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PREDICTORS AND PROFILE OF HEARING LOSS IN HIGH RISK NEONATES: A CROSS-SECTIONAL ANALYTICAL HOSPITAL BASE STUDY.

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Abstract

Introduction:

Loss of hearing during early infancy leads to delayed development of language, communication, and cognition which affects the social, emotional, and academic achievements of a child. Early identification of hearing impairment improves age-related language and communication skills.

Aim & Objectives:

To find out the prevalence and profile of hearing loss among high-risk neonates in a hospital setup.

Material and Methods:

This was a prospective observational study being conducted over two years at VIMSAR, Bulra, Sambalpur, Odisha. 264 high-risk neonates admitted to Neonatal Intensive Care Unit were screened using evoked otoacoustic emission (EOAE) and Brainstem Evoked Response Audiometry (BERA). Neonates who tested refer on EOAE were subjected to BERA and those having a unilateral or bilateral hearing threshold for more than 40 dB in BERA were defined as hearing impaired.

Results:

Most of the study neonates were having multiple significant risk factors. Multivariate logistic regression analysis of significant risk factors for hearing loss revealed gestational diabetes of the mother, mechanical ventilation for more than 5 days, hyperbilirubinemia requiring exchange transfusion, hypoglycemia during the early neonatal period, and duration of hospitalization for more than 5 days were the independent risk factors associated with hearing loss.

Conclusion:

This study implies a high incidence of hearing impairment in neonatal intensive care unit(NICU) graduates and a change in the distribution of risk factors for hearing loss. Gestational diabetes, mechanical ventilation for more than 5 days, hyperbilirubinemia with exchange transfusion, neonatal hypoglycemia, and NICU stay for more than 5 days were significant independent clinical risk factors for predicting hearing impairment in high-risk neonates.

Recommendation:

Universal newborn screening for hearing loss in high-risk neonate and early identification of risk factors and exposure reduction should be done, so that the devastating effects of hearing impairment could be prevented before it starts.

Keywords: Hearing loss, Neonate, High risk, Submitted: 2023-07-09 Accepted: 2023-07-12

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1. Introduction:

Hearing is a part of normal speech and language development by which the child is able to hear the spoken language, contact with environment, communicate and acquire skills [1]. Most crucial time for development of speech and language is the first year of life especially during the initial six months of infancy[2] .Hearing loss is a hidden disability which occurs gradually, mimic forgetfulness, inattentiveness and mental disability [3]. It is recognized usually at two to three years when the child's speech and language ability is irreversibly affected.Hearing impairment has not only deleterious and detrimental impact on development of neonates but also psychological well being of the families. Decreased auditory input has adverse effect on development of central auditory nervous system and poor impact on speech perception that interferes with growth in social, emotional, behavioral and cognitive domains, academic achievement, employment opportunities and economic self-sufficiency [4]. As the most important period for language and speech development is the initial six months, early hearing detection and intervention activities soon after birth have positively impacted the outcomes for children who are deaf, hard of hearing and their families [5].

In India around 63 million (6.3%) people suffer from significant hearing loss according to population based surveys [6]. Four in every1000 children suffer from severe to profound hearing loss and 100,000 babies are born with hearing deficiencies every year [7]. Neonatal hearing loss has a prevalence that is more than twice of other newborn disorders like hypothyroidism and phenylketonuria[8,9]. Different studies done in India using different hearing screening protocols have reported a prevalence of hearing impairment ranging from 0.09 to 2.3% in normal neonates and 0.3 to 20.68 % in high risk neonates [10]. The Joint Committee on Infant Hearing (JCIH),2007 and American Academy of Pediatrics (AAP) advocated universal screening of newborn hearing before 3 months and remedial measures, to maximize linguistic and communicative competence and literacy development for hearing impaired children [11]. India being a developing country havingin adequate infrastructure, limited resources and lack of public awareness one could focus initially on at high risk neonates to adopt a cost effective way of detecting hearing loss [12].The JCIH,2007 position statement emphasizes on implementation of 1-3-6 goals which means screening, confirmation and treatment of hearing impairment must commence at 1 month,3months and 6 months of age of an infant respectively [11].

The present study was undertaken to evaluate the possible burden of hearing loss in high risk neonates, identification of risk factors and planning out local strategies in future for hearing screening in newborn.

Aim :To find out the prevalence and profile of hearing loss among high risk neonates in a hospital set up.

