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Use of serum bilirubin/albumin ratio for early prediction of bilirubin induced neurological dysfunction

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Abstract

Background: Kernicterus or bilirubin encephalopathy is a preventable cause of handicap, still occurs in our country. The aim of the current study was to assess the role of bilirubin/albumin ratio in improving the morbidity of the cases with unconjugated hyperbilirubinemia and to estimate of the cutoff value for B/A ratio for prevention and early management of bilirubin-induced neurological dysfunction.

Results: The mean gestational age was 37.1 ± 2.11 weeks; the mean age of onset of jaundice was 2.36 ± 1.04 days; the mean level of total bilirubin was 26.14 ± 7.36 mg/dl. At chosen cutoff value of bilirubin albumin ratio (B/A) 6.68, sensitivity was 82% while specificity was 64% and accuracy was 95%.

Conclusion: Bilirubin encephalopathy still occurs in significant number in our country though it is a preventable cause of handicapping. TSB is a sensitive but not a specific indicator of ABE, B/A ratio is more specific indicator of the neurologic outcome and should be utilized in the decision of early intervention.

Keywords: Hyperbilirubinemia, Bilirubin/albumin ratio, Bilirubin encephalopathy

Background

Neonatal hyperbilirubinemia is a common problem. Approximately 60–70% of term and ~ 80% of preterm infants develop jaundice in the first week of life [10]. Neonatal jaundice if inappropriately managed may result in significant bilirubin-induced mortality and disability [20, 21].

Jaundice due to either indirect (unconjugated) or direct (conjugated) bilirubin within the first 24 h of life should be taken seriously. Early identification and proper management are needed to prevent the serious neurological complications associated with it [3, 27]

Although 99.9% of unconjugated bilirubin in the circulation is bound to albumin, a relatively small fraction (only less than 0.1%) remains unbound (free bilirubin) and it can go into the brain across an intact blood-brain barrier. According to the experimental studies, the concentration of free bilirubin is believed to dictate the biologic effect on jaundiced newborns, including its neurotoxicity [11].

In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However, in some infants, entry of unconjugated bilirubin into the brain can cause both short-term and long-term neurological dysfunction (bilirubin encephalopathy). In this case, unconjugated hyperbilirubinemia is potentially harmful for the central nervous system and may cause severe and permanent neurological sequelae that is defined as bilirubin-induced neurological dysfunction (BIND) [5].

Bilirubin-induced neurologic dysfunction (BIND) is the term applied to the spectrum of neurologic abnormalities associated with hyperbilirubinemia. It can be further divided into characteristic signs and symptoms that appear in the early stages (acute) and those that evolve over a prolonged period (chronic) [12].

The pathogenesis of BIND is multifactorial and includes interaction between the level of unconjugated bilirubin, free bilirubin, bilirubin bound to albumin, bilirubin passed through brain-blood barrier and nerve damage [15].

Kernicterus, or bilirubin encephalopathy, is a condition caused by bilirubin toxicity to the basal ganglia and

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various brain stem nuclei. Surviving infants usually develop a severe form of athetoid cerebral palsy, hearing loss, dental dysplasia, paralysis of upward gaze and, less often, intellectual, and other handicaps [1].

It could be also presented in the form of subtle neurodevelopmental delay or learning disabilities without classical findings of kernicterus that, after careful evaluation, appears to be due to bilirubin neurotoxicity [25]. The susceptibility to the neurotoxic effects of bilirubin varies according to cell type, brain maturity, and brain metabolism. Also, the concentration of bilirubin in the brain and the duration of exposure to bilirubin are important determinants of the neurotoxic effects of bilirubin, whereas the correlation between the serum bilirubin concentration and bilirubin encephalopathy is poor in infants without hemolysis [16].

BIND score is a scoring system, in which characteristics of mental state, muscle tone, and cry are grouped into three levels of increasing abnormality: stage IA, minimal signs; stage IB, progressive but reversible with treatment; stage II, advanced and largely irreversible, but may be significantly decreased by treatment [16]. There is also a modified BIND score (BIND-M) [23].

