Original Article

Correlation between total serum bilirubin and clinico-laboratory parameters of babies admitted for neonatal jaundice in a resource-limited setting

Uchenna Ekwochi, Chidiebere D. I. Osuorah[1], Ikenna Kingsley Ndu

Department of Paediatrics, Enugu State University of Science and Technology, Enugu State, Nigeria, [1]Child Survival Unit, Medical Research Council UK, The Gambia Unit, Fajara, Gambia

Abstract

Background: Neonatal jaundice (NNJ) is one of the most frequent reasons newborn babies in low- to middle-income countries visit the hospital during the neonatal period. If not promptly managed, it could lead to serious neurological sequela and mortality. The level and type of bilirubin in serum are an important determinant of the management option in NNJ. Unfortunately, this simple but fundamental investigation is not readily available in many hospitals in low- to middle-income countries, and where available, needs to be done serially, an expenditure most clients cannot afford.

Methodology: This study enrolled 83 newborns admitted and managed for NNJ at the Enugu State University Teaching Hospital during an 18-month period. We report correlation between total serum bilirubin (TSB) and selected newborn clinical and laboratory parameters.

Results: A total of 83 newborns were admitted for NNJ during the study. The mean TSB (mTSB) was 307 ± 145.2 μmol/L. Preterm infants ($T = 0.462, P = 0.500$), neonates with birth weight <2.5 kg ($T = 0.219$, $P = 0.804$), female neonate ($T = 0.314$, $P = 0.578$), and those that presented with skin level at the lower body region ($T = 28.52$, $P = 0.001$) had a higher mTSB at presentation to the special care baby unit. Similarly, mTSB at presentation was higher in neonates with PCV <40% ($T = 0.005$, $P = 0.942$), negative malaria parasite film ($T = 0.01$, $P = 0.933$), and those that were Glucose-6-Phosphate dehydrogenase deficient ($T = 1.59$, $P = 0.221$). Only skin level of jaundice at presentation was significantly correlated to the TSB ($R = 0.818$ $P = 0.001$) while gestational age ($R = 0.096$, $P = 0.500$), age at presentation ($R = 0.197$, $P = 0.157$), and birth weight ($R = -0.107$, $P = 0.459$) were not. Linear regression analysis showed that for every regional rise in skin level of jaundice (X), the TSB (Y) in μmol/L increases by a factor of 89.74 expressed in a regression equation as, $Y = -10.66 + 89.74\ X$.

Conclusions: The skin level of jaundice can be used as a rough guide in the estimation of total bilirubin in newborns with jaundice. This is especially useful in resource-limited setting where facilities for testing bilirubin level are lacking.

Keywords: Clinical features, Enugu, jaundice, laboratory parameters, newborns, total bilirubin

Address for correspondence: Dr. Chidiebere D. I. Osuorah, Child Survival Unit, Medical Research Council UK, The Gambia Unit, 78 Atlantic Boulevard, Fajara, Gambia.
E-mail: chidi.osuorah@gmail.com