Objectives : To estimate the prevalence,clinical & demographic profile of hearing impairment in high risk neonates as per joint committee of infant hearing 2007 guidelines from amongst graduates of special newborn care unit(SNCU) and NICU at VIMSAR and determine the predictors of hearing loss in those neonates.

2. Material & Methods:

This study was conducted from November 2020 and continued up to October 2022 at SNCU, NICU, High-risk Neonate follow-up clinic, Department of Paediatrics and Auditory Screening Room, Department of Otorhinolaryngology, VIMSAR, Burlaafter getting clearance from institutional ethical committee. It was a cross-sectional analytical hospital-based study. 264 neonates were included who qualified for the inclusion criteria.

2.1. Inclusion criteria of cases:

Neonates having 1.Birth weight< 1500gm [as per documents],2.Gestational age < 37

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weeks[as per documents or history and assessment),3.Gestational diabetes mellitus[as per operational definition],4.Maternal hypothyroidism. 5. Gestational hypertension.6.Family history of hereditary sensorineural hearing loss in first-degree relatives.7.Born out of consanguineous marriage,8.Moderate to severe HIE (Levene's classification),9.Hyperbilirubinemia requiring exchange transfusion,10. Bacterial meningitis is defined by CSF characteristics,11. Culture-proven sepsis,12.Mechanical ventilation for > 5 days.13.TORCH infection as defined by serum Ig M characteristics,14.Ototoxic medication during hospital stay(aminoglycosides, loop diuretics, and others),15.Syndromes which include sensory neural or conductive deafness (clinical diagnosis)(Down Syndrome, Treacher Collin Syndrome, Pendredsyndrome, Waardenburg syndrome, Goldenhar syndrome, Stickler syndrome, Usher syndrome, CHARGES syndrome, Crouzen syndrome, Brachio-oto-renal syndrome, Alport syndrome)

2.2. *Exclusion criteria of cases:*

Hemodynamically unstable neonates.

2.3. *Study Tools, Techniques, and Interventions:*

2.3.1. *Preparatory phase [November 2019 to October 2020]:*

During that period a blueprint of the proposed dissertation was made. Data regarding the prevalence of hearing impairment in high-risk neonates and their profiles related to the study were collected and prevailing practices regarding the screening of hearing were discussed with the experts in the field. It was found that hearing impairment starts from early infancy and timely intervention can prevent further disability in speech, language, and cognitive development. Though universal hearing screening was ideal to study but due to a lack of manpower and infrastructure only high-risk neonates were included for screening for hearing impairment. After discussing with the inter-departmental personnel and institution ethics committee, a flow chart of the study was formulated. The sample size was calculated and the principal study was commended.

2.3.2. *Data collection Phase (November 2020 to October 2022):*

The study was conducted between November 2020 to October 2022. Each patient was enrolled in the study after informed written consent was taken from the parents. Case performed for each patient was filled and data was collected as described in detail in the study procedure.

2.3.3. *Data Analysis and Interpretation (November 2022)*

Data collected from the study were processed, and checked for internal errors, internal and external validation was done during masterV2 software and SPSS V24 software (IBM.NEW YORK). Data were analyzed in terms of Omnibus Tests of Model coefficients, Hosmer and Lemeshow Test, Cross tab design, Univariate, and Multiple regression analysis and results were interpreted.

2.3.4. *Presentation and Report writing (December 2022)*

A final review of the study was done before the Institutional ethical committee and needed modifications were done after the expert opinion of the ethical board members. Finally, the study was ready and the results of the study were reported in the form of a thesis dissertation, paper publication in standard scientific journals of the world including India.

Neonates with high-risk factors were identified during the NICU stay. At 1 week of age or at the time of discharge whichever was later, the neonates were planned for OAE screening. After taking informed written consent from parents and counseling the neonates were given sypTrichlofos at 20mg/kg/dose orally for sedation. A team consisting of an audiologist, staff nurse, counselor, and pediatrician was organised for screening.OAE testing was done by an ERO-SCAN machine manufactured by MAICO Diagnostic Gmbhsalzufer 13/14, 10587 Germany. Both the external auditory meatus was closed with appropriate size occluder and the low-pitch sound stimulus was delivered into the ear canal through the probes. The

otoacoustic emissions from the cochlea were interpreted and those neonates tested PASS were declared as having normal hearing and those tested REFER were declared as positive screening for hearing impairment and planned for a second OAE test.

