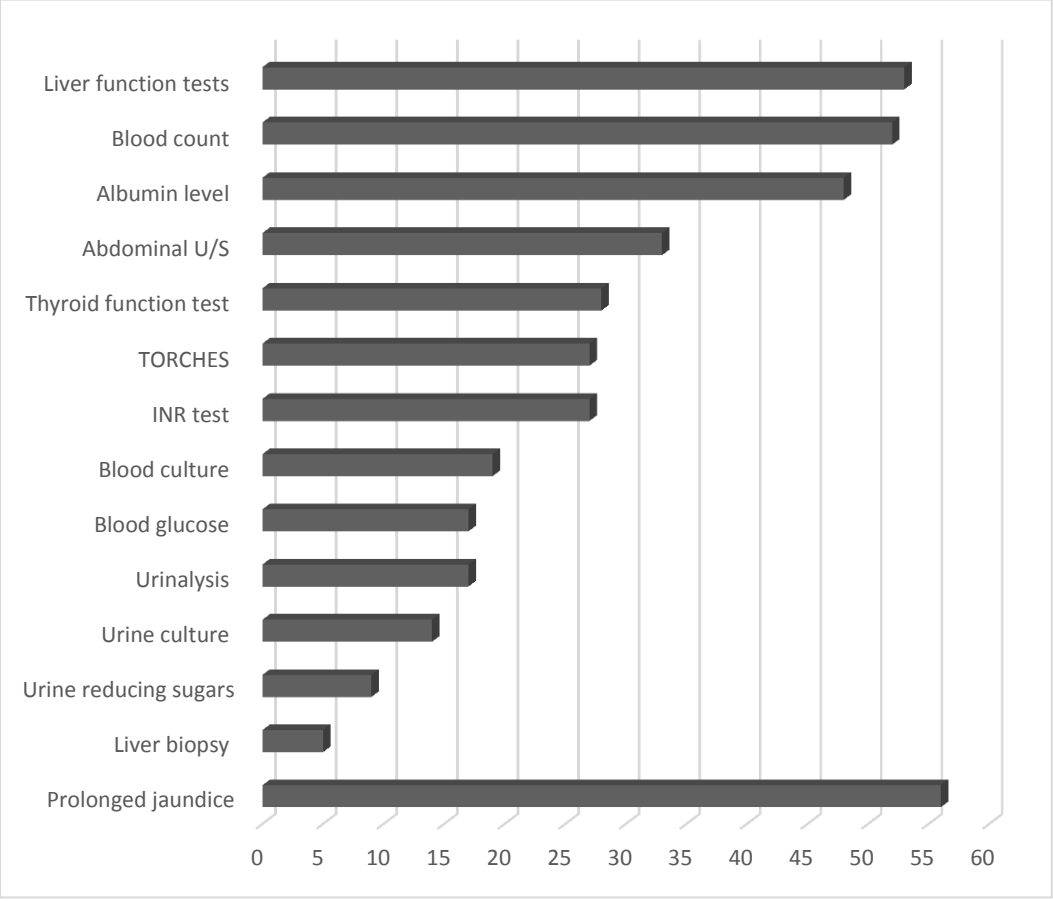


Figure 3: Bar graph showing tests done relative to number of neonates with prolonged jaundice

Table 5: Laboratory investigations done and results of patients with prolonged neonatal jaundice in tier 1.