Indirect (unbound) bilirubin concentration is a better predictor of brain uptake and toxicity of bilirubin than TSB [26]. Free bilirubin (Bf) crosses the blood-brain barrier and exhibits neurotoxicity. In accordance, Bf is thought to predict bilirubin neurotoxicity more reliably than the total serum bilirubin (TSB), as assessed by clinical and electrophysiological parameters, i.e., neurodevelopmental outcome and maturation of automated brain stem responses, respectively [29].

There is presently no method available for measuring free bilirubin concentrations accurately in plasma or serum; therefore, adjunct measurements of albumin concentration and bilirubin albumin ratio may provide more insight into the likelihood of bilirubin-induced encephalopathy [14]. The B/A ratio is considered a surrogate parameter for free bilirubin and an interesting additional parameter in the management of hyperbilirubinemia [4, 20, 21].

Retrospective data have favored an additional role for high B/A ratios as risk factors for bilirubin-induced neurotoxicity and only limited data exist regarding B/A ratios in the management and neurodevelopmental outcome of preterm infants with unconjugated hyperbilirubinemia [24].

Methods

This prospective cohort study was performed over a period of 6 months from January 2016 to June 2016 on neonates admitted to the NICU department, at Abuelrish Pediatric Hospital with severe hyperbilirubinemia reached critical level of phototherapy or exchange transfusion according to the American Academy of Pediatrics guidelines. The current study included 100 newborn infants classified into 2 groups. Group (1) included 50 neonates with indirect hyperbilirubinemia without neurological manifestations. Group (2) included 50 neonates with indirect hyperbilirubinemia with neurological manifestations.

Inclusion criteria included infants diagnosed by pediatrician as icteric requiring admission in neonatal ward for treatment, unconjugated hyperbilirubinemia developed at 1st week of age.

Exclusion criteria included infants with hydrops fetalis, congenital nephritic syndrome, and other diseases that mimic BIND e.g. convulsions due to intracranial hemorrhage etc. as well as death due to other reasons will be excluded.

All the cases were subjected to the following: (1) Clinical Evaluation: thorough history taking including prenatal history (maternal illness, PROM, maternal blood group and Rh, maternal drugs, fever, history of other siblings with jaundice), natal history (mode of delivery, resuscitation), and postnatal history (gestational age, gender, weight, type of jaundice, age at admission). (2) Full clinical examination including the following: general examination: vital signs, anthropometric measures, presence of cephalohematoma, apparent congenital anomalies; systemic examination: cardiac, abdominal, chest, neurological examination and assessment of neonatal reflexes.

Modified bilirubin-induced neurological dysfunction (BIND) score was done on admission for the patients who were presenting with neurological manifestations and was used to assess the severity of ABE through examining the mental state, muscle tone, and cry pattern (Table 1).

Laboratory workup

A. Serum bilirubin and serum albumin on admission before starting any treatment.
B. Type of jaundice was assessed using blood group of the baby and the mother, reticulocytic count and Coombs test.
C. Hemoglobin and hematocrit level was recorded.
D. Serum bilirubin albumin ratio was calculated.

Treatment implemented

Whether exchange transfusion, intensive or conventional phototherapy was recorded.

Sample size

Sample size was calculated to determine the minimum proper sample size. Sample size calculation was done using StatCalc, Epi Info version 7 for MS Windows, Centers for Disease Control and prevention (CDC), USA (Table 2).

Table 1 Modified bilirubin-induced neurological dysfunction (BIND) score

Clinical sign	Score	Severity	Date/time
Mental status			
Normal	0	None	
Sleepy but arousable Decreased feeding	1	Mild	
Lethargy Poor suck and/or Irritable/jittery with short-term strong suck	2	Moderate	
Semi-coma Apnea Seizures Coma	3	Severe	
Muscle tone			
Normal	0	None	
Persistent mild hypotonia	1	Mild	
Moderate hypotonia Moderate hypertonia Increasing arching of neck and trunk on stimulation without spasms of arms and legs and without trismus	2	Moderate	
Persistent retrocolis Opisthotonus Crossing or scissoring of arms or legs but without spasms of arms and legs and without trismus	3	Severe	
Cry pattern			
Normal	0	None	
High pitched	1	Mild	
Shrill	2	Moderate	
Inconsolable crying or Cry weak or absent in child with previous history of high pitched or shrill cry	3	Severe	
Occulomotor or eye movements			
Normal	0	None, mild	
Sun-setting Paralysis of upward gaze	3	Severe	
Total ABE score			

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Statistical methods

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 23. Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of bilirubin and B/A ratio for detection of neurological dysfunction. *P* values less than 0.05 were considered as statistically significant.

