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Prevalence and factors associated with hyperbilirubinemia and the utility of transcutaneous bilirubin among neonate admitted to Bugando Medical Centre, Mwanza-Tanzania

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Abstract*:* *Background:* Neonatal hyperbilirubinemia can result into clinical jaundice and progress to kernicterus that significantly increases the risk of morbidity, long-term disabilities and mortality. Transcutaneous bilirubin (TcB) is a non-invasive screening tool, which serves as a guide to prompt initiation of treatment. However, TcB has not been extensively used in low-income countries (LIC).
Methods: This hospital-based cross-sectional study was conducted in order to determine the prevalence, factors associated with hyperbilirubinemia and utility of TcB among newborn babies admitted to Bugando Medical Centre, Mwanza-Tanzania. Pre-tested questionnaire was used to collect socio-demographic, maternal and neonates information. Blood sample was drawn from the neonates for total serum bilirubin (TSB) measurement, blood culture, complete blood count and blood grouping. TcB measurements were done using JM105 Dragger machine. Data was analyzed using STATA software version 13.
Results: Out of 389 neonates, 153 (39.3%) had neonatal hyperbilirubinemia. Neonates aged 2 – 7 days (p-value 0.031), whose mothers had prolonged labor (p-value 0.029) and mothers who used herbal medicines during pregnancy (p-value 0.002) were associated with neonatal hyperbilirubinaemia. TcB had sensitivity of 87.6% and specificity of 95.7%. There was a statistically significant linear correlation between TSB and TcB (r=0.89; p-value<0.001).
Conclusion: The observed high prevalence of hyperbilirubinemia is alarming and was associated with herbal medicine use during pregnancy, prolonged labour and it occurred mostly in neonates aged 2-7 days. TcB should be used in screening neonates for hyperbilirubinemia to guide prompt initiation of treatment.

Keywords: neonates, hyperbilirubinaemia, transcutaneous bilirubin

Résumé: ***Contexte***: L'hyperbilirubinémie néonatale peut entraîner un ictère clinique et évoluer vers un ictère nucléaire qui augmente considérablement le risque de morbidité, d'handicap à long terme et de mortalité. La bilirubine transcutanée (BTc) est un outil de dépistage non invasif qui permet d'initier rapidement un traitement. Cependant, la BTc n'a pas été largement utilisée dans les pays à faible revenu.
Méthodes: Il s'agit d'une étude transversale en milieu hospitalier, menée dans le but de déterminer la prévalence, les facteurs associés à l'hyperbilirubinémie et l'utilité de la BTc chez les nouveau-nés admis au centre médical de Bugando, à Mwanza, en Tanzanie. Un questionnaire pré-testé a été utilisé pour recueillir des informations sociodémographiques, maternelles et néonatales. Un échantillon de sang a été prélevé chez nouveau-nés pour mesurer la bilirubine sérique totale (BST), l'hémoculture, l'hémogramme et le groupage sanguin. La mesure de la BST a été effectuée à l'aide de l'appareil JM105

Dragger. Les données ont été analysées à l'aide du logiciel STATA version 13.
Résultats: Sur 389 nouveau-nés, 153 (39,3 %) présentaient une hyperbilirubinémie néonatale. Les nouveau-nés âgés de 2 à 7 jours (p= 0,031), dont les mères ont eu un travail prolongé (p= 0,029) et les mères qui ont utilisé des médicaments à base de plantes pendant la grossesse (p= 0,002) étaient associés à l'hyperbilirubinémie néonatale. LaBTc avait une sensibilité de 87,6 % et une spécificité de 95,7 %. Il existait une corrélation linéaire statistiquement significative entre la BST et la BTc (r=0,89 ; p-value<0,001).
Conclusion: La prévalence de l'hyperbilirubinémie observée est alarmante. Elle est associée à l'utilisation de médicaments à base de plantes pendant la grossesse, à un travail prolongé, et est survenue principalement chez les nouveau-nés âgés de 2 à 7 jours. LaBTc devrait être utilisée pour dépister l'hyperbilirubinémie chez les nouveau-nés afin d'initier précocement un traitement.

