Original Article

Threshold and Correlation of Total Serum Bilirubin with Screening Automated Auditory Brainstem Response Among Newborns with Hyperbilirubinemia in National Hospital Abuja

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Abstract

Objective: To determine the total serum bilirubin (TSB) cut-off value predictive of hearing impairment among newborns with hyperbilirubinemia at the National Hospital Abuja.

Setting: This was a cross-sectional study conducted in the Special Care Baby Unit (SCBU) and Neonatal Intensive Care Unit (NICU) of National Hospital Abuja between August 2020 and February 2021.

Methods: A universal sampling of eligible participants was done, and consent was obtained from the parent. Using the TSB and results of hearing screening carried out with the Otoport advance from Otodynamics®, the proportion of automated auditory brainstem response (AABR) screening failure was determined, and the receiver's operating characteristics (ROC) curve coordinates were used to find the threshold bilirubin level for the risk of hearing loss. The Spearman-Rho correlation assessed the relationship between TSB level and AABR findings.

Results: 160 newborns below 28 days of age, delivered at 34 weeks gestation and above, who had clinical jaundice were recruited. The prevalence of screening AABR failure in at least one ear was 26.2%. The correlation between TSB and AABR was weakly positive (rs = .189, p = .093) and the TSB cut-off for AABR failure was 16.3 mg/dl (sensitivity 45.5%, specificity 81%, Youden's-J statistic = 0.265).

Conclusion: The TSB threshold for AABR screening failure was 16.3 mg/dl, but TSB did not correlate well with screening AABR. Serum bilirubin above 15 mg/dl in late preterm and term neonates should be actively treated with phototherapy and/or exchange blood transfusions where feasible, particularly in resource-poor settings.

Keywords

AABR, newborn, hyperbilirubinemia, bilirubin threshold, hearing screening

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Introduction

Hyperbilirubinemia, which means excessive bilirubin in the blood, is found in almost all newborns in the first several days of life.[1] Its clinical manifestation, termed jaundice, is a yellowish coloration of skin and sclera,[2] but neonates generally do not appear jaundiced until the total serum bilirubin (TSB) exceeds 5 mg/dl (86 µmol/L).[1] The anti-oxidant properties of bilirubin, an end product of red blood cell (RBC) hemoprotein catabolism in the reticuloendothelial cells, are well known.[3] However, excessive unconjugated bilirubin (UCB) in the blood, irrespective of the cause, is toxic to the developing nervous system,[2] including the auditory system.

Normal hearing is defined as a hearing threshold of 20 decibels (dB) or better in both ears.[4] The inability to hear as well as someone with normal hearing is known as hearing loss, and this has functional, economic, social, and emotional consequences.[5] Newborn hearing loss poses a significant public health concern due to economic underachievement in adulthood, particularly in developing countries with limited resources for interventions such as hearing aids and cochlear implants. More so, preventable causes, including hyperbilirubinemia, account for the high proportion of hearing loss in middle- and lower-middle-income countries (75%) compared to high-income areas (49%).[6] Nigeria has one of the highest rates of sensorineural hearing loss (SNHL) in sub-Saharan Africa, up to 28 per 1,000 live births.[7] Severe hyperbilirubinemia is a known risk factor for hearing loss, specifically SNHL. Among term and preterm newborns

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with hyperbilirubinemia in the exchange transfusion threshold (ETT) range,[8] the incidence of SNHL was as high as 45.5%.

Neonatal hyperbilirubinemia, when excessive, leads to a condition known as kernicterus (chronic bilirubin encephalopathy) that is characterized by bilirubin staining of the brainstem nuclei and cerebellum[3,9] and manifests as deafness, athetosis, and dysarthric speech. This is undesirable and preventable through direct action in line with guidelines from the American Academy of Pediatrics (AAP).[9] Yet the bilirubin threshold for intervention to mitigate hearing loss remains indeterminate.

Bilirubin can be accurately measured by laboratory estimation of the serum concentration; however, the TSB comprises the direct "acting" bilirubin, which is the conjugated bilirubin (CB), and the indirect "acting" bilirubin or UCB.[10] According to Shapiro,[11] the TSB is a better indicator of the risk of bilirubin encephalopathy than the UCB because the non-toxic CB also competes with the UCB for albumin binding sites. Although more recent studies suggest that free or unbound bilirubin (UB) is a better indicator of neurotoxicity and auditory system damage among preterm neonates, TSB estimation is more readily available in resource-limited settings such as ours.