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INTRODUCTION

Neonatal jaundice (NNJ) is one of the nine danger signs of neonatal illness recognized by the World Health Organization.[1] It is a neonatal emergency and should be reviewed as urgently as possible to determine the causative factors, clinical course, and the best treatment option to avert the associated neurological sequel. Several treatment options for NNJ exist. A key determinant of the treatment option(s) employed is to a large extent dependent on the serum bilirubin level. For instance, in our center, EBT is recommended at total serum bilirubin (TSB) level >20 mg/dl and >15 mg/dl for the term and preterm newborns, respectively, while phototherapy is recommended at two-thirds of the respective TSB level for EBT.[2] One of the setbacks in the use of SB level is lack of readily available laboratory facilities for immediate serum bilirubin estimation, especially in a resource-limited setting like ours. Furthermore, a previous study in our setting has documented that the cost of managing a newborn with jaundice was significantly increased by the cost of serial TSB tests.[3] In the authors experience, during management of newborns with jaundice, most parents were unwilling or unable to pay for the serial TSB tests as recommended. Hence, most experienced physicians sometimes resort to clinical findings in deciding the best treatment option(s). There is a need for a convenient, cost-effective clinical tool that will correlate positively with TSB. Such tool will enhance immediate and effective clinical decision when managing jaundice in a resource-limited setting. Kramer correlated the skin zones of jaundice in white children with the serum bilirubin level and discovered that as serum bilirubin level rises, jaundice progresses cephalocaudally.[4] However, this finding was in developed setting where currently its use may not be of essence following the availability of more sophisticated effective point-of-care serum bilirubin estimation facilities. There is need to validate this clinical tool among blacks in resource-limited settings where there is obvious need for such a cost-effective tool. The authors therefore, attempted to correlate TSB with some clinical and laboratory parameters in babies admitted for NNJ at the Enugu State University Teaching Hospital (ESUTH).

METHODOLOGY

Study area

This research is the second part of an evaluation survey done on newborns admitted for NNJ in the special care baby unit (SCBU) of ESUTH. It is an 18-month study conducted between April 2015 and October 2016. The SCBU is equipped with facilities and manpower for care of sick newborns within the first 28 days of life. It is located within the ESUTH which is a tertiary healthcare institution situated in the capital city of Enugu State, southeast Nigeria. It serves as a referral hospital for other healthcare facilities within the state and its environs.

Study design and recruitment of participants

This is a descriptive and analytical study of newborns admitted for jaundice at the SCBU of ESUTH. On presentation, mothers and/or caregivers of the admitted newborns are informed of the content of this research. They are assured that participation is voluntary and they are at liberty to exit the research at any point without consequences to themselves or their babies. They were also assured that data collected was strictly confidential and will only be utilized for research purpose only. No form of inducement or incentive was offered to influence their decision to participate. Babies of mothers who gave consent were consecutively enrolled at presentation. Demographic characteristics of interest such as gestational age at birth, place of birth, birth weight, gender, time of notice of jaundice, and time of presentation to hospital were documented on admission into the SCBU. In every newborn enrolled, the skin level of jaundice at presentation was carefully and cautiously assessed under daylight or whitelight independently by two pediatric specialists not involved in the study. In a handful of cases where there is difference in the documented skin level of icterus, a third specialist was invited as the decider. Skin levels of jaundice were documented and stratified as follows: Level 1, for yellowish skin discoloration limited to the head-and-neck region; Level 2, for jaundice appearing anywhere between the upper chest to the umbilical line; Level 3, for discoloration visible below the umbilical line down to the knee joint; Level 4, for skin discoloration noticeable in the leg region between the knee and ankle joint and level 5 for jaundice appearing on the palm of hand, the sole of the foot or that is generalized [Figure 1]. Furthermore, as part of the management protocol, blood samples were collected at presentation from all admitted newborn for serum bilirubin estimations, glucose-6-phosphate dehydrogenase (G6PD) status, blood film for malaria parasite, and neutrophilic band forms/toxic granulations. The final outcome of the babies were also noted as alive for babies discharged home or dead for those who died while still on admission.

Data management

The anthropometric data of enrolled newborns, clinical features, and laboratory results were collected in the relevant sections of the questionnaire and later transferred into a Microsoft Excel sheet. Mean total bilirubin of enrolled newborns in various subcategories was calculated

and compared using Student's *t*-test. Correlation between bilirubin level and selected newborns and laboratory parameters was done using the Pearson coefficient. Partial correlation analysis was used to control for newborn variable of interest. Enrollees with significant missing information were excluded from the data analysis. Data was analyzed using IBM® SPSS version 20 (SPSS Inc., Chicago, IL, USA), and statistical significance was set at <0.05.