Investigations	Prolonged jaundice (N=56)
Total blood count done	
Yes	52 (93)
No	4 (7.1)
WBC counts[$]	
<4	7 (14)
4 to 20	34 (65)
>20	11 (21)
Haemoglobin g/dl[$]	
<6	2 (3.9)
6 to 12	24 (46)
>12	26 (50)
Liver function tests done	
Yes	53 (95)
No	3 (5.4)
Serum bilirubin levels[$]	
<85.5	0
≥85.5	52 (100)
Conjugated bilirubin levels[%]	
<17	5 (9.4)
≥17	48 (91)
Urinalysis done	
Yes	17 (30)
No	39 (70)
Nitrities; median (IQR	0.0 (0-0)
Leucoytes; median (IQR	0.0 (0-0)
Urine culture done	
Yes	14 (25)
No	42 (75)
Bugs isolated from urine	6 (11)[#]
Blood glucose	
Yes	17 (30)
No	39 (70)
INR test done	
Yes	27 (48)
No	29 (52)
NORMAL	17 (63)
ABNORMAL(HIGH)	10 (37)
Thyroid function test done	
Yes	28 (50)
No	28 (50)
TSH levels; low	1(4)
T4 levels; high	1 (4)
Normal thyroid functions	27 (96)
Blood culture	
Yes	19 (34)
No	37 (66)
Bugs isolated from blood	4 (7.1)*
Urine reducing sugars done	
Yes	9 (16)

No	47 (84)
NORMAL	7 (78)
ABNORMAL	2 (22)
Albumin level done	
Yes	48 (86)
No	8 (14)
NORMAL	26 (54)
LOW ALBUMIN	22 (46)
$-4 records missing data, %-3 records missing data, #-Isolated bugs from urine were E.coli-2, Klebsiella pneumonia-2, Enterococcus-2,*-Isolated bugs from blood were staph epidermidis, staph haemolyticus, staph lantus, coagulase negative staph	