Table 2 Sample size

Sample size	
Group 1	14
Group 2	14
Total	28

Results

Comparison between the demographic data of the neonates in both groups is represented in (Table 3).

Cause of jaundice was studied among all patients. It was due to hemolytic cause in 34 (34%) patients, 6 (17.64%) of them were due to RH incompatibility, 17 (50%) of them were due to ABO incompatibility, and 2 (5.88%) of them were due to ABO + RH; other causes of hemolysis such as minor blood group incompatibilities occurred in 9 patients. Non-hemolytic causes in 66% of the cases, 29 of them were due to ABO incompatibility

Table 3 Demographic data of all studied groups of neonates (n = 100)

		Group				
		Patients without neurological manifestations		Patients with neurological manifestations		*P* value
		N = 50	%	*N* = 50	%	
Preterm or full term	Preterm	11	22.0	13	26.0	0.64
	Full term	39	78.0	37	74.0	
Single or twins	Single	47	94.0	50	100.0	0.242
	Twins	3	6.0	0	0.0	
Sex	Male	29	58.0	27	54.0	0.687
	Female	21	42.0	23	46.0	

P value < 0.05 is considered significant

without evidence of hemolysis in (43.93%) and 37 of them with unknown causes (56%) (Table 4).

The results of BIND-M score were studied which describes the characteristics of the mental state, muscle tone, cry pattern, and eye movement (Table 5).

The mean BIND score among all the studied patients was 2.15 ± 2.75 (Table 6).

The grade of BIND-M score among group (2) in which maximum total score for BIND-M is 12; a score of 1–4 was predicted to be indicative of mild ABE, which is generally considered to be reversible if treated promptly and aggressively which was seen in 25 patients representing 50% of the cases in group (2); and an intermediate score (5–6) was predicted to be indicative of moderate ABE, which might be reversible with urgent and prompt bilirubin reduction which was seen in 18 patients representing 36% of the cases in group (2); and higher scores (> 7) would likely indicate severe/very severe ABE, probably representing irreversible brain damage in most infants and it was seen in seven patients representing 14% of the cases in group (2) (Table 7).

There was no statistically significant correlation between Bind score and B/A ratio (Table 8)

There was no statistically significant difference between the two groups as regards hemoglobin level, hematocrit, retics count, total leukocyte count, platelet count, and direct bilirubin and albumin.

There was statistically significant difference between the two groups as regards TSB and bilirubin albumin ratio (Table 9).

Neurological dysfunction using bilirubin albumin ratio in all patient is illustrated in Fig. 1.

At chosen cutoff value of bilirubin albumin ratio (B/A) 6.68, sensitivity was 82% while specificity was 64% and accuracy was 95%. This means that at a (B/A) of < 6.68, most of the neonates had no neurological manifestations.

P value less than 0.05 is considered significant.

There was statistically significant difference between the two groups as regards bilirubin albumin ratio (Table 10).

Detection of neurological dysfunction using total serum bilirubin in all patients is illustrated in Fig. 2.

At chosen cutoff value of bilirubin 28.55, sensitivity was 66% while specificity was 84% and accuracy was 95%. There was no statistically significant difference between the two groups as regards total serum bilirubin (Table 11).

Detection of neurological dysfunction using albumin in all patients is illustrated in Fig. 3 and Table 12.

Discussion

Kernicterus or bilirubin encephalopathy, a preventable cause of handicap, still occurs in our community. The crash cart approach to babies with severe hyperbilirubinemia and rapid intervention with intensive phototherapy and exchange transfusion is the only known measures to prevent the occurrence of bilirubin-induced neurological damage [8, 9].