RESULTS

Characteristics of newborn surveyed

Of the 83 newborns enrolled for this study, 65% were term deliveries, whereas 48% had birth weight <2.5 kg and 6% were over 4 kg at birth. The remaining newborns had birth weight in the normal range (2.5–4.0 kg). Male-to-female ratio was roughly 3:2. Thirteen percent of the mothers said that they noticed jaundice in their newborn within the 1st day of life, 81% between 2 and 7 days of life, and 6% after 1 week of life. Eight (10%) mothers presented to the hospital on the same day jaundice were noticed, majority (71%) between 2 and 7 days and 19% presented after 7 days of life. Approximately 41% and 59% of neonates admitted for jaundice were born within and outside the study setting. The skin level of jaundice at presentation was noted at level 1, 2 and 3 in 9%, 13% and 25% of cases respectively while 21% and 32% of newborn were admitted with yellowish skin discolouration at level 4 and 5. A case fatality of 6% was documented among surveyed newborns [Table 1].

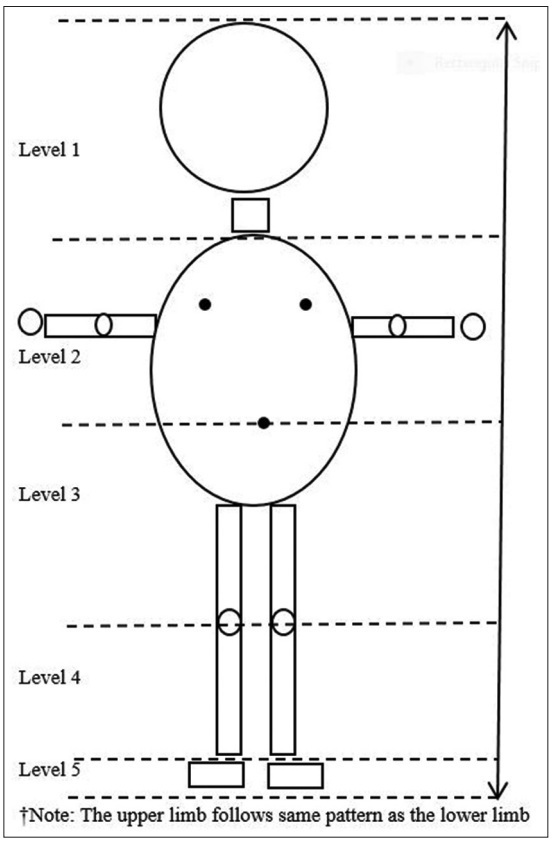

Figure 1: Visual classification of newborns at presentation based on skin level of icterus

Total serum bilirubin at presentation by clinical and laboratory parameters

The mean TSB (mTSB) was 307.7 ± 145.2 μmol/L in surveyed neonates. The mean value for unconjugated and conjugated bilirubin was 257.5 ± 127.6 μmol/L and 48.7 ± 83.7 μmol/L, respectively. Table 2 shows the mTSB stratified by newborn parameters. Preterm infants had a higher mean bilirubin compared to term neonates (297 ± 134 vs. 328 ± 177 μmol/L; $T = 0.462$, $P = 0.500$). Similarly, neonates with birth weight < 2.5 kg had a higher mean total bilirubin level (325 ± 164 μmol/L) compared to those with normal (298 ± 150 μmol/L) and large birth weights (290 ± 57.0 μmol/L) ($T = 0.219$, $P = 0.804$).

Female newborns also presented with a higher mean total bilirubin than male (322 ± 159 vs. 299 ± 138, $T = 0.314$, $P = 0.578$). None these, however, attained statistical significance. Newborns that presented with jaundice at more caudal location had significantly higher mean level of total bilirubin compared to those that presented at more cephalic region, i.e., 122 ± 34.6 μmol/L for Level 1 presentation, 164 ± 21.8 μmol/L for Level 2 presentation, 246 ± 37.0 μmol/L for Level 3 presentation, 311 ± 52.9 μmol/L for Level 4, and 462 ± 130 μmol/L for Level 5