In 1998, Soorani-Lunsing et al.[12] reported that levels of hyperbilirubinemia ranging from 13.7 to 26.1 mg/dl were associated with an increased risk of minor neurologic dysfunction in healthy term newborns without hemolytic disease, and residual abnormalities were found at 12 months of age in those with peak TSB above 19.7 mg/dl. Two decades later, González et al.[13] reported a 2.13% prevalence of SNHL in newborns at TSB levels below 20 mg/dl. Similarly, persistent brainstem auditory evoked response (BAER) abnormalities were reported among term newborns with TSB less than 15 mg/dl.[14,15] These reports suggest that the specific bilirubin level at which hearing becomes impaired is ill-defined. Furthermore, in 2015, Corujo-Santana et al.[16] reported hearing loss in 13 preterm and two term newborns with bilirubin levels of 5−13.99 mg/dl, while 11 preterm and five term newborns had hearing loss at bilirubin levels of 14 to 19.99 mg/dl. Despite these findings, screening for hearing loss has been recommended at bilirubin levels higher than 20 mg/dl or 1% of birth weight.[17] Overall, some studies reported an incidence of hearing loss at bilirubin levels at and above the ETT range[18,19] while others found a high risk of deafness at TSB levels below 20 mg/dl[15,20] among term and preterm infants. This raises the question of at what TSB level hearing becomes impaired.

Therefore, this study assessed the correlation between TSB and screening automated auditory brainstem response (AABR) findings and determined the bilirubin threshold at which AABR failure and the risk of hearing impairment occur among late preterm and term neonates with hyperbilirubinemia at the National Hospital, Abuja (NHA). The findings should serve to advise policymakers on measures to appropriately manage newborn hyperbilirubinemia and prevent hearing loss in this high-risk population.

Material and Methods

This study was conducted at the NHA, which is in the North-Central region of the country and serves as a referral center for many other hospitals. It is a government-owned tertiary health facility that provides level IIb neonatal care services. The participants were recruited from the Special Care Baby Unit (SCBU) and Neonatal Intensive Care Unit (NICU) wards of the neonatal unit of the pediatric department, NHA.

In a cross-sectional study where a total of 160 participants were enrolled, the sample size was determined using the formula for the determination of proportions for populations less than 10,000.

Selection and Description of Participants

A universal sampling of consecutive patients presenting at the study site was done as shown in Figure 1. Out of the 826 babies who were delivered in, or presented to the NHA during the study period, 201 had neonatal jaundice and were admitted into the SCBU or NICU. All babies who met the study criteria were recruited after the parent's consent was obtained.

Technical Information

A universal sampling of consecutive patients presenting at the study site was done after obtaining the parent's consent. All newborns delivered at ≥34weeks GA, who presented to and/or were admitted into the NHA SCBU/NICU within the first 28 days of life and had jaundice or were diagnosed with hyperbilirubinemia with an Apgar score of 7 and above in 5 min were recruited into the study. Newborns who were diagnosed with perinatal asphyxia (Apgar scores less than 7 in 5 min) or hearing loss or had a family history of deafness or were admitted with suspected or confirmed TORCHES, and so on, infection, and meningitis were excluded from the study.

Ethics

A written informed consent was obtained from either parent of the newborn. Confidentiality was maintained during and after the screening. The result of the AABR screening was communicated to the parents, and those babies who failed to obtain a PASS were referred to the otolaryngologist for further evaluation and full assessment.

Data Collection

Using a proforma, each baby's data were recorded as obtained either from medical records or from a history taken from the parent. Biodata, including GA (determined from last