Neonates who tested REFER during the first OAE screening were planned for a second screening by OAE after 1 month of initial screening. Those infants who tested REFER were planned for BERA evaluation at 12 weeks of age. After sedating the infant with oral Trichlofos syrup, they were subjected to BERA testing on an EPA PreAmplifier machine manufactured by InteracousticsPvt.Ltd. The skin at the point of placement of electrodes was cleaned with 'an abrasive strip. Recording of BERA was carried out in a quiet and semi-darkened room. Surface electrodes were placed at the vertex (CZ), both mastoids (Ai and Ac), and forehead (ground). The resistance was kept below 5K. Monoaural auditory stimulus consisting of rarefaction clicks of 100 microseconds were delivered through electrically shielded earphonesattherateof11.1/sec. Contralateralearwasmaskedwithpurewhitenoise of 40dB. A bandpass of 150-3000Hz was used to filter out undesirable frequencies in the surroundings. Responses to 2000 click presentations were averaged.

BERA threshold for each ear with absolute latencies of wave I, II, III, IV, and V waves interpeak latencies (IPL) of I-III, I-V, and III-V, and amplitude ratio V/I was calculated and interpreted accordingly.

2.4. Bias:

There was no bias as we strictly stick to the operational definition. Every care was taken to avoid bias.

2.5. Study variables and operational definition:

2.5.1. Continuous variables:

1. Age of the baby at time of evaluation,
2. Birth weight,
3. Gestational age in weeks,
4. RBS in mg/dl.
5. Oxygen saturation,
6. Respiratory rate,
7. Capillary refill time,
8. IgM titer of TORCH serology

2.5.2. Categorical variables:

1. Gender of the baby
2. Moderate to severe HIE,
3. Syndromes associated with hearing impairment, Culture proven sepsis
4. CSF proven meningitis
5. Family history of sensorineural hearing loss,
6. Duration of mechanical ventilation
7. Ototoxic medication during NICU stay
8. Jaundice with exchange transfusion
9. NICU stay> 5 days
10. Neurological deficit at the time of discharge.

2.6. Data Analysis:

Continuous data were expressed in mean±SD; categorical data were expressed in proportions. Data normalcy testing of continuous data was done and no transformation was required. All the descriptive statistics were done by SPSS v 25(IBM, New York) .For all statistical purposes p value < 0.05 was considered significant.

3. Observation:

3.1. Study Flow Chart:

Out of 3059 neonates admissions 1220 babies constituted the study population. As many as 264 were enrolled as study subjects based on the inclusion and exclusion criteria laid down. There were 141(53.4%) males and 123(46.5%) females, reflecting an M: F ratio of 1.14:1 . Mean age at which initial screening was done was 14.19±3.45 days in all high-risk neonates while 20.2±3.66 days in neonates with hearing loss. The mean age at which hearing loss was confirmed was 96.4±4.64 days

There were 130 (49.2%) preterm babies.72 (27.3 %) VLBW, 15(5.7%) ELBW, 91(34.5%) moderate to severe HIE, 37(14.0%) had consanguinity among parents, 11(4.2%) were associated with syndromes including hearing loss, 24(9.1%) had family history of deafness, 60 (22.7%) neonates