Mots-clés : Nouveau-nés, hyperbilirubinémie, bilirubine transcutanée

Introduction

Neonatal hyperbilirubinemia, occurs when total serum bilirubin level (TSB) is above 5 mg per dl (86 µmol per L) and it occurs in 60% of term and 80% of preterm-infants in the first week of life. [1,2] It can progress to severe hyperbilirubinemia and hence lead to kernicterus which accounts for 70% morbidity and 10% mortality globally.[3] About 5% of neonates develop a significantly high bilirubin levels (more than 17mg/dl) whereas 1.2% develop severe neonatal hyperbilirubinemia (TSB >20mg/dl).[4]
Recent global and regional estimates report that Sub Saharan Africa (SSA) and South Asia respectively have the highest burden among low income countries.[5] Neonates surviving from severe hyperbilirubinemia may acquire long term neuro-developmental sequelae such as cerebral palsy, sensory neural hearing loss, intellectual difficulties, and developmental delay.[6]
Neonatal hyperbilirubinemiahas been found to be associated with maternal illness during pregnancy, use of oxytocin during labour, prematurity, neonatal sepsis, Rhesus (Rh) and ABO incompatibility, cephalohematoma and inadequate or delayed exclusive breastfeeding.[7,8] Phototherapy is the most available treatment to reduce bilirubin levels in these infants and hence protect these neonates for the effects of kernicterus [9] with an absolute risk reduction of 10% to 17% in neonates with TSB level of >20mg/dl.[10]
Total serum bilirubin is the gold standard measure of hyperbilirubinaemia, though transcutaneous bilirubin (TcB) has been suggested to be a potential non-invasive alternative screening tool [11] with a good correlation between TSB and TcB.[10,12] There are limited African studies on accuracy of TcB, with two studies reporting to overestimate TSB in African neonates.[13,14] Hence this study aimed to provide information on the prevalence and associated factors of neonatal hyperbilirubinaemia as well as utility of TcB in our setting so as to facilitate its usage to enable prompt management of neonates with jaundice.

Materials and Methods

Study design and study area

This cross-sectional study was conducted in neonatal wards at Bugando Medical Centre (BMC) in Mwanza-Tanzania from December 2018 to April 2019. BMC is a teaching and referral hospital for the lake and western zones of the United Republic of Tanzania with 1,200 beds and serves a catchment population of above 13 million people.

Sample size

The minimum sample size of 389 was calculated by Bruderer's formula for utility of TcB using the sensitivity and specificity obtained from the study done in Zimbabwe.[14]

Study Population

We included all admitted neonates with birth weight of 1.5 kgs or more, whose mothers consented to participate in the study. Those with birth weight below 1.5kg were excluded because they had high chance of having neonatal hyperbilirubinaemia and frequent drawing of blood could increase their chance of being anaemic.

Data Collection

We used a structured questionnaire to collect social demographic data and other relevant information from the mother and neonate. A thorough general and systemic examination was carried out for each neonate. We measured the TcB level using a JM 105 Dragger bilirubin meter at bedside. Measurements were taken from the forehead. Gentle pressure was applied with the fiber optic probe placed against the forehead to exert even contact and results were recorded. We assessed the sensitivity, specificity, positive and negative predictive values of TcB versus TSB to determine the utility of transcutaneous bilirubin.

Laboratory Procedures

Four mls of blood was drawn for TSB, complete blood count (CBC), blood grouping and for blood culture and sensitivity. TSB was measured by the Cobas integras 400 Plus machine using diazo method where by diazosulfanilic acid was mixed with neonatal serum and diazo reagent forming azobilin. The increase in absorbance at 552nm was directly proportion to the total bilirubin concentration. Blood samples were protected from direct light, as bilirubin is photo labile. Serum bilirubin >5mg/

dl was considered as hyperbilirubinemia and severe hyperbilirubinemia when TSB was >20mg/dl.
A drop of blood from red top tube was placed in a white tile for blood grouping using a tile method. A drop of each antisera, anti A, anti B, and anti D was added and mixed with each blood sample with the aid of glass rod. Blood group was determined on the basis of agglutination. For mothers whose blood group was not known, blood sample was drawn for grouping using the same method.