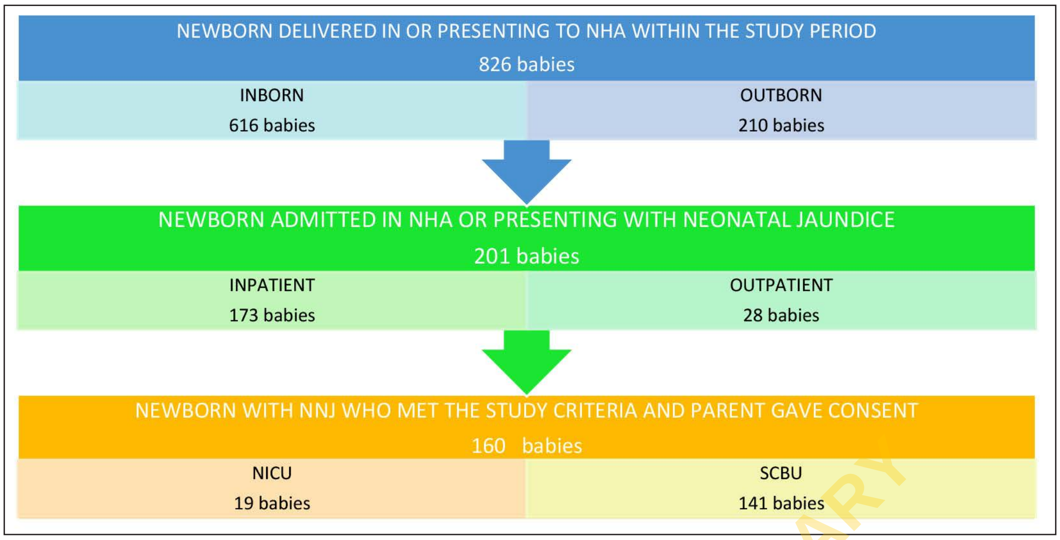

Figure 1. Flow Diagram Illustrating the Selection of Study Participants.

menstrual period (LMP), expected date of delivery (EDD), early scans, and new Ballard score), birth weight (grams), and sex, were documented. Each subject had serum bilirubin taken at presentation as per unit protocol. This was analyzed in the NHA laboratory using a chemical analyzer that employs the colorimetric diazo method, and the results were documented in the proforma.

Before the screening, the babies were fed and soothed to sleep. Screening AABR was done at or shortly after presentation using the Otoport Advance OAE+ABR device from Otodynamics®, which was still within the manufacturer's first calibration period. Each ear was assessed separately. The skin was prepared by applying an abrasive gel to reduce impedance, and pre-gelled snap electrodes were sited according to the manufacturer's recommendations. The active (positive) electrode was placed on the forehead, the reference (negative) electrodes were placed on the cheek, and the earth (neutral) electrode was placed on the nape. Each ear was evaluated one time using a chirp sound at a rate of 85 Hz, a stimulus intensity of 35 dBnHL, and a frequency of 1,000 Hz. The stimulus was presented through inserted earphones, and pre-gelled snap electrodes on the forehead, cheek, and nape were used to record the signal.

A PASS result was obtained from the device when there was a response to the stimulus at 35 dBnHL and the pass criteria were met. The criteria are based on the template correlation and the conventional FSP methodology, which is a statistical measure of the likelihood that a response is present. The response is detected using template correlation (waveform identification), which is an in-built template constructed from responses from 30 neonates and is optimized for infants from 34 weeks of gestation to 6 weeks of age. The ambient noise level measured did not exceed 40 dBA at each testing. The test stop criteria were set to automatically terminate the test when the auditory brainstem response (ABR) PASS has been achieved or within 10 min to limit the sound exposure if a response is not detected. To reduce false positives, the test is repeated twice for that ear before a REFER result is documented.

Data Management

Data were cleaned and analyzed using the IBM SPSS Statistics version 22.0, and the results were presented in tables, graphs, and charts. Numerical variables were summarized using the mean and standard deviation, while categorical variables were summarized using frequencies and percentages. The student's t-test was used to analyze continuous variables such as TSB values and to compare the mean bilirubin between late preterm and term participants. The proportion of AABR screening failures was determined by a REFER result in at least one ear. Spearman Rho correlation was performed to assess the relationship between bilirubin level and AABR findings, while the coordinates of the receiver's operating characteristics (ROC) curve were used to determine the threshold bilirubin level for the risk of hearing loss.

Results

A total of 160 neonates who had hyperbilirubinemia were studied. The age range was between 2 days and 25 days, as shown in Table 1. The mean age (days) ± SD was 5.81 ± 3.45, the mean GA (weeks) ± SD was 37.98 ± 2.49, and the mean birth weight (grams) ± SD was 2974.8 ± 758.5. There were 97 (60.6%) males, while 55 (34.4%) were late preterm neonates. Severe hyperbilirubinemia (TSB ≥ 20 mg/dl) was

Table 1. Bio-Demographic and Medical Characteristics of Study Participants.