Table 1: Characteristics of babies admitted for neonatal jaundice to the special care baby unit of Enugu State University Teaching Hospital from April 2015 to October 2016

Characteristics	Variable	*n* (%)
Gestational age (*n*=82)	Term	53 (65)
	Preterm	29 (35)
Birth weight (*n*=77), kg	<2.5	37 (48)
	2.5-4.0	35 (46)
	>4.0	5 (6)
Gender (*n*=83)	Male	49 (59)
	Female	34 (41)
Age jaundiced was noticed† (*n*=83), DOL	1	10 (13)
	2-7	63 (81)
	>7	5 (6)
Age at presentation to hospital (*n*=83), days	1	8 (10)
	2-7	59 (71)
	>7	16 (19)
Skin level of jaundice at presentation (*n*=53)	Level 1	5 (9)
	Level 2	7 (13)
	Level 3	13 (25)
	Level 4	11 (21)
	Level 5	17 (32)
Place of birth (*n*=83)	Inborn	34 (41)
	Out-born	49 (59)
Outcome (*n*=83)	Alive	78 (94)
	Dead	5 (6)

†DOL: Day of life

Table 2: Comparison of the mean total serum bilirubin at presentation with clinical and laboratory parameters of babies admitted for neonatal jaundice

Parameters	Variables	*n*	Total bilirubin (μmol/L), mean±SD	*T*-test	*P*
Gestational age	Term	38	297±134	0.462	0.500
	Preterm	14	328±177		
Birth weight (kg)	<2.5	19		0.219†	0.804
	2.5-4.0	27	298±150		
	>4.0	4	290±57.0		
Gender	Male	33	299±138	0.314	0.578
	Female	20	322±159		
Skin level of jaundice at presentation	Level 1	5	122±34.6	28.52†	0.001
	Level 2	7	164±21.8		
	Level 3	13	246±37.0		
	Level 4	11	311±52.9		
	Level 5	17	462±130		
Place of birth	Inborn	24	315±137	0.094	0.760
	Out-born	29	302±154		
Duration of hospital stay (days)	≥5	9	273±143	0.216†	0.807
	6-10	9	297±53.8		
	>10	13	270±88.7		
Outcome	Alive	43	316±154	0.626	0.433
	Died	3	244±72.9		
Positive malaria parasite	Yes	13	317±92.6	0.007	0.933
	No	29	321±169		
G6PD deficiency	Yes	4	302±126	1.590	0.221
	No	19	217±95.7		
Pack cell volume	<40%	14	288±117	0.005	0.942
	≥40%	17	285±133		
Presence of band cell on blood film	Yes	12	315±143	0.247	0.623
	No	22	290±140		

†ANOVA. SD: Standard deviation, ANOVA: Analysis of Variance

presentation (T = 28.52, P = 0.001). Total bilirubin in babies with presentation PCV < 40% versus ≥40% was 288 ± 117 μmol/L versus 285 ± 133 μmol/L (T = 0.005, P = 0.942). Finally, newborn that had negative malaria parasite film (321 ± 169) and those that were G6PD deficient (302 ± 126 μmol/L) also had a higher mTSB compared to those who are malaria parasite positive (317 ± 92.6 μmol/L, T = 0.01, P = 0.933) and those not deficient (217 ± 95.7 μmol/L, T = 1.59, P = 0.221).

Figure 2 shows the correlation between TSB and selected parameters in newborns surveyed. Gestational age (R = 0.096, P = 0.500), age at presentation to the hospital (R = 0.096, P = 0.157) and birth weight (R = −0.107, P = 0.459) were not significantly correlated with TSB. However, the level of skin discoloration on presentation was significantly correlated with the TSB on admission (R = 0.818, P =0.001).