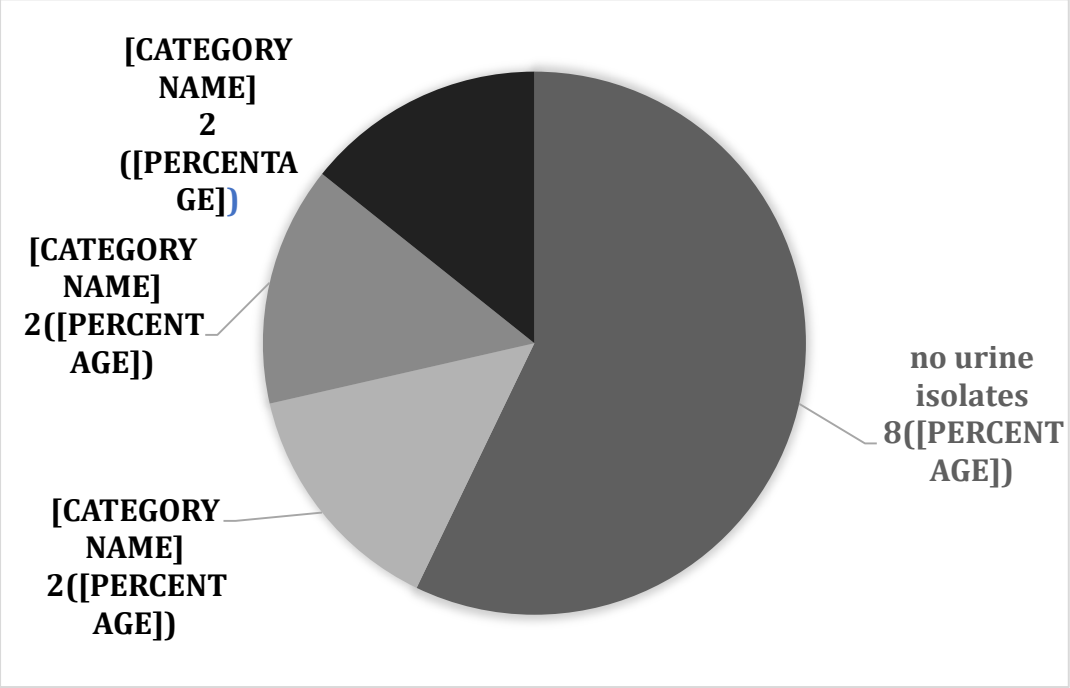


Figure 4: Bacteria isolated from urine cultures

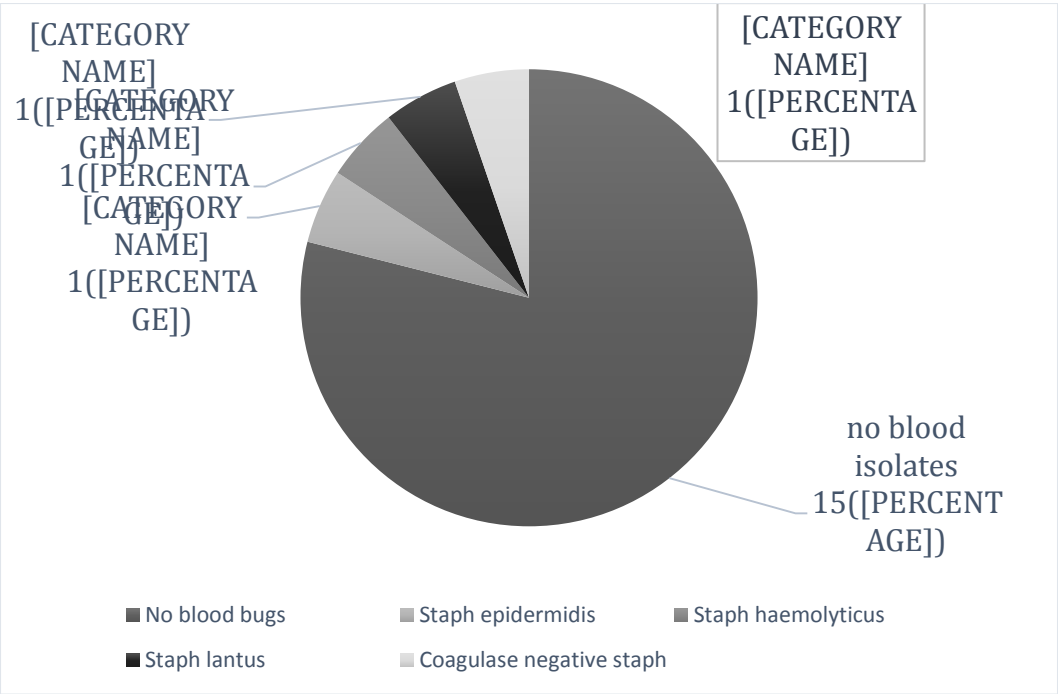


Figure 5: Bacteria isolated from blood cultures

Among the 56 neonates with prolonged jaundice, 27(48%) had TORCHES tests done, of which, 2 (7.4%) and 1 (3.7) had positive Toxoplasma-IgG and Toxoplasma-IgM results respectively. There were 8 (30%) and 12 (44%) Rubella-IgG and Rubella-IgM positive results respectively. A total of 12 (44%) and 5 (19%) neonates had positive CMV-IgG and CMV-IgM results respectively. There were 2 (7.4%) neonates with positive Herpes-IgG results. No neonate had a positive Herpes-IgM, Syphilis-IgG, Syphilis-IgM (Table 6).

Triple serology tests were done for 29 (52%) neonates, of which 1(3.5%) and 1 (3.5%) had positive Hepatitis B-Ag(antigen) and Hepatitis B-Ab(antibody) respectively, none had positive Hepatitis C-Ag or Ab result. Only one (1.8%) of the neonates had positive HIV results (Table 7).

Table 6: TORCHES screen done among 56 neonates with prolonged jaundice

TORCHES done	N = 27
Toxoplasma-IgG	
Positive	2 (7.4)
Negative	20 (74)
Missing data	5 (18.6)
Toxoplasma-IgM	
Positive	1 (3.7)
Negative	21 (78)
Missing data	5 (18.6)
Rubella-IgG	
Positive	8 (30)
Negative	15 (56)
Missing data	4 (14)
Rubella-IgM	
Positive	3 (11)
Negative	19 (70)
Missing data	5 (18.6)

CMV-IgG	
Positive	12 (44)
Negative	9 (33)
Missing data	6 (23)
CMV-IgM	
Positive	5 (19)
Negative	15 (56)
Missing data	7 (25)
Herpes-IgG	
Positive	2 (8)
Negative	18 (67)
Missing data	7 (25)
Herpes-IgM	
Positive	0
Negative	20 (74)
Missing data	7 (26)
Syphilis-IgG	
Positive	0
Negative	24 (89)
Missing data	3 (11)
Syphilis-IgM	
Positive	0
Negative	24 (89)
Missing data	3 (11)