Measurements of albumin concentration and bilirubin/albumin (B/A) ratio may provide much more insight into the likelihood of BIND. The B/A ratio is considered

Table 4 Types of jaundice among the studied neonates

Type	Number of cases	Subtypes
Hemolytic cause	34/100 (34%)	RH incompatibility, 6/34 (17.64%)
		ABO incompatibility, 17/34 (50%)
		ABO+RH, 2/34 (5.88%)
		Others, 9/34 (26.47%)
Non-hemolytic cause	66/100 (66%)	ABO incompatibility without evidence of hemolysis, 29/66 (43.93%)
		Unknown causes, 37/66 (56%)

Table 5 Frequency of distribution modified BIND score (BIND-M) among the neonates in group (2)

		n = 50	%
Mental state	Mild	7	7.0
	Moderate	40	40.0
	Severe	3	3.0
	Normal	50	50.0
Muscle tone	Mild	18	18.0
	Moderate	16	16.0
	Severe	5	5.0
	Normal	61	61.0
Cry pattern	Mild	16	16.0
	Moderate	8	8.0
	Severe	1	1.0
	Normal	75	75.0
Eye movement	Normal	94	94.0
	Severe	6	6.0

a surrogate parameter for free bilirubin and an interesting additional parameter in the management of hyperbilirubinemia [5].

The current study included 100 newborn infants and was conducted as a prospective cohort study on neonates with hyperbilirubinemia reached critical level of phototherapy or exchange transfusion according to the American Academy of Pediatrics admitted to the NICU department, at Abuelrish pediatric Hospital, over a period of 6 months from January 2016 to June 2016.

In our study, we found that the male to female ratio was 1.2:1. The male predominance was also noted in the group of patients with neurological manifestation with a ratio of 1.2:1.

This correlates well with the study done by [7, 22].

This also correlates well with the study done by Iskander et al. [15] who reported 68% for males and 31.4% for females, (male/female ratio = 1.16:1).

[28] suggested that this increased susceptibility to bilirubin-induced injury in male neonates may be due to an impact of gonadotropin surge during late embryonic and early postnatal life on CNS development or innate gender-based neuronal differences independent of circulating sex steroids.

In the present study, the mean age of onset of jaundice was 2.36 ± 1.04 days and the mean age of neonatal ICU admission of the babies was 4.97 ± 2.46. In a Turkish study, [6] studied neonates > 35 weeks and documented that the day the family noticed jaundice was 2.9 days (± 1.7 SD) and the postnatal age at admission was of 4.6 ± 2.3 days. Iskander et al. [15] related this late presentation to early discharge from maternity units (< 24 h) often with no neonatal clinical examination prior to discharge, no evaluation for the risk of developing jaundice, or any instructions for follow-up, lack of available or affordable phototherapy, and false sense of security regarding the potential consequences of severe jaundice by both physicians and parents.

Table 6 Results of BIND-M score in studied neonates in group (2)

	Mean ± standard deviation	Median	Range
Bind score	2.15 ± 2.75	1	0–11

Table 7 The grade of BIND score in group (2)

Grade of BIND score	*N* = 50	%
Mild (1–4)	25	50
Moderate (5–6)	18	36
Severe (> 7)	7	14

Signs of acute bilirubin encephalopathy (ABE) were studied in the group of patients with neurological manifestations who were representing 50% of the studied neonates on admission. The BIND score was used to assess the severity of acute bilirubin encephalopathy through examining mental state, muscle tone, and cry. Subtle ABE was found in 25 patients (50%) with BIND score (1–4), 18 patients (36%) had signs suggestive of moderate ABE with BIND score (5–6) while only 7 patients (14%) showed signs suggestive of advanced ABE with BIND score (> 7).

In a 2-year British study by [19], they reported an incidence of ABE of 12% which correlates well with our results.

On the other hand, a higher percentage was found by [12], who reported 40% of their cases suffered from ABE on admission and 14% still had evidence of BE at discharge. This higher incidence of ABE on admission could be explained by their inclusion criteria which required a higher admission TSB (> 25 mg/dl) compared with our study.