After controlling for birth weight and gestational age at birth using partial correlation analysis, there was respectively, a slight increase (R = 0.821, P = 0.001) and decrease (R = 0.813, P = 0.001) of the correlation co-efficient between TSB and level of skin discoloration while gender of newborn had no effect (R = 0.818, P = 0.001) on the relationship. Linear regression analysis showed that for every level of caudal progression of jaundice, the TSB (in μmol/L) increases by a factor of 89.74 giving a regression equation represented as Y = −10.66 + 89.74 X, where Y is the estimated TSB in μmol/L and X is the observed skin level of jaundice at presentation to the hospital [Table 3].

DISCUSSION

The study noted a higher level of mean total bilirubin in newborns with a more distal skin discoloration at presentation. This is hardly surprising as it is expected that the higher the level of bilirubin in the blood, the more likely it would appear in more distal parts of the body. A similar study involving 145 newborns also noted that a caudal progression of icterus in newborn corresponded to an increasing bilirubin concentration in blood. The only exception noted in the referenced study was two extremely low birth weight newborns with weight <1000 g that presented with generalized jaundice at a lower level of TSB.[5] Several other studies have shown good correlation between serum bilirubin levels and skin zones of jaundiced children.[6-7]

From the newborn parameters assessed in this current study, birth weight, age at presentation, and hemoglobin level were not significantly correlated with serum bilirubin in newborns with jaundice. Imani Mahmood *et al*. in a similar study in Iran also reported no correlation between serum bilirubin and gestational age, newborn age, and weight.[8] In our study, only the level of skin discoloration