Table 7: Triple serology screen done among the 56 neonates with prolonged jaundice

Triple serology done	***N = 29***
Hepatitis C - Antigen	
Positive	0
Negative	28 (97)
Hepatitis C - Antibody	
Positive	0
Negative	27 (93)
Hepatitis B- Antigen	
Positive	1 (3.5)
Negative	28 (97)
Hepatitis B- Antibody	
Positive	1 (3.5)
Negative	26 (90)
HIV status	
Positive	1 (1.8)
Negative	36 (64)

Table 8: Abdominal ultrasound and liver biopsy done in neonates with prolonged jaundice

Investigations	Prolonged jaundice (N=56)
Abdominal U/S done	
Yes	33 (59)
No	23 (41)
Liver biopsy done	
Yes	5 (8.9)
No	51 (91)

Among the 56 neonates with prolonged jaundice, 33 (59%) had Abdominal U/S tests done, and biliary atresia noted in 7 (13%). Liver biopsy was done for 5 (8.9%) patients (table 8). The main reason of doing the above tests was to rule out biliary atresia. Other diagnoses given were not recorded.

6.4 Possible Aetiology Recorded For Patients With Prolonged Neonatal Jaundice

Aetiology was determined by the diagnosis given according to the doctors' notes in collaboration with the results of the investigations recorded above. Most common diagnosis assigned included: viral hepatitis 14 (25%), bacterial sepsis 13(23%), 3 (5%) Cholecystitis and 4 (7%) Breastfeeding jaundice (Figure 6). Biliary atresia reported in 7(13%) of patients who had either diagnosis from abdominal ultrasound or liver biopsy. 12 (21%) of patients had no known diagnosis.

Alagille syndrome, downs syndrome and breastfeeding jaundice were among the diagnoses recorded as per expert consultants' opinion. No specific tests were recorded to prove these diagnoses.