Severe neonatal hyperbilirubinemia due to hemolytic causes represented 34% of our cases of which 50% and 17.64% of the cases were due to ABO incompatibility and Rh incompatibility respectively, while undiagnosed hemolytic causes represented 26.47% of the total number of cases. The latter could be attributed to minor blood group incompatibilities which are not routinely tested for. On the other hand, non-hemolytic jaundice occurred in 66% of our cases. A study by [30] documented that 21.8% of neonates with hyperbilirubinemia above 20 mg/dl had ABO incompatibility, and 2.9% had Rh incompatibility in their study. The incidence of Rh incompatibility in our country is still high compared with the developed world. This is due to the defective antenatal Rh screening for mothers and timely provision of anti-D

Table 8 Relation between BIND score and B/A ratio in patients with neurological manifestation

		B/A ratio			*P* value
		Mean ± standard deviation	Median	Range	
Grade of BIND	Mild ABE	8.06 ± 1.77	7.79	5–12.5	0.092
	Moderate ABE	7.99 ± 2.54	8.25	2.89–11.71	
	Severe ABE	10.53 ± 2.79	11.90	6.25–13.45	

P value less than 0.05 is considered significant

antibody which is an essential component of primary prevention of Rh disease and its consequences.

In our study, 10 of 14 infants with Rh incompatibility (71.4%) developed BE but only one (7.1%) developed chronic bilirubin encephalopathy, 22 of 46 (47.8%) infants with ABO hemolytic disease developed BE but only 2 (4.3%) developed kernicterus. On the other hand, 21 of 66 (31.8%) infants with non-hemolytic jaundice developed BE but only 3of 66 (4.5 %) developed kernicterus.

This suggests that hemolysis is a risk factor for the occurrence of acute bilirubin encephalopathy and that timely intervention may stop the progression to chronic bilirubin encephalopathy and is in agreement with the risk factors defined by the AAP guidelines in 2004 [30]. also reported that kernicterus was more common in neonates with blood group incompatibility compared with other causes of jaundice.

In our study, the risk factors in cases in order were prematurity in 24 newborns (24%), ABO incompatibility in 46 newborns (46%), RH incompatibility in 14 newborns (14%), infants of diabetic mothers in 2 newborns (2%), and history of neonatal jaundice in previous babies in 15 newborns (15%).

In a study by Zabeen et al., [31] on 60 jaundiced newborn infants in a tertiary hospital to detect different risk factors for neonatal jaundice, they found that prematurity, IDM, septicemia, and ABO incompatibility were observed in 44 (73.3%), 21 (35%), 16 (26.6%), and 8 (13.3%) cases respectively. G6PD deficiency was found in only one (1.7%) case. They agree with our study in that prematurity was the risk for neonatal jaundice in most cases and G6PD deficiency was the least risk factor.

In the present study, the mean peak TSB level in all cases was 26.14 ± 7.36 mg/dl. A statistically significant difference was found between the mean peak TSB level in the patients with neurological manifestations (29.24 ± 7.78 mg/dl) and the mean peak TSB level in the patients without neurological manifestations was (23.04 ± 5.41 mg/dl).

The total serum bilirubin level in patients on admission without neurological manifestations on admission (22.8 mg/dl) was lower than the median TSB level for patients with neurological manifestations which was 30 mg/dl.

Although the TSB was higher in the group 2, higher bilirubin levels were recorded in those with moderate ABE than those with severe ABE. This question whether TSB can be relied upon as an independent prognostic factor for poor neurological outcome.