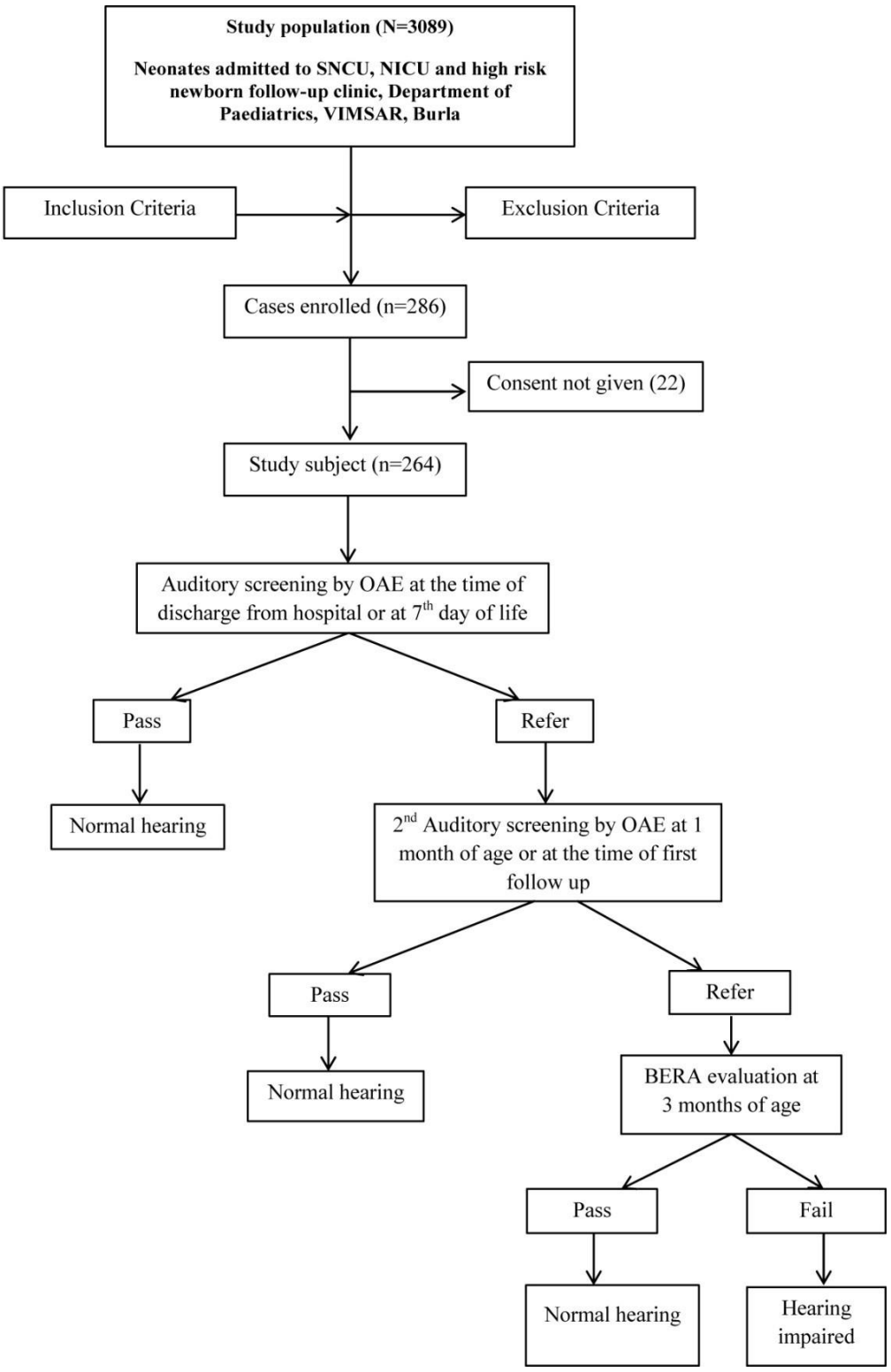

Figure 1: Study Flow Chart

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Table 1: Baseline variables of studysubjects [n=264]

Variables	Number	Percentage
Preterm	130	49.2
VLBW	72	27.3
ELBW	15	5.7
HIE-moderate/severe	91	34.5
Family History of Deafness	24	9.1
Pregnancy induced Hypertension	46	17.4
Gestational hypothyroidism	22	8.4
Gestational diabetes	34	12.9
Consanguinity	07	2.3
Syndrome with hearing loss	11	4.2
Culture positive sepsis	60	22.7
CSF proven Meningitis	28	10.6
TORCH positive	32	12.1
Mechanical ventilation > 5 days	40	15.2
Ototoxic medication	211	79.9
Jaundice with exchange transfusion	26	9.8
RDS	48	18.2
Shock	53	20.1
Hypoglycemia	53	20.1
NICU stay > 5 days	69	26.1
Neurological deficit	53	20.1
Oxygen supplement >48hrs	117	44.3

treated culture positive sepsis, 28(10.6%) diagnosed as meningitis by CSF characteristics, 32(12.1%) TORCH infected, 40 (15.2%) had undergone mechanical ventilation for more than 5 days, 211(79.9%) exposed to ototoxic medication, 26(9.8%) had hyperbilirubinemia and required exchange transfusion, 48(18.2 %) diagnosed as RDS, 53(20.1%) had shock during hospital stay, 53 (20.1%) had hypoglycemic episodes during hospitalisation, 69 (26.1%) had duration of NICU stay more than 5 days and 53 (20.1%) were discharged with residual neurological deficit. Many of them were having more than one risk factor.