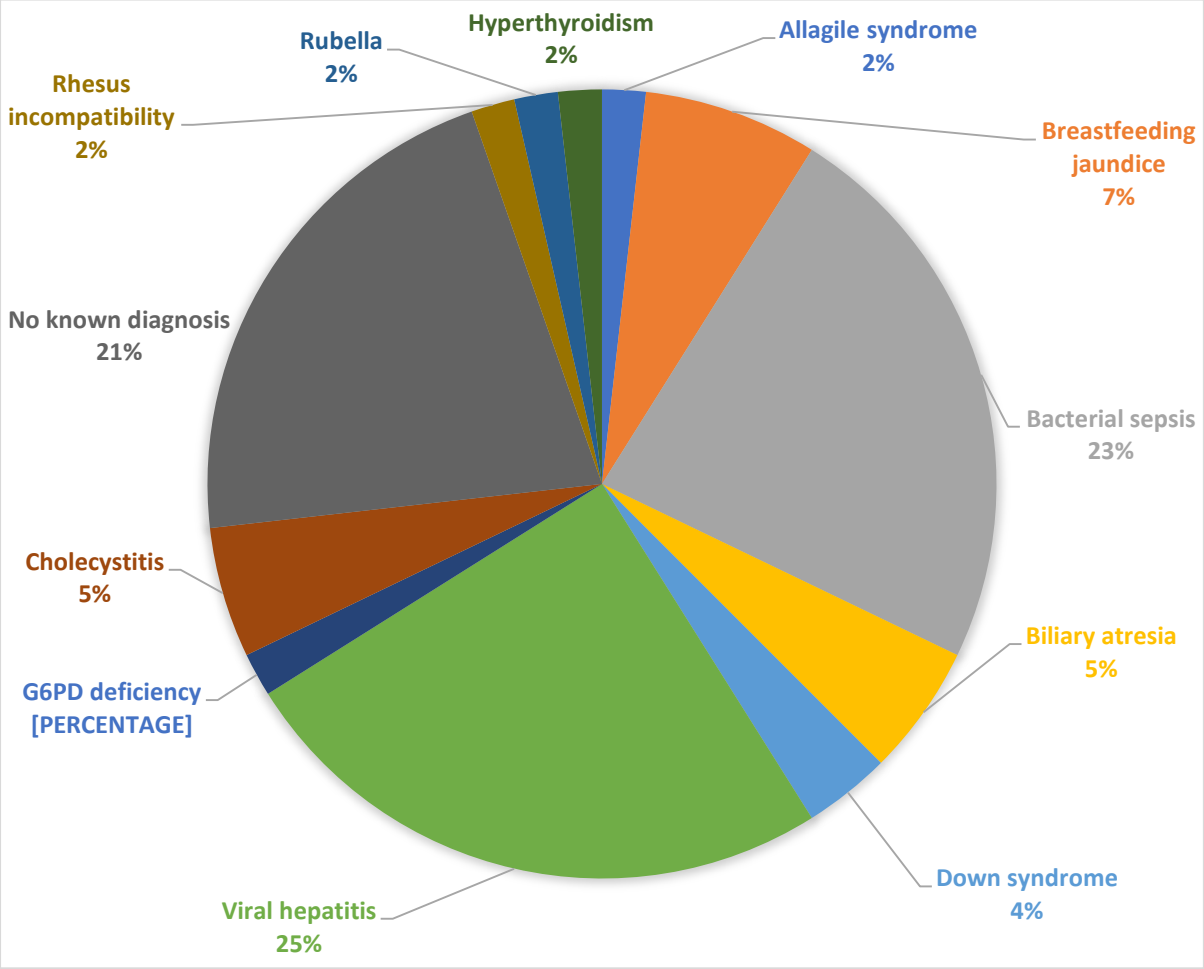


Figure 6: List of diagnoses associated with prolonged neonatal jaundice (N=56)

6.5 Hospital Discharge Outcomes

Of the 360 neonates enrolled to the study, 328 (91%) were discharged home while 32 (8.9%) neonates died. The age of onset of jaundice was noted to be much later, median of 7 (2-6) days, in patients who were discharged home, while for those who died at first admission, jaundice was noted much earlier, median 1(1-6) days. Among the 67 preterm; 8 (12%) died and from the 293 term neonates; 24 (8.2%) died. From the 56 neonates with prolonged jaundice, 5 (8.9%) died while 27 (8.9%) among the 304 neonates without prolonged jaundice died. In the preterm neonates, distribution of deaths between those with and without prolonged jaundice did not differ; 1 (13%) and 7 (12%) respectively, P=0.96. While in the term neonates, 4 (8.3%) and 20 (8.2%) neonates with and without prolonged jaundice died respectively, P=0.97. Among neonates with prolonged jaundice, there was minimal difference between those discharge home and those who died with regards to their gender (P=0.16), gestation age in weeks (P=0.88) and time with jaundice (p=0.58) **Table 9**

Table 9: Short-term outcomes of patients with neonatal jaundice

	Discharged home (N=51)	**Died (N=5)**	**P-value**
Age when jaundice noted in days#	7 (2-6)	1 (1-6)	0.27
Gender-Female	23 (85)	4 (15)	0.16
Male	27 (96)	1 (3.6)	
Gestation in weeks#	38 (37-38)	38 (38-38)	0.88
Born preterm	7 (88)	1 (12)	0.55
Born term	44 (92)	4 (8)	
Time with jaundice in days#	43 (25-99)	32 (30-34)	0.58
#-results presented as median (IQR), P-values of variables with median are from Wilcoxon ranksum test, the rest are from Fisher's exact test.			

7 DISCUSSION

In this descriptive, retrospective study, the prevalence of prolonged neonatal jaundice was at 16% of all neonates admitted with jaundice. The general characteristics of patients did not vary much among those with prolonged and non-prolonged jaundice nonetheless, this study was not powered to make statistically significant comparisons. A brief description of laboratory and radiological investigations was carried out and it was noted that none of the patients had a full work-up even from baseline tests required, thus it was only possible to give a summary of the work-up done. Expert opinion had to be included to get the diagnoses in each case so as to be able to analyze the aetiology. Mortality was calculated to be 8.9% of all patients with prolonged neonatal jaundice.