About 1ml of blood was collected in a purple test tube containing the Ethylene Diamine Tetra Acetic Acid (EDTA). Blood was thoroughly mixed with EDTA anticoagulant and thereafter cell counts were measured using the cell Dyne 3700 machine (Abbot diagnostic).
Two mls of blood were placed into Brain Heart Infusion broth (BHI) in a ratio of blood: BHI of 1:10 and transported to the microbiology laboratory for incubation and subsequent processing. After 24 hours of incubation, aerobic and anaerobic cultures were done for 7 days and reports of culture and susceptibility testing were made available to clinicians in the ward and recorded by the researcher for data analysis.
We defined neonatal sepsis as a clinical syndrome characterized by signs and symptoms of infection, with or without accompanying bacteremia or positive blood culture results in the first month of life. Prolonged labour was considered when the mother had duration of labour of more than 14 hours as observed from the patograph or reported by the mother. Delayed breastfeeding was determined when neonates were initiated breastfeeding or expressed breast milk after 24 hours.

Data Management

Data from coded questionnaire was entered into data entry screens using EPIDATA version 3.02. The PI carried out cleaning and checking for any inconsistencies. The final data set was exported to STATA version 13-computer software package for analysis. The main outcome variable was total serum or transcutaneous bilirubin levels while independent variables were socio demographic, maternal and neonatal factors. Data was analyzed using STATA software version[13]. Factors associated with hyperbilirubinemia were analyzed by univariate logistic regression followed by multivariate logistic regression model. Odds ratios (OR) and 95% confidence intervals (CI) were computed. Factors with a p-value <0.05 was considered statistically significant.

Ethical Consideration

Ethical clearance was sought from the joint CUHAS/ BMC Research Ethics and Review Committee with clearance certificate number CREC/322/2018. Prior to recruitment, the purpose of the study was explained to the participant's mother. Consent forms were signed prior to their involvement in the study. Confidentiality was assured and important findings were shared with clinicians who were attending those with hyperbilirubinemia to guide them on appropriate management.

Results

During the study period, a total of 746 neonates were admitted to our neonatal wards. We excluded 150 neonates who were admitted for observation and 144 premature with birth weight below 1.5kg. Among the remaining 452 (60.6%) neonates, 42 (9.3%) neonates did not meet the inclusion criteria. Twenty-one (4.6%) of the remaining 410 neonates' mothers did not consent. We therefore remained with 389 (86.1%) neonates in this study (Fig 1).

Socio-demographic characteristics

Of the 389 study participants, 198 (50.9%) were males with the male to female ratio of 1:1 while 266 (68.4%) were aged 2-7 days with the median age of 2 days and interquartile range of 2 – 4 days. The mean birth weight was 2.98 (SDV ± 0.77) kg. The mother's mean age was 27 (SDV± 6.10) years while 341 (87.7%) mothers were in the age group of less than 35 years (Table 1).

Maternal and Neonatal Clinical Characteristics

Mothers who used oxytocin during delivery were 105 (27.0%), while 93 (23.9%) mothers used local herbs during pregnancy and 10 (2.6%) had prolonged labour. Among 389 neonates, the most common presenting symptom was difficulty in breathing 145 (37.3%), followed by fever 92 (23.7), delayed breastfeeding 84 (21%) and 28 (7.2%) neonates had clinical jaundice. Blood cultures were positive in 65 (16.7%) neonates (Table 2).