The mean gestational age was 35.97 3.6±75 weeks in all high-risk neonates while it was 36.66±3.544 weeks in neonates with hearing loss. Mean birth weight was 2480.50±917.275 grams among high-risk neonates while high-risk neonates were having birth weightof 2560±942.657 grams. The mean age at which initial screening was done was 14.19±3.45 days in all high-risk neonates while 20.2±3.66 days in neonates with hearing loss. The mean age at which hearing loss was confirmed was 96.4±4.64 days.

The above table shows no significant association between consanguinity among parents and hearing loss in neonates as evidenced by p>0.05. Similarly, gestational hypertension in the mother, family history of deafness, and hypothyroidism during pregnancy also had no significant association with hearing impairment during the neonatal period as evidenced by p>0.05 in all cases. The above table demonstrates a strong association between gestational diabetic mothers and hearing impairment in the neonates as evidenced by Pearson chi-square(1)=45.643,p< 0.05.

The above table signifies out of all(n=99) preterm neonates, 31(23.8%) were diagnosed as hearing impaired. Among VLBW and ELBW

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Table 2: Descriptive analysis of demographic variables among high-risk neonates

Characteristics		High risk neonates (n=264)	Neonates with hearing loss(n=64)
Gestational age in weeks	Mean ±SD [wks]	35.97 ± 3.675	36.66± 3.544
	Median [wks]	37	37
Birth weight in grams	Mean ± SD[gms]	2480.50±917.275	2560.87±942.657
	Median [gms]	2817	2856
Age of initial screening,	Mean ±SD[]days]	14.19±3.45	20.2±3.66
	Median[day]	10	18
Age at]confirmation of hearing loss	Mean [days]	–	96.4
	Median [days]	–	89.2

Table 3: Distribution antenatal risk profile

Risk factor	pass Count(n)	Per(%)	Fail Count(n)	Percent(%)	x^2(df)	p	95% C I lower	Upper
Consanguinity	5	83.3	1	16.6	0.000(1)	0.990	0.447	2.260
Gestational hypertension	37	80.4	9	19.6	0.664(1)	0.415	0.327	1.5888
Gestational hypothyroid	15	68.2	7	31.8	0.730(1)	0.392	0.585	3.876
Gestational diabetes	10	29.4	24	70.6	45.643(1)	**0.002**	5.058	25.695
Family history	17	70.8	07	29.2	0.349(1)	0.555	0.522	3.347

df- degree of freed om, p value < 0.05 is considered to be statistically significant, CI- confidence interval

Table 4: Profiles of risk factors(gestational age, birth weight and HIE) on hearing impairment

Risk factor	pass Count(n)	Percent(%)	Fail Count(n)	Percent(%)	x^2(df)	P	OR	95% CI Lower	Upper
Preterm	99	76.2	31	23.8	0.022(1)	0.882	0.958	0.546	1.683
VLBW	51	70.8	21	29.2	1.307(1)	0.253	1.427	0.774	2.629
ELBW	11	73.3	04	26.7	0.051(1)	0.822	1.145	0.352	3.730
HIE	54	59.3	37	40.7	20.379(1)	**0.002**	3.705	2.062	6.658

df- degree of freedom, p value < 0.05 is considered to be statistically significant, CI- confidence interval, OR- odds ratio

neonates 21 (29.2%) and 04(26.7%) were diagnosed as hearing impaired respectively.07(29.2%) neonates having family history of hearing loss were diagnosed as hearing impaired while 37(40.7%) hearing impaired neonates were diagnosed as moderate to severe HIE. prematurity, VLBW and ELBW were non significant risk factors as evidenced by p>0.05 in all cases. There found to be significant association (p<0.05) among neonates with moderate to severe HIE and hearing impairment.