The prevalence of prolonged neonatal jaundice, being at 16% (95% CI 12 to 20%) of all patients admitted with neonatal jaundice at Kenyatta National Hospital, was comparable to previous studies. A study done in North America found prevalence of 21%(13) whereas Chaudhary et al (2006) in Eastern Nepal found prevalence to be 9.2%(21). In Africa, Olusanya et al (2009) in Nigeria, reported that 6.7% of all newborn babies had prolonged neonatal jaundice(23). We also noted that preterm babies had prevalence of 12% (95% CI 5.2 to 22%) and term neonates of 16% (95% CI 12 to 21%). There was minimal difference in prevalence of prolonged neonatal jaundice among term and pre-term babies. We did not find any study to compare that finding.

There was no difference in male: female ratio in the neonates admitted with prolonged neonatal jaundice. This was also comparable to studies done in Iran(4) by Sana Ullah et al, where no difference in gender was reported. The mean age at which jaundice subsided was 49days with inter-quantile range of 30 – 120days, which was also the case

in Nepal(21) and Iran(41) where infections played a significant role as a cause of prolonged neonatal jaundice. It was also reported by Gundur et al in northern India(36), prolonged jaundice subsided by 5weeks in almost all cases admitted to their tertiary level hospital.

Clinical evaluation to be done for prolonged neonatal jaundice have been outlined in the ESPGHAN and NASPGHAN guidelines. This study aimed to review tests done from the first tier of investigations and evaluate the results.
The laboratory investigations done in the study group was varied, with almost all neonates having full blood count and liver function tests done. The remaining tests were done in less than 50% of patients with prolonged neonatal jaundice. Lack of local guidelines to assist in evaluating these patients and also lack of resources to perform certain tests like TORCHES screen in full, urine reducing sugars which were supposed to be sent to outside laboratories and financial implications on the patients' guardians, were all attributed to hinder full evaluation.

The main radiological investigation done was abdominal ultrasound, in 33 (59%) of patients in the study group. Of these, 7 (13%) had confirmed biliary atresia. Liver biopsy noted to be done in only 5patients. This was due to the fact that only stable patients with no known diagnosis and were financially able to cater costs were taken for liver biopsy.

A descriptive analysis of the results of investigations was done. For complete blood count, 7(14%) were noted to have leucopenia and 11(21%) with leukocytosis. In the literature by ESPGHAN, these were reported to be associated with poor outcomes in neonates with prolonged jaundice(21). In the study group selected, 48 (91%) of patients had cholestatic or mixed hyperbilirubinemia. This is very different from studies done in North America, described by American Academy of Pediatrics(AAP)(2) and also by Scrafford et al in Nepal (15) where they noted unconjugated hyperbilirubinemia to be comprising of more than 90% of all patients with prolonged jaundice. Another study done in Hong Kong by Siu et al(3) reported 1.4% of all patients with prolonged jaundice had cholestatic jaundice. This could be attributed to the study site, being a referral center, the stable neonates with prolonged unconjugated jaundice were possibly not referred. We could only take into account those neonates with unconjugated hyperbilirubinemia, admitted directly to KNH from home.

The other liver functions like coagulation profile, albumin levels and blood sugars were noted to be done in less than 50% of patients. INR was prolonged in 10 (37%) of patients, indicating features of liver failure and poorer outcomes. This was mentioned in an article by Wadhwani from the United States(38). A full analysis was not possible as not all patients with prolonged jaundice had the tests done, therefore results were not compared to any other studies done previously.

The insufficient evaluation may have an implication on accuracy of results and the possible aetiology reported in this study. Nonetheless a strong point is that the recorded

aetiology taken into account was made by the Paediatric Gastroenterologist on board, so it was assumed to be accurate.