Fig 1: Flow chart of the study participants

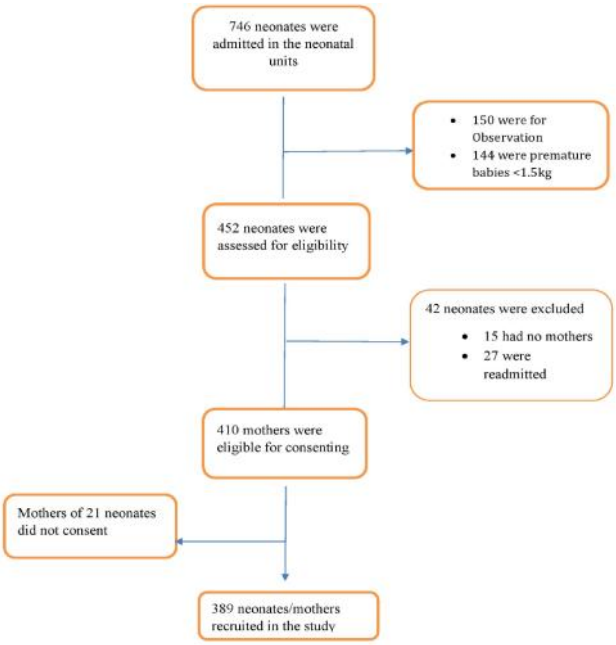


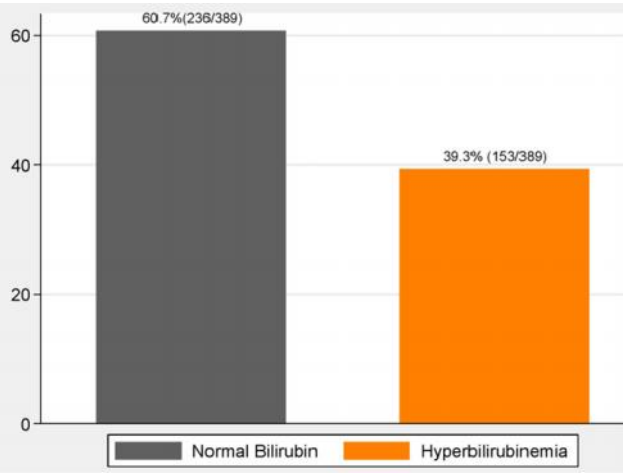
Table 1: Socio-demographic Characteristics among Neonates and Nursing Mothers at Bugando Medical center (N=389)

Variables	Number (n)	Percent (%)
Neonatal characteristics		
Age (days)		
Within a day (1)	72	18.5
2 – 7	266	68.4
>7	51	13.1
Birth Weight (kg)		
Low (1.5-2.4)	87	22.4
Normal (2.5-3.9)	266	68.4
Above normal (≥4)	36	9.3
Sex		
Male	198	50.9
Female	191	49.1
Maternal characteristics		
Age of mother (years)		
Less than equal to 35	341	87.7
Greater than 35	48	12.3

Table 2: Distribution of Clinical Characteristics Data of 389 mothers and neonates

Variable	Number (n)	Percent (%)
Maternal characteristics		
Maternal diabetes	6	1.5
Maternal oxytocin use	105	27
Herbal use during pregnancy	93	23.9
Prolonged Labour	10	2.6
Blood Group		
A	77	19.8
B	53	13.6
AB	47	12.1
O	212	54.5
Neonatal characteristics		
Cephalohematoma	11	2.8
Delayed Breast Feeding	84	21.5
Fever	93	23.7
Jaundice	28	7.2
Pallor/anemia	14	3.8
Temperature (^0C)		
<38	352	91.0
>38	37	9.0
Positive blood culture results	65	16.7

Fig 2: Prevalence of Hyperbilirubinemia among 389 neonates



Prevalence of Hyperbilirubinemia among neonates admitted to BMC

Among neonates who were evaluated for TSB, 153 (39.3%) [95% CI; 34.5% – 44.2%] had hyperbilirubinemia (TSB >5mg/dl) (Figure 2) while 6 (3.9%) of them had severe hyperbilirubinemia (TSB >20mg/dl). Among the 153 neonates who had hyperbilirubinemia, 49(32%) neonates were treated with phototherapy based on BMC protocol.

Factors associated with hyperbilirubinemia among neonates admitted to BMC

In univariate analysis, neonates aged 2–7 days had 1.9 higher odds of hyperbilirubinemia compared with neonates aged 1 day (OR: 1.9; 95% CI: 1.1 – 3.3; p-value 0.029). In multivariate analysis, after adjusting for other factors this factor remained statistically significant (OR: 2; 95% CI: 1.1 – 3.7; p-value 0.031). Neonates whose mothers had prolonged labour had 5.5 times higher odds of hyperbilirubinemia compared with those without prolonged labour on multivariate analysis (OR:5.5; 95% CI:1.2 – 25.7; p-value 0.029). Herbal medication during pregnancy was statistically significantly associated with hyperbilirubinemia in both univariate and multivariate analysis, in that, neonates of mothers who used herbal medicines had 3.2 times higher odds of developing neonatal hyperbilirubinemia (OR: 3.2; 95% CI: 1.6 – 6.7; p-value 0.002) (Table 3).