Variables	Frequency	Percentage (%)
Age (days)		
2−14	156	97.5
>14	4	2.5
Mean ± SD; Min, Max		
5.81 ± 3.45; 2, 25		
Birth weight (g)		
1,500–,2499	42	26.3
2,500–3,999	110	68.7
4,000 and above	8	5.0
Mean ± SD; Min, Max		
2,974.8 ± 758.5; 1,640, 4,200		
Gestational Age (weeks)		
34–36 6/7	55	34.4
≥37	105	65.6
Mean ± SD; Min, Max		
37.98 ± 2.49; 34, 42		
Pattern of hyperbilirubinemia (TSB)		
Mild	101	63.1
Moderate	36	22.5
Severe	6	3.8
Extreme	10	6.2
Hazardous	7	4.4
NICU stay		
≤5 days	17	10.6
≥5 days	2	1.3
Not applicable	141	88.1
Diagnoses		
Acute bilirubin encephalopathy	10	6.3
NNJ without encephalopathy	150	93.7
Intervention		
Follow-up	32	20.0
Phototherapy	107	66.9
Exchange blood transfusion	21	13.1

Abbreviations: TSB, total serum bilirubin; NICU, neonatal intensive care unit; NNJ, neonatal jaundice.

Table 2. Distribution of AABR Findings by Bilirubin Level among the Study Participants.

AABR Findings	Gestational Age	Hyperbilirubinemia				
		Mild n (%)	**Moderate n (%)**	**Severe n (%)**	**Extreme n (%)**	**Hazardous n (%)**
PASS	34–37 weeks	30 (78.9)	4 (10.5)	2 (6.3)	2 (5.3)	0 (0.0)
	37 weeks and above	50 (62.5)	22 (27.5)	5 (6.3)	0 (0.0)	3 (3.7)
REFER	34–37 weeks	8 (44.4)	8 (44.4)	0 (0.0)	2 (11.2)	0 (0.0)
	37 weeks and above	13 (54.2)	2 (8.3)	0 (0.0)	5 (20.8)	4 (16.7)

Abbreviation: AABR, automated auditory brainstem response.

found in 23 (14.4%) of the participants. The maximum TSB level among the participants was 40.9 mg/dl, and the mean TSB (mg/dl) ± SD was 13.90 ± 7.10. The prevalence of AABR failure, that is, the proportion of participants with a REFER result in at least one ear, was 26.2%. The TSB mean ± SD for those with AABR failure in this study was 16.06 ± 9.61 mg/dl. More than half of the term participants with AABR failure had mild and moderate hyperbilirubinemia (13 (54.2%) and 2 (8.3%), respectively) as shown in Table 2. The bilirubin level (TSB) had a positive but weak relationship with the screening AABR finding (rs = .189, *p* = .093), as shown in Figure 2. The ROC curve of TSB with area under the curve (AUC) = 0.556, standard error = 0.02, 95% CI = 0.395–0.716, and *p* = .444, as shown in Figure 3. The TSB cut-off level that predicts screening AABR failure is 16.25 mg/dl (sensitivity = 0.455, 1 – specificity = 0.19, and maximum Youden's-J statistic value = 0.265), as shown in Table 3.

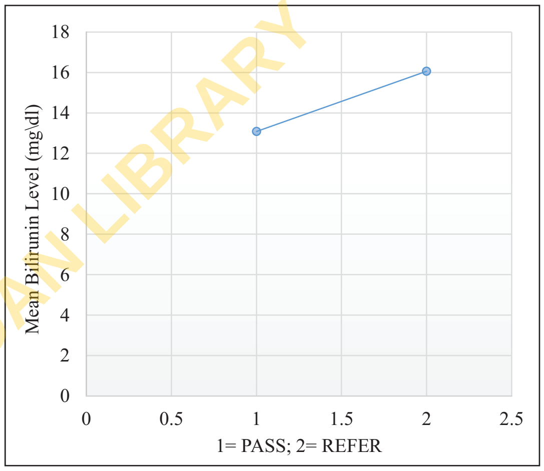

Figure 2. Correlation of Bilirubin Level and AABR Finding among the Study Participants.