In developed countries, biliary atresia reported to be most common cause of prolonged jaundice, followed by inherited syndromes(1). Viral infections comprised of minimal percentage of reported causes(16), whereas in some developing countries like Sarlahi in Nepal reported their cultural practices to be causing prolonged jaundice(15). In yet another category of countries including Nigeria and Iran, revealed the main cause of prolonged neonatal jaundice attributed to bacterial infections, especially urinary tract infections with E. Coli(42)(18). In Egypt, study done at a university hospital revealed CMV and Reovirus being attributed to cholestatic jaundice in neonates (19).

In this study, the cause of prolonged neonatal jaundice was majorly attributed to viral hepatitis. This was based on positive IgG or IgM titers on the TORCHES screen done, in absence of any other possible cause from other tests done. The main viruses reported positive were CMV in 12(44%) and rubella in 8(30%).
This was followed by bacterial sepsis (23%) from either neonatal sepsis or underlying UTI. Full description of bacteria isolated was not possible but from the patients who had cultures done, the main isolates included staphylococcal species, E.Coli, Klebsiella Pneumonia and Enterococcus.

From the study group, 21% had no known cause. Lack of full evaluation could be an attributing factor, in addition to idiopathic neonatal jaundice. Biliary atresia, breastfeeding jaundice, cholecystitis, G6PD deficiency on the other hand only accounted for 5%, 7%, 5% and 2% respectively.

From urine cultures, the main isolates were E.Coli, Klebsiella and Enterococcus at roughly similar percentages of 15%, 14% and 14% respectively. This result could vary if 100% of patients had urine cultures done, instead of the reported only 25% of study participants having the test done. Blood cultures were done on 34% of patients and main causative organism reported to be Staphylococcal spp. The bacterial isolates noted were comparable to studies done in other developing countries like Nepal, New Zealand and Iran(18)(33)(41)

The survival of patients with prolonged neonatal jaundice reported to be good, with estimates of 70%-90% in various studies(10) with good supportive care and timely management of treatable causes, whereas noted to be as low as 10% if not intervened within first 60days of life(31).
In this study, 91% of neonates were discharged home for follow up and 8.9% died at first admission. This may not be accurately comparable to other studies since all other studies reviewed long term outcomes for 2-15 years of age. This study was looking at short-term outcome, at first admission. We were not able to review any study done on short-term outcomes from the database searched.

The total number of patients with prolonged jaundice, who died was 5 (8.9%). There was a similar finding noted in patients with non-prolonged jaundice, in whom 27(8.9%)

died. Among patients with prolonged jaundice, there was no difference between those discharge home and those who died with regards to their gender (P=0.16) or gestation age in weeks (P=0.88).

However, neonates in whom jaundice was noted at a very young age were more likely to die compared to those who started developing jaundice at later age in days; median (IQR) of 1 (1 – 6) Vs. 7 (2 – 6) respectively, P=0.007. This was attributed to worse clinical condition or co-morbidities of patients presenting early in the course of disease compared to those presenting at a later age in days.

Study limitations:

The main study limitations encountered during this study were:

- Missing data on laboratory and radiological tests done, with results. This was analysed as a separate category for tests in which this was a major concern, including TORCHES screen and triple serology.
- None of the study participants had a full list of baseline investigations done and this had a major impact on looking for aetiology of prolonged jaundice. This was improved by including diagnoses made by expert opinions and later follow-up reviews. This had an impact on finding out causes of prolonged jaundice in the patients who died, though it was not in the scope of this study.
- I did not collect actual data on which ward the patient was admitted at KNH and so could not account on how many patients were enrolled from each ward of interest.
- Some missing files were noted but since the sample size was exceeded, it did not make a major impact on study objectives to be analysed.
- This study was looking at short-term outcomes of patients with prolonged neonatal jaundice. There were no studies noted for comparison as most studies looked at long term survival. This objective could only be described and not be compared with other studies.