Gamaleldin study 2011 reported that out of 106 infants who were disease free, 26% had a TSB level of > 31.5 mg/dl and the lowest bilirubin level at which kernicterus occurred was 25 m/dl [18]. also showed that all kernicteric babies in their study had TSB levels > 30 mg/

Table 9 Comparison between the two groups regarding laboratory investigations done

	Group						*P* value
	Group 1 *N* = 50			Group 2 *N* = 50			
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
HB (g/dl)	12.72 ± 2.99	12.77	4–18.7	12.84 ± 3.23	12.15	6.50–19.6	0.978
HCt (%)	37.25 ± 7.76	37.45	12–51.9	36.13 ± 10.15	35.25	0.90–55.7	0.408
Retics (%)	5.11 ± 9.86	2.15	0.0–65	5.43 ± 5.40	3.1	0.0–20.8	0.544
TLC (10^3/mm^3)	7.15 ± 1.51	7.1	3.1–10.8	7.12 ± 0.87	7.1	5.3–9.1	0.920
PLt (10^3/mm^3)	284.3 ± 70.55	310	160–420	297.84 ± 68.59	308.5	183–423	0.440
T. Bil	23.04 ± 5.41	22.8	12.30–33	29.24 ± 7.78	30	8.1–46.5	< 0.001
D. Bil	1.13 ± 0.83	1	0.1–5	1.73 ± 1.70	1.1	0.1–9	0.1
Alb	3.63 ± 0.55	3.7	2–4.7	3.54 ± 0.70	3.55	2–5	0.389
B/A ratio	6.46 ± 1.84	6.09	3.85–14	8.38 ± 2.34	8.08	2.89–13.45	< 0.001

P value less than 0.05 is considered significant

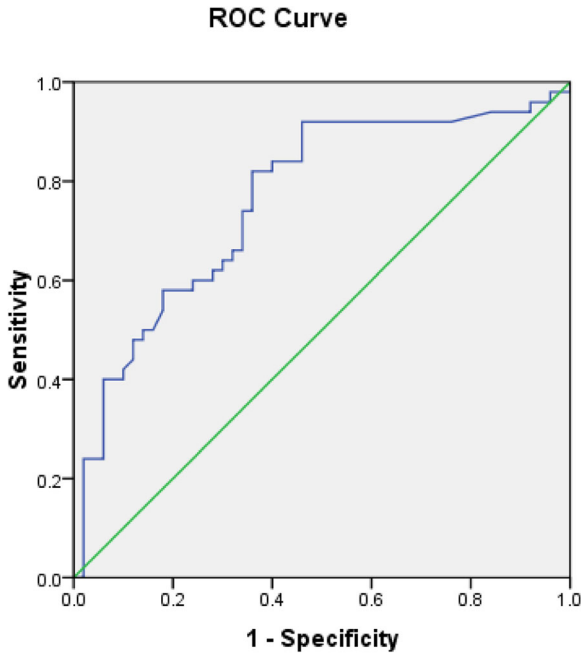

Fig. 1 ROC curve for detection of neurological dysfunction using bilirubin/albumin ratio in all patient

dl. These findings prompt us to agree with [17] that in the absence of risk factors i.e. in healthy full-term neonates, such levels are detected (serum bilirubin less than 30 mg%).

[25] reported that subtle neurotoxicity may appear later or even at school age as learning disabilities. This could be important in making long-term follow-up a necessity.

It is clear from the previous results that there exists a wide variation in the individual response to TSB which indicates that though serum bilirubin is sensitive, yet it is not specific in many cases. This also indicates that the pathogenesis of BE involves critical plasma and/or host defense variables that have yet to be identified.

Free bilirubin and not TSB is the principal determinant of bilirubin neurotoxicity. There is presently no method available for measuring free bilirubin concentrations accurately in plasma or serum so the bilirubin albumin ratio (B/A) is considered as a surrogate parameter for free bilirubin and an additional parameter in the prediction of BE [13].

The mean B/A ratio among the neonates with neurological manifestations was (8.38 ± 2.34), whereas among the jaundiced neonates without neurological manifestations was (6.46 ± 1.84) and this difference was statistically significant.

[2] reported that the mean B/A ratio among patients with BE was (10 ± 1.6), whereas among other jaundiced neonates was (6.1 ± 2.4). They also reported that neurotoxicity does not occur until the molar concentration of bilirubin approached the concentration of albumin (B/A ratio = 8.8). As TSB exceeds this binding capacity, free bilirubin increases dramatically and the final deposition is governed by the availability of alternative plasma binding loci and ultimately by the low solubility of free bilirubin.