Discussion

The correlation of bilirubin level (TSB) with AABR findings in this study was positive but weak (rs = .189, *p* = .093). Jiang et al.[21] also reported a weak correlation among apparently healthy term neonates in China (r = .24, *p* = < .05). Although one-third of our participants were late preterm neonates, similar findings were reported by Nam et al.[22] among preterms in Korea (R^2 = 0.043, *p* = .09); however, a better correlation was found when UCB was used in that study. Some studies reported no correlation between TSB and abnormal ABR findings among late preterm neonates with hyperbilirubinemia[23] while others found a strong correlation when peak TSB was used among late preterm and term neonates with severe hyperbilirubinemia.[24] A stronger association between auditory toxicity and UB than peak TSB was also found in the Indian study. However, one study reported no statistically significant difference between UB and TSB as predictors of hearing loss.[24]

In a systematic review, Teixeira et al.[25] reported a statistically significant correlation between audiological (ABR) changes and bilirubin levels, although TSB, UCB, or CB was used in the studies reviewed. According to that review, where

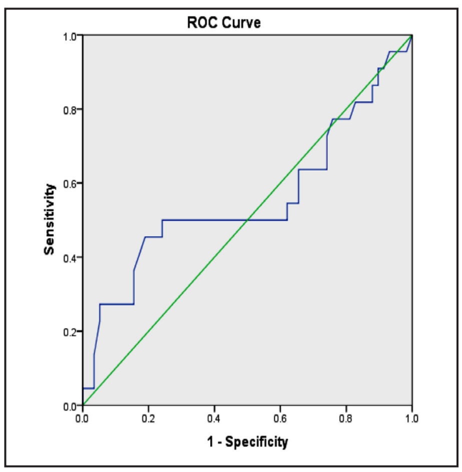

Figure 3. Receiver Operating Characteristics (ROC) Curve of Bilirubin Threshold for Screening AABR Failure among the Study Participants (Positive Predictive Value of 47.50% and a Negative Predictive Value of 79.65%).

Note: The straight line is the expected curve (unity), if the variable has no predictive value (area under unity curve 0.5).

Table 3. Bilirubin Threshold for Screening AABR Failure among Study Participants.

TSB	Sensitivity	1 – Specificity	Youden's-J statistic
10.75	0.500	0.621	−0.121
10.05	0.545	0.655	−0.110
9.63	0.636	0.741	−0.105
10.25	0.545	0.638	−0.093
9.68	0.636	0.724	−0.088
11.20	0.500	0.586	−0.086
10.45	0.545	0.621	−0.076
11.45	0.500	0.569	−0.069
7.80	0.818	0.879	−0.061
9.55	0.682	0.741	−0.059
9.75	0.636	0.690	−0.054
11.60	0.500	0.552	−0.052
8.15	0.818	0.862	−0.044
8.50	0.773	0.810	−0.037
9.85	0.636	0.672	−0.036
11.95	0.500	0.534	−0.034
7.15	0.864	0.897	−0.033
5.75	0.955	0.983	−0.028
8.25	0.818	0.845	−0.027
9.95	0.636	0.655	−0.019
12.25	0.500	0.517	−0.017
7.35	0.864	0.879	−0.015
9.30	0.727	0.741	−0.014
6.00	0.955	0.966	−0.011
8.35	0.818	0.828	−0.010
6.45	0.909	0.914	−0.005
8.70	0.773	0.776	−0.003
4.60	1.000	1.000	0.000
12.35	0.500	0.500	0.000
41.90	0.000	0.000	0.000
6.14	0.955	0.948	0.007
32.25	0.045	0.034	0.011
6.90	0.909	0.897	0.012
8.95	0.773	0.759	0.014
6.19	0.955	0.931	0.024
33.60	0.045	0.017	0.028
12.65	0.500	0.466	0.034
37.85	0.045	0.000	0.045
12.95	0.500	0.448	0.052
30.45	0.091	0.034	0.057
13.25	0.500	0.431	0.069
13.60	0.500	0.414	0.086
26.95	0.136	0.034	0.102
13.80	0.500	0.397	0.103
17.60	0.273	0.155	0.118
17.90	0.273	0.138	0.135
18.30	0.273	0.121	0.152
14.00	0.500	0.345	0.155
17.35	0.318	0.155	0.163
19.70	0.273	0.103	0.170
14.20	0.500	0.328	0.172
25.05	0.227	0.052	0.175
20.95	0.273	0.086	0.187
14.35	0.500	0.310	0.190
21.10	0.273	0.069	0.204
16.90	0.364	0.155	0.209
15.45	0.455	0.241	0.214
23.10	0.273	0.052	0.221
14.45	0.500	0.276	0.224
15.75	0.455	0.224	0.231
16.50	0.409	0.172	0.237
14.60	0.500	0.259	0.241
15.95	0.455	0.207	0.248
14.95	0.500	0.241	0.259
16.25	0.455	0.190	0.265

Abbreviation: AABR, automated auditory brainstem response.

no such correlation can be found, the reasons were differences in the bilirubin levels defined as critical to the start of treatment as well as the type of bilirubin used in the studies. However, because the participants were seen only once and to widen the scope of bilirubin values, the TSB results used in this study were those taken at or within 24 h of recruitment, irrespective of the treatment status. Though several studies agree on the correlation of serum bilirubin levels with abnormalities in hearing tests,[14,26–28] the bilirubin threshold for hearing loss was not determined.