Utility of Transcutaneous Bilirubin in diagnosing neonatal hyperbilirubinemia

In this study, we found a high positive linear correlation between TSB and TcB. This relationship was statistically significant (r=0.89, p-value<0.001) (Figure 3).
Sensitivity, specificity, positive and negative predictive value of transcutaneous bilirubin (TcB) levels
In this study, TcB had shown the sensitivity of 87.6% [95% CI; 82.2% – 92.8%] and the specificity of 95.7% [95% CI; 93.2% – 98.3%] in detecting hyperbilirubinemia. The Positive and Negative Predictive Values were 93.0% [95% CI; 88.9% – 97.2%] and 92.2% [95% CI; 88.9% – 95.6%] respectively. The accuracy was 92.5% [95% CI; 89.9% – 95.2%].

Fig 3: Scatter diagram of TSB against TcB Test

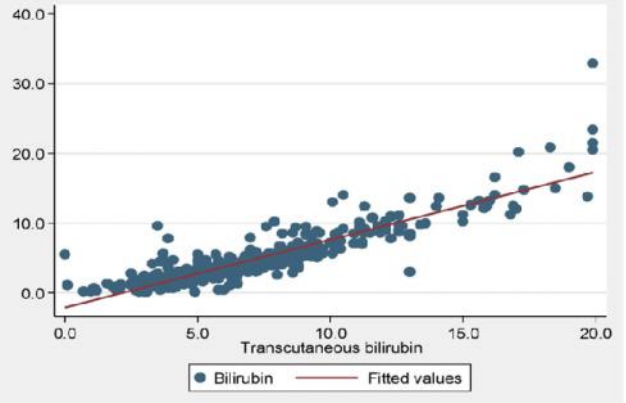


Table 3: Social Demographic, Maternal and Neonatal Factors associated with Hyperbilirubinemia at Bugando Medical Centre (N=389).

Variables	Hyperbilirubinemia		Univariate		Multivariate	
	Yes N (%)	No N (%)	OR [95%CI]	p- value	OR [95%CI]	p-value
Neonatal Age (days)						
Within 1 day	20 (27.8)	52 (72.2)	1.00		1.0	
2-7	112 (42.1)	154 (57.9)	1.9 [1.1 –3.3]	0.029	2.0 [1.1 – 3.7]	0.031
Above 7 days	21 (41.2)	30 (58.8)	1.8 [0.9 –3.9]	0.122	2.1 [0.8 – 4.6]	0.116
Birth weight (Kg)						
Low (1.5-2.4)	41 (47.1)	46 (52.9)	1.0		1.0	
Normal (2.5-3.9)	96 (36.1)	170 (63.9)	0.6 [0.4 – 1.0]	0.068	0.8 [0.4 – 1.8]	0.682
Above normal(>3.9)	16 (44.4)	20 (55.6)	0.9 [0.4 – 2.0]	0.786	1.4 [0.5 – 3.7]	0.509
Labour Duration (hours)						
Not recorded	33 (35.1)	61 (64.9)	1.0			
Above 14 hours	7 (70.0)	3 (30.0)	4.3 [1.1 – 17.8]	0.043	5.5 [1.2─25.7]	0.029
Below 14 hours	113 (39.6)	172 (60.4)	1.2 [0.8 – 2.0]	0.433	1.6 [0.9 – 2.7]	0.125
Mode of delivery						
C/S	74 (38.5)	109 (59.6)	1.0			
SVD	79 (38.5)	127 (61.5)	0.9 [0.6 – 1.4]	0.674	0.9 [0.5 – 1.4]	0.640
ABO incompatibility						
No	148 (39.1)	231 (61.0)	1.0			
Yes	5 (50.0)	5 (50.0)	1.5 [0.4 – 5.5]	0.492	1.7 [0.5 – 6.4]	0.417
Herbal medication						
No	111 (37.5)	185 (62.5)	1.0			
Yes	42 (45.2)	51 (54.9)	1.4 [0.9 – 2.2]	0.188	3.2 [1.6 – 7.1]	0.002
Cephalohematoma						
No	5 (45.5)	5 (54.6)	1.0			
Yes	6 (54.6)	230 (60.9)	1.3 [0.4 – 4.3]	0.679	1.1 [0.3 – 4.4]	0.888
Neonatal sepsis						
No	84 (38.9)	132 (61.1)	1.0			
Yes	69 (40.6)	101 (59.4)	1.1 [07 – 1.6]	0.735	1.1 [0.7 ─1.7]	0.663