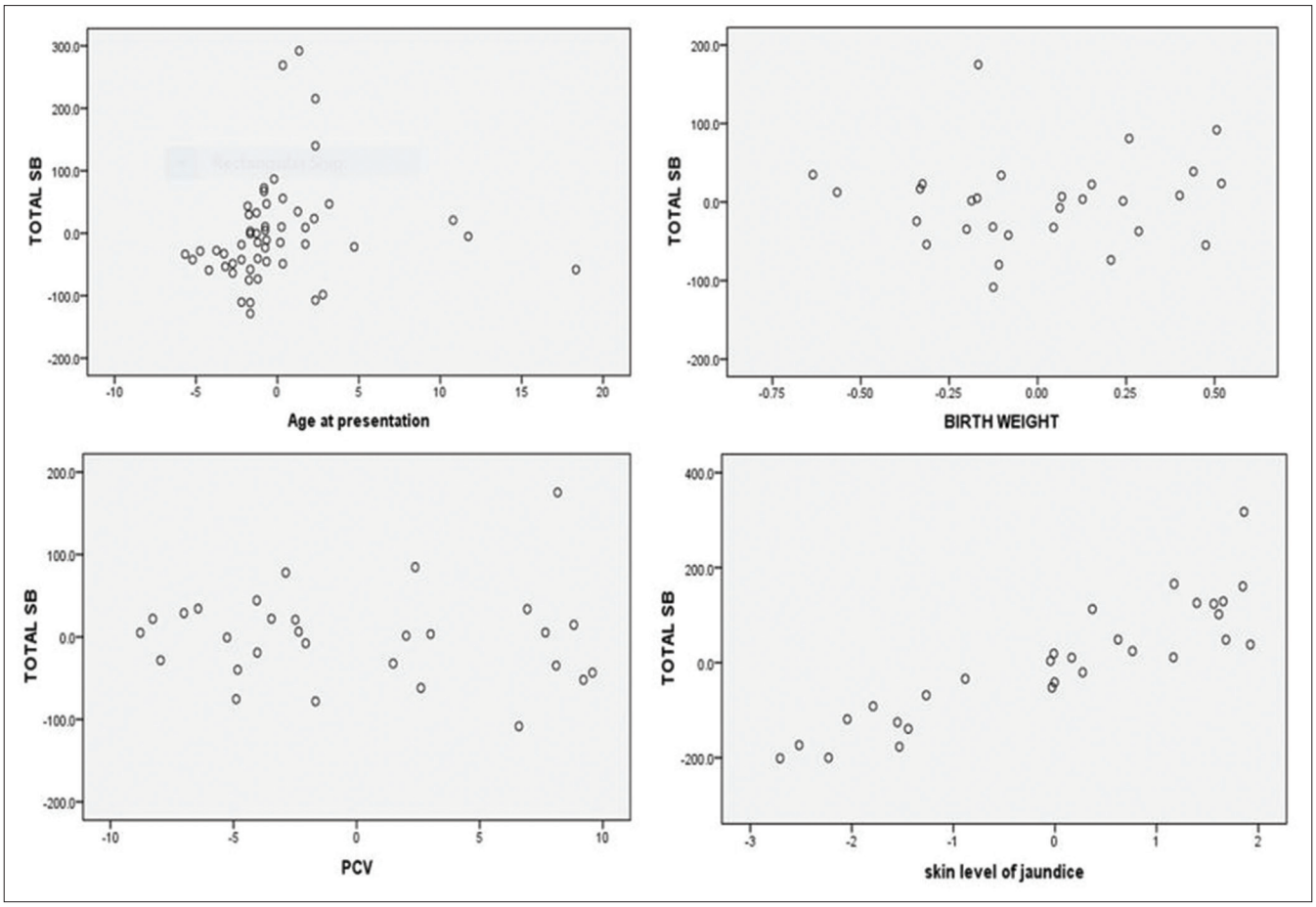

Figure 2: Scatterplots of total serum bilirubin and selected neonatal parameters at presentation

Table 3: Linear regression analysis of total serum bilirubin and skin level of jaundice at presentation in babies admitted for neonatal jaundice

Model	Unstandardized coefficient		Standardized coefficient		
	B	SE	β	*t*	*P*
Constant	−10.66	33.42		−0.32	0.750
Skin level of Jaundice	89.74	8.84	0.82	10.15	0.001

Dependent variable: Total serum bilirubin. SE: Standard error

of neonates admitted for jaundice was significantly correlated to the TSB at presentation. This positive correlation has been reported in other studies.[9,10] Unlike our study, both studies found that beyond dermal zone III, skin discoloration of jaundice was no longer significantly correlated with serum bilirubin. This difference in finding is probably because both reference studies were conducted in low birth weight babies in whom icterus is more easily visible because of their highly transparent skin. Furthermore, because low birth weight newborns have a lower bilirubin-albumin binding capacity, the progression of dermal icterus is usually more rapid compared to term infants who were the clear majority in our study.[9,11]

Finally, our study showed that for every regional descent in skin level of jaundice, the TSB increases by a roughly a factor of 90 μmol/L. No other similar studies were found for comparison. This may have practical application in the field where the facility for serum bilirubin estimation is lacking because of the simplicity of calculation involved. Kramer in 1969 also noted a progressive increase in serum bilirubin with craniocaudal development of skin discoloration.[4] He estimated that serum bilirubin was approximately 100 μmol/L for skin discoloration at zone 1 (head and neck), 150 μmol/L at zone 2 (chest and upper abdomen), 200 μmol/L at zone 3 (lower abdomen and thigh), 250 μmol/L at zone 4 (between the knee and ankle joint), and >250 μmol/L at zone 5 (hand and/or foot).[4]

Despite the correlation between skin level and serum bilirubin levels found in this study, dermal zone assessment is not meant to replace serum bilirubin estimation using laboratory method but as an improverised estimation formula where laboratory facilities are lacking or unaffordable.[9] Because the treatment of NNJ is determined to a great extent by the serum bilirubin level,

this alternative assessment method for serum bilirubin concentration in newborns could be lifesaving in resource poor settings.[12,13]

CONCLUSION

We conclude that the skin level of jaundice can be used as a rough guide in the estimation of total bilirubin in newborns with jaundice, especially in resource-limited setting where facilities for testing bilirubin level are lacking and/or not serially affordable by parents of newborn admitted for neonatal jaundice.

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Conflicts of interest
There are no conflicts of interest.

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