8 CONCLUSION

i) The prevalence of prolonged neonatal jaundice was high at 16%. There was no male or female predilection.
ii) Majority of the patients did not have the full evaluation done as per tier 1, with only 3.5% of patients noted to have full work up with results. Missing data on results of investigations also contributed to this.
iii) The most common cause was noted to be viral hepatitis especially CMV and rubella, followed by bacterial sepsis.
iv) The patients discharged home were noted to be >90%, with a high mortality of 8.9% of neonates with prolonged jaundice. The patients with early onset had a higher chance of dying than those who had a later onset of jaundice in days.

9 RECOMMENDATIONS

- Patients with prolonged neonatal jaundice should be fully evaluated to be able to get accurate diagnoses.
- Currently available international guidelines should be followed closely so as to ascertain the aetiology better, before being able to evaluate the disease further.
- Availability of basic tests like TORCHES screen in full, urine reducing sugars within the hospital at all times to be able to evaluate patients more accurately.
- Further analysis needs to be done into this topic, after above recommendations have been instituted, to be able to come up with Kenyan guidelines of clinical evaluation and management of prolonged neonatal jaundice.

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11 APPENDICES

The following are my study budget, time-frame and data abstraction tools used during this process.

11.1 Data abstraction form.

Characteristic		
age	months	<14days/21days
	days	>14days/21days
gestation	At birth	At presentation
	Preterm - term-	
sex	male	female
Age at which jaundice noted	Days	Prolonged-
Age of jaundice subsided	Days	Non-prolonged
Investigations done		
Total blood count done	YES	NO
	WBC -	Hb -
Liver function tests done	YES	NO
	Serum bilirubin-	Direct bilirubin -
Urinalysis done	YES	NO
	Nitrites -	Leucocytes -
Urine culture done	YES	NO
Bugs isolated		
Blood glucose done	YES	NO
INR Done	YES	NO
Result	NORMAL	ABNORMAL
Thyroid function test done	YES	NO
	TSH levels	T4 levels
Blood culture done	YES	NO
Bugs isolated		
Urine reducing sugars done	YES	NO
Result		
Albumin level done	YES	NO
	Normal	Abnormal
TORCHES done	YES	NO
Toxoplasma	IgG	IgM
Rubella	IgG	IgM
CMV	IgG	IgM
Herpes	IgG	IgM
Syphilis	IgG	IgM
Triple serology done	YES	NO
Hepatitis A	IgG	IgM
Hepatitis B	IgG	IgM
HIV		
Radiological investigations		
Abdominal U/S done	YES	NO
Biliary atresia	yes	no
Liver biopsy done	YES	NO
Others		
Diagnoses	1) 2) 3)	
Outcome	Discharged home	Death

11.2 Time frame- Starting from December 2017 – May 2019

Activity	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Proposal Development and Presentation	■	■																
Submission of proposal for ethical approval			■	■	■	■	■	■	■									
Pretesting and seeking permission										■	■	■						
Data Collection													■	■				
Data Analysis														■	■	■		
Thesis writing																	■	■
Thesis submission																		■

11.3 Study budget.

Category	Remarks	Units	Unit Cost (KShs)	Total (KShs)
Proposal Development	Printing drafts	500 pages	5	2,500
	Proposal Copies	10 copies	350	3,500
Data Collection	Stationery Packs (Pens, Paper and Study Definitions)	10	100	1000
	Research assistant	8 weeks	1000	8, 000
Data Analysis	Statistician	1		30,000
Thesis Write Up	Computer Services			5,000
	Printing drafts	1000 pages	5	5,000
	Printing Thesis	10 copies	500	5,000
Contingency funds				20,000
Total				**80,000**

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20th February, 2019

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KENYATTA NATIONAL HOSPITAL APPROVED 20 FEB 2019 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI

Dear Dr. Hassan

RESEARCH PROPOSAL – PREVALENCE AND CLINICAL CORRELATES OF PROLONGED NEONATAL JAUNDICE AMONG NEONATES WITH JAUNDICE AT KENYATTA NATIONAL HOSPITAL (P685/09/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 20th February 2019 – 19th February 2020.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Protect to discover

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

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The Director, CS, KNH
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