Discussion

The prevalence of neonatal hyperbilirubinemia was 39.3% in our study.This was consistent with studies which were conducted in Southern Nigeria and Ethiopia which reported the prevalence of 35% and 37% respectively.[8,16] However, our prevalence was lower compared to the study which was done in Bloemfontein, South Africa which showed high prevalence of 55.2%.[17] The reason may be explained by the fact in South Africa they used TcB, which has been reported to overestimate hyperbilirubinaemia unlike our study which measured TSB level. Another study, which was done in Malaysia, showed low prevalence (16.4%) of hyperbilirubinemia.[18] The observed difference could be explained by the fact that they included neonates who had clinical jaundice only and it was a prospective cohort study which was different from our study. Neonatal hyperbilirubinemia is extremely common because almost every neonate develops unconjugated serum bilirubin during their first week of life, and occurs due to breakdown of red blood cells (RBC) in order to acquire the adult hemoglobin level.[1,2]The current study also revealed the presence of severe neonatal hyperbilirubinemia being 1.5%, similar with the study which done in Italy which reported 1.2%.[19]

In this study, 42.1% of neonates developed neonatal hyperbilirubinemia on day 2 – 7 and they had higher odds of developing neonatal hyperbilirubinaemia which is similar to studies done in Nigeria and Northern Ethiopia.[8,16] This can be explained by the fact that most of our neonates who are admitted are not breastfed on the first day of life that leads to delay in passage of meconium and subsequent increase in enterohepatic circulation, hence increases risk of hyperbilirubinemia.

We observed a statistically significant association between neonatal hyperbilirubinaemia and use of herbal medicines in our study similarly to the retrospective study which was done in Nigeria by Onyearugha which reported that mothers of inborn (2.4%) and outborn (35.2%) neonates used herbal medication during pregnancy which was significantly associated with neonatal hyperbilirubinemia.[8] Some studies have reported that ingestion of herbs during pregnancy has effects on shortening the length of gestation and may affect the intrauterine growth of the babies which increases the risk of hyperbilirubinemia.[20] In Taiwan, mothers who ingested CoptidisRhizoma gave birth to babies with low birth weight and small for gestation age.[21] A Nigerian study, found a high incidence of threatened miscarriage and preterm deliveries in mothers who used herbs.[23]Herbs are known to cause injury to the liver leading to herb induced liver injury (HILI) which commonly presents with jaundice.[24]In contrast, there was no significance correlation found between herbal use during pregnancy

and neonatal hyperbilirubinemia in the study done by Ahmed et al 1995 in Zaria Nigeria.[23] Differences in these studies is due to differences in races, amount of herbal medication taken and also the components of herbal taken in different places in the world, as other components of herbal are not causing harm. Our findings call for more studies on effects and reasons for herbal medicine use during pregnancy.

Prolonged labour has been found to be associated with neonatal hyperbilirubinemia in this study which correlates with studies done in Ethiopia and Nepal.[17,25] This could be explained by the fact bruising and cephalohematoma as the result of prolonged labour may increase the risk of neonatal hyperbilirubinemia.[16,26] Moreover in this study, the use Oxytocin for augmentation of labour has been associated with neonatal hyperbilirubinemia though it was not statistically significant. This finding is correlated with the findings from the study which was done in Welsh national school of medicine, which showed that there is an association between Oxytocin and neonatal hyperbilirubinemia.[27]The possible explanation here is that the amount of oxytocin used for induction of labour in this study is probably different from the ones used in other studies, that is why it showed the weak association with hyperbilirubinemia.