In our study, a TSB of 16.25 mg/dl (277.9 µmol/L) was determined as the cut-off level for AABR failure (REFER) and risk of hearing impairment (AUC 0.556) among late preterm and term neonates with hyperbilirubinemia. This is consistent with the findings of Nam et al.[22] (AUC 0.591), although only a UCB threshold of 13 mg/dl (222.3 µmol/L) was reported. Likewise, a study among very preterm neonates with hyperbilirubinemia in the Netherlands reported an AUC of approximately 0.5 using TSB as a predictor of hearing loss.[29] However, Amin et al.[24] reported a higher AUC of 0.809 using peak TSB, but no cut-off value was given. Esmaeilnia et al.[30] also reported a significant correlation between abnormal ABR and increased bilirubin levels, with abnormal ABR being associated with a minimum bilirubin level of 15.8 mg/dl (270.2 µmol/L). Similarly, Peyvandi et al.[17] found an association between abnormal screening ABR and bilirubin levels below 20 mg/dl (342 µmol/L) in children who were delivered at term and reported 0.6% of birth weight in grams as the TSB cut-off level for abnormal ABR. Conversely, in a smaller group of newborns, Ezzeldin et al.[26] reported 21 mg/dl as the TSB threshold for abnormal ABR (AUC 0.785). This difference may be because of the lower gestational age of participants in our study (mean GA ± SD of 37.9 ± 2.49), unlike the mean GA ± SD of 38.6 weeks ± 0.56 in that study.

There are some concerns raised by our findings. First, at the bilirubin threshold (16.25 mg/dl) documented in our study, there is no recommendation for intervention (phototherapy) going by the 2004 AAP neonatal hyperbilirubinemia treatment guidelines in well infants who are 35 weeks GA and above at 84 h of life, neither in those who are 38 weeks GA and above with risk factors such as sepsis, acidosis, and so on, nor in well infants who are 38 weeks GA and above at 60 h of life, when hospitalized.[9] Second, screening for hearing loss was recommended at bilirubin levels higher than 20 mg/dl or 1% of birth weight in grams,[17] but as in our study, abnormal ABR has been reported at lower bilirubin levels.[13,28] Furthermore, preterm infants with TSB levels equal to or above 14 mg/dl have been reported to have a higher risk of deafness.[20] Mirajkar and Rajadhyaksha[15] also found persistent abnormal ABR in infants who retrospectively had TSB levels between 12 and 15 mg/dl when they were screened before 3 months of age, whereas none of those with TSB levels above 25 mg/dl had abnormal ABR findings at follow-up. Since it may be difficult to eliminate all other risk factors for hearing loss in hospitalized newborns with hyperbilirubinemia, as seen in our study, the foregoing suggests that hyperbilirubinemia alone may not be responsible for the hearing test abnormalities observed, as opined by some authors.[16,21]

Conclusion

The TSB level predictive of screening AABR failure and the risk of hearing impairment among late preterm and term newborns with hyperbilirubinemia in this study was 16.25 mg/dl.

We recommend a review of current guidelines on bilirubin thresholds for intervention in the management of hyperbilirubinemia among late preterm and term infants. Review treatment modalities to reduce the incidence of hearing impairment in newborns with hyperbilirubinemia, especially in resource-poor settings. Routine hearing screening of newborns with hyperbilirubinemia for early detection, diagnosis, follow-up, and prompt intervention.

Strength

This study provides a baseline for the assessment and prevention of hearing loss in newborns with hyperbilirubinemia and highlights lacunae in measures for reducing the burden of hearing impairment in these high-risk infants.

Limitations of this study are that the peak TSB is unknown because it may have happened before or after recruitment and that the participants' baseline AABR data were not available because only one contact was made with them as there is no NHS program in place elsewhere in the nation.

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Data Accessibility

The data file for this study is available and will be uploaded on request.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The Institutional Review Board of the National Hospital Abuja gave approval for the study with approval number NHA/EC/045/2019.

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Informed consent

The participant has consented to the submission of the article to the journal.

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