The above table depicts,4 out of 11 (36.4%) neonates having syndromes associated with hearing loss were later declared as deaf. 21 (35.0%) hearing-impaired neonates were treated as a case of culture-positive sepsis. Out of 28 neonates di-

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Table 5: Distribution of riskfactors(congenital syndromes of hearing loss, sepsis, meningitis, mechanical ventilation, TORCH infection and ototoxic medication) among high-risk neonates

Risk factor	pass Count(n)	Per(%)	Fail Count(n)	Per(%)	x^2(df)	P	OR	95% CI Lower	Upper
Congenital syndromes hearing loss	07	63.6	4	36.4	0.918(1)	0.338	1.838	0.520	6.494
Culture positive Sepsis	39	65.0	21	35.0	4.893(1)	**0.027**	2.016	1.076	3.779
Meningitis	06	21.4	22	78.6	50.430(1)	**0.000**	16.937	6.470	44.337
Mechanical ventila-tion > 5 days	11	27.5	29	72.5	59.778(1)	**0.000**	14.236	6.512	31.123
TORCH infection	10	31.3	22	68.8	39.276(1)	**0.033**	9.952	4.389	22.570
Ototoxic drug	154	73.0	57	27.0	4.397(1)	**0.036**	2.432	1.032	5.698

df- degree of freedom, p value < 0.05 is considered to be statistically significant, CI- confidence interval, OR- odds ratio

agnosed with meningitis by CSF characteristics 22(78.6%) became hearing impaired. 40 neonates who undergone mechanical ventilation for > 5 days 29(72.5%) were diagnosed hearing impaired during follow up. 32 neonates were diagnosed TORCH positive by IgM serology and out of them 22 (68.8%) were hearing impaired. 211 neonates were exposed to ototoxic medication during their hospital stay and 57(27%) became hearing impaired.

There is a significant association between hearing impairment and risk factors like meningitis($p<0.05$), mechanical ventilation for more than 5 days($p<0.05$), TORCH infection($p<0.05$), ototoxic medication($p<0.05$), and culture positive sepsis($p<0.05$) while syndromes with congenital hearing loss($p>0.05$) had no statistical significance.

The above table depicts 18(69.2%) neonates who had undergone exchange transfusion for hyperbilirubinemia,17(35.4%)neonates with RDS soon after birth, 31(58.5%) neonates who develop shock during a hospital stay,29(54.7%) neonates with symptomatic hypoglycemia during hospitalisation,29(54.7%) neonates having residual neurological and 51(73.9%) neonates having a hospital stay for more than 5 days were diagnosed as hearing impaired during follow up evaluation.

There is a significant statistical association of hearing impairment in neonates with neonatal hyperbilirubinemia requiring exchange transfusion, RDS, shock during a hospital stay, symptomatic hypoglycemia, residual neurological deficit at discharge, and hospitalisation for more than 5 days as evidenced by $p<0.05$.

Initial screening with OAE was done for the high-risk neonates after completion of the first week of life or at the time of discharge among whom 172 (65.2%) passed and 92 (34.8%) preferred. Those neonates who were referred to the first OAE were undergone repeat OAE at 1 month of age or during the first follow-up, among whom 4 were lost during follow-up. In the remaining 88 infants, only 10(11.3%) passed and 78 (88.6%) were referred. But considering the total population 29.5 % of high-risk neonates failed in the

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Table 6: Distribution of riskfactors(Jaundice with exchange transfusion, RDS, Shock, Hypoglycemia, Residual neurological deficit, Duration of hospitalisation) among high-risk neonates

Risk factor	pass		Fail		x^2(df)	P	OR	95% CI	
	Count(n)	Percent(%)	Count(n)	Percent(%)				Lower	Upper
Jaundice with Exchange transfusion	8	30.8	18	69.2	31.783(1)	**0.002**	9.391	3.846	22.933
RDS	31	64.6	17	35.4	3.989(1)	**0.046**	1.972	1.005	3.869
Shock	22	41.5	31	58.5	42.352(1)	**0.036**	7.601	3.926	14.716
Hypoglycemia	24	45.3	29	54.7	33.533(1)	**0.028**	6.076	3.168	11.654
Neurological deficit	24	45.3	29	54.7	33.533(1)	**0.000**	6.076	3.168	11.654
Duration of hospitalization >5 days	18	26.1	51	73.9	125.492(1)	**0.000**	39.667	18.219	86.382

df- degree of freedom, p value < 0.05 is considered to be statistically significant, CI- confidence interval, OR- odds ratio