All babies with B/A ratio > 13.1 developed BIND. However, we observed one baby with normal outcomes at B/A ratio of 12.5 mg/g. This suggests that additional bilirubin binding sites other than albumin must exist in plasma.

Receiver operating characteristics (ROC) analysis identified B/A ratio cutoff value for predicting bilirubin-induced neurological dysfunction was 6.68 (AUC 0.76) with sensitivity of 82% and specificity of 64% and these results were statistically significant, whereas TSB cutoff value of 28.55 mg/dl showed sensitivity of 66% and specificity of 84% and these results were statistically significant [2]. identified B/A cutoff value for predicting acute BIND of 8 (AUC 0.957) with sensitivity of 100% and specificity of 94%, whereas a TSB cutoff value of 25 mg/dl in their study showed sensitivity of 100% and specificity of 85%. According to this finding, B/A ratio was more specific than TSB in the prediction of poor neurological outcome. Variations in the expanded buffering capacity combined with variation in blood-brain barrier function and host defenses at the cellular level provide the only explanation for the limited specificities of TSB and B/A in predicting outcome.

Until now, the precise threshold at which TSB or bilirubin albumin ratio may be neurotoxic in a given infant is unknown. We therefore agree with [16] that it is very important to study and identify the individual differences in the ability to destroy bilirubin in the brain and the factors that expedite or delay its neuronal exit which may help identify the baby prone to neuronal damage and therefore aid in the prevention of kernicterus.

Table 10 AUC, cutoff value, sensitivity, and specificity of B/A ratio for detection of neurological dysfunction

Area under curve	*P* value	95% confidence interval		Cutoff value	Sensitivity (%)	Specificity (%)
		Lower bound	Upper bound			
.763	< 0.001	.667	.858	6.6866	82	64

AUC (area under the curve) = 0.763; *P* value less than 0.05 is considered significant

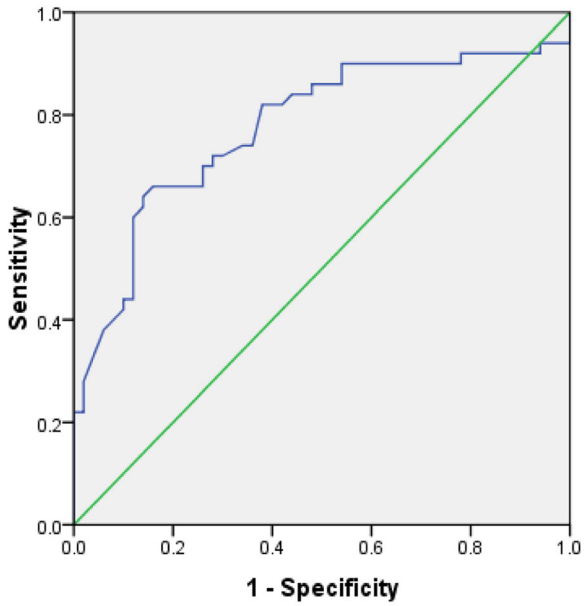

Fig. 2 ROC curve for detection of neurological dysfunction using total serum bilirubin in all patients

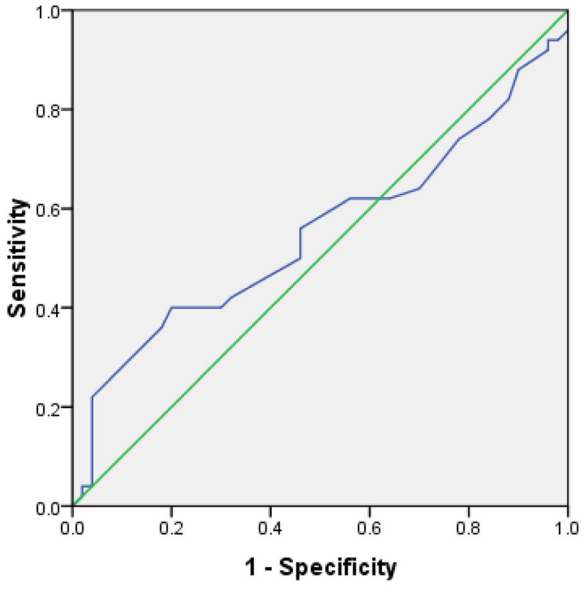

Fig. 3 ROC curve for detection of neurological dysfunction using albumin in all patients