Neonates who have sepsis are likely to develop high level of bilirubin due to increase in hemolysis and defective conjugation of bilirubin.[28,29] In this study, the odds showed association of sepsis with neonatal hyperbilirubinemia but it was not statistically significant, which is in contrary with many studies, which showed strong association of sepsis and neonatal hyperbilirubinemia. But the study which was done in Nigeria by Onyearugha et al 2011 showed that the leading cause of neonatal hyperbilirubinemia is sepsis.[8] This difference, can be explain by the fact that most of mothers of neonates included in this study were from urban areas and most of them are able to easily access antenatal clinic and seek medical attention which reduces the chances of transmitting infections to their fetus. The other difference can be attributed by the differences in the criteria used to determine sepsis in which in this study, we used temperature, tachypnea, respiratory rate and elevated white blood cell counts while in Onyearugha's study, their criteria were not mentioned.

We also did not find any significant association between Rhesus incompatibility and neonatal hyperbilirubinemia, which was consistent with the previous study.[16] However, other studies have found the association between Rh incompatibility and hyperbilirubinemia during the first day of life.[30] Children born by Spontaneous Vaginal Delivery (SVD) have high risk of developing hyperbilirubinemia due to different manipulations as the baby is engaged in the pelvis for delivery preparation and hence leading to cephalohematoma, which may lead to hyperbilirubinemia. In this study no association was observed between neonatal hyperbilirubinaemia and either spontaneous vaginal delivery or cephalohematoma which was consistent to the study done at Ethiopia.[16]
The current study demonstrated the significant positive correlation between TcB and TSB. We have also shown that the TcB test had a sensitivity of 87.6% and specificity of 95.7% implying that TcB has high capacity of diagnosing those who do not have hyperbilirubinemia. This finding was in agreement with studies done by Maisels et al in China and Lam et al.[13,31] Another study done in Zimbabwe showed a strong correlation between TSB and TcB but difference in sensitivity (62%) compared to our study but had similarities in specificity of 95%, with slight difference in the positive predictive and negative predictive values of 80% and 90% respectively.[14] This could be contributed by the fact that the TcB machine used in this study was Draega JM 105 unlike the Draega JM103, which was used in Zimbabwean study. Rubaltelli at al in 2001suggested that TcB method measures the amount of bilirubin that has moved from serum to the tissues, possibly mimicking the bilirubin moving from serum to blood brain barrier into brain tissue, where the laboratory-based method measures only bilirubin in the blood. Thus TcB actually offers additional information not provided by TSB measurement.[32] However, the correlation coefficient does not provide the clinical significance of the diagnostic test, but it was found that when the level of serum bilirubin increases the difference between values of TSB and TcB increases as well. However, a lower level of TSB upon which treatment begins can cause frequent monitoring of blood sampling, a painful procedure with possible complications. TcB can therefore be used as a screening tool to determine the need for TSB measuring.[33]
The authors would like to acknowledge the following limitations. The TcB machine (Dragger JM105) had the maximum limit. A "dash-zero-dash" was displayed when bilirubin levels were higher than 19.9mg/dl. Also the TcB test does not differentiate between conjugated or unconjugated bilirubin.

Conclusions

The observed high prevalence of hyperbilirubinemia is alarming though small proportion of neonates had severe form of hyperbilirubinemia.Transcutaneous bilirubinometer has shown high sensitivity and specificity in detecting hyperbilirubinemia and should therefore be used for initial screening for hyperbilirubinaemia. Screening for hyperbilirubinemia among neonates aged 2-7 days, those who are born from mothers who used local herbs during pregnancy and had prolonged labour and should be strengthened.

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Author contributions
MM, BK, AH, RR and RK conceptualized and designed the study. MM collected data. BK, MM and RR performed data analysis. RK drafted the manuscript. MM, BK, AH, RR and RK revised the manuscript and approved the final manuscript.
Conflict of interest: None
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