Table 7: Time trend analysis of the neonatal hearing screening tests

Test	Outcome			
	Pass		Refer/Fail	
	Count(n)	Percent(%)	Count(n)	Percent(%)
First OAE[n=264] (At Day 7 /Discharge)	172	65.2	92	34.8
Second OAE[n=88] (At 1 month/follow up)	10	11.3	78	88.6
BERA[n=72] (At 12 week)	8	11.1	64	88.8

second OAE. Out of 78 neonates tested referred during the second OAE evaluation, 6 were lost to follow-up at the time of the BERA study. Among these infants, 64 (88.8%) failed during BERA test indicating a hearing impairment of 24.2% among the high-risk neonates

The p values for STEP, BLOCK and MODEL are 0.000 which is significant (i.e.<0.05). This means there has been significant improvement in predictory power as compared to the previous step. A model with predictors (independent variables) is significantly better than a model with constant only. The model is good to fit as the value of Cox and Snell R square =0.032 and Nagelkerke R square =0.047. This model fits the data as Hosmer and Lemeshow chi-square test(7):=5.710(7),p=0.639.

As most of the neonates were exposed to multiple risk factors, excluding the variables which are not showing significant association in the previous regression model another multivariate regression model for hearing impairment was considered

The Multivariate regression analysis of the significant risk factors revealed that out of all associated risk factors Gestational diabetes, Mechanical ventilation requirement for more than 5 days, hyperbilirubinemia requiring exchange transfusion, hypoglycemia during early neonatal period and duration of hospitalization for more than 5 days were independent risk factors(p<0.05).

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Table 8: Univariate statistical analysis of risk factors

Risk factors	Hearing impairment		x^2(df)	OR	(95% CI)	p value
	Present	Absent				
Prematurity	31(23.8%)	99(76.2%)	0.022(1)	0.958	0.546-1.683	0.882
VLBW	21(29.2%)	51(70.8%)	1.307(1)	1.427	0.774-2,629	0.253
ELBW	04(26.7%)	11(73.7%)	0.051(1)	1.145	0.352-3.730	0.822
Gestational hypertension	09(19.6%)	37(40.7%)	0.664(1)	0.721	0.327-1.588	0.415
Gestational diabetes	24(70.6%)	10(29.4%)	45.643(1)	11.400	5.058-25.695	**0.002**
Gestational hypothyroidism	07(31.8%)	15(68.2%)	0.730(1)	1.506	0.585-3.876	0.393
Consanguinity	01(16.6%)	05(83.6%)	0.333(1)	1.005	0447-2.260	0.990
Family history	07(29.8%)	17(70.8%)	0.349(1)	1.322	0.522-3.347	0.555
O_2 Requirement	26(22.2%)	91(77.8%)	1.105(1)	1.353	0.769-2.379	0.293
Congenital syndrome ofhearing loss	04(36.4%)	07(63.6%)	0.918(1)	1.838	0.520-6.494	0.338
Mod to severe HIE	37(40.7%)	54(59.3%)	20.379(1)	3.705	2.062-6.658	**0.000**
Culture positive sepsis	21(35%)	39(65%)	4.8939(1)	2.016	1.076-3.779	**0.027**
Meningitis	22(78.6%)	06(21.45)	50.340(1)	16.937	6.3470-44.337	**0.000**
Mechanical ventilation > 5 days	29(72.5%)	11(27.5%)	59.778(1)	14.236	6.512-31.123	**0.000**
TORCH infection	22(68.8%)	10(31.2%)	39.276(1)	9.952	4.389-22.570	**0.033**
Ototoxic drug	57(27%)	154(73%)	4.397(1)	2.432	1.038-5.698	**0.036**
Jaundice with exchange transfusion	18(69.2%)	08(30.8%)	31.783(1)	9.391	3.846-22.933	**0.002**
RDS	17(35.4%)	31(64.6%)	3.989(1)	1.972	1.005-3.869	**0.046**
Shock	31(58.5%)	22(41.5%)	42.352(1)	7.601	3.926-14.716	**0.036**
Hypoglycemia	29(54.7%)	24(45.3%)	33.533(1)	6.076	3.168-11.654	**0.028**
Neurological deficit	29(54.7%)	24(45.3%)	33.533(1)	6.076	3.168-11.654	**0.000**
Hospital stay >5 days	51(73.9%)	18(26.1%)	125.492(1)	39.667	18.219-86.362	**0.000**

df- degree of freedom, p value < 0.05 is considered to be statistically significant, CI- confidence interval, OR- odds ratio

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Table 9: Multivariate regression