Among the group of patients with neurological manifestations showed a male predominance (54%), nine (33%) of them had ABO incompatibility, seven of them (25%) had RH incompatibility, none of them had sepsis, and 13 had jaundice of unknown cause. The TSB and B/A ratio were significantly higher in all the patients with neurological manifestations. All received intensive phototherapy in the Bilisphere and all had exchange transfusions.

Limitations of the study

1. Our study included 74% of the patients were full-term babies and 26% of them were preterm babies which gave no chance to accurately test the predictive value of bilirubin/albumin ratio for early detection of neurological dysfunctions in the preterm babies.
2. The number of cases and duration along which our cases were collected in our study were limited, so further studies needed on a larger sample size and on a longer duration to confirm our results.
3. Varity and overlapping of the etiological risk factors as ABO, Rh incompatibility, and sepsis.
4. Inability to do routine G6PD enzyme assay and large category of unknown causes (37% 0f cases).

Conclusions

- Kernicterus is a preventable cause for brain injury resulting from severe untreated neonatal hyperbilirubinemia.
- There is a high prevalence of severe hyperbilirubinemia and kernicterus in the NICU of CUPH.
- The most frequent causes of severe hyperbilirubinemia in our population are ABO incompatibility and Rh incompatibility. Undetermined causes are still present in a big number of cases.

Table 11 AUC, cutoff value, sensitivity, and specificity of total serum bilirubin for detection of neurological dysfunction

Area under curve	*P* value	95% confidence interval		Cutoff value	Sensitivity (%)	Specificity (%)
		Lower bound	Upper bound			
.776	< 0.001	.681	.870	28.55	66	84

AUC (area under the curve) = 0.776; *P* value less than 0.05 is considered significant

Table 12 AUC and *P* value for albumin for detection of neurological dysfunction

Area under curve	*P* value	95% confidence interval	
		Lower bound	Upper bound
.550	.391	.434	.665

P value less than 0.05 is considered significant

- Total serum bilirubin was sensitive but not specific to neurologic affection.
- Estimation of B/A ratio proved to be a more specific indicator of the neurologic outcome of neonates with severe hyperbilirubinemia.

Abbreviations

ABE: Acute bilirubin encephalopathy; B/A ratio: Bilirubin/albumin ratio; BE: Bilirubin encephalopathy; Bf: Free bilirubin; BIND: Bilirubin-induced neurologic dysfunction; CBC: Complete blood count; CUPH: Children University Pediatric Hospital; DSB: Direct serum bilirubin; RH: Rhesus; TcB: Transcutaneous bilirubin; TSB: Total serum bilirubin; UCB: Unconjugated bilirubin

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Authors' contributions

All authors reviewed the final version of the manuscript, believe it represents valid work, and approve it for publication. As an Author, I certify that none of the material in the Article has been published. RS and DM contributed to the study conception and design. NA, ME, and DM contributed to data acquisition. ME, NA, DM, and RS contributed analysis and data interpretation. DM and RS contributed to drafting of the manuscript. RS and DM contributed to critical revision.

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Availability of data and materials

The corresponding author had full access to all of the data and takes full responsibility for the veracity of the data and statistical analysis.

Ethics approval and consent to participate

The trial was based on Master of Science thesis approved by Pediatric Department Committee for Post-Graduate Studies and Research, and by Post-Graduate Studies and Research administration, Faculty of Medicine, Cairo University, Egypt. Approval date was 21/12/2015.
Written consents were obtained from parents of study participants. Investigations and all lines of treatments were clarified.

Consent for publication

Written consents were obtained from parents of study participants. Investigations and all lines of treatments were clarified. Consents included agreement for publication.

Competing interests

The authors declare that they have no competing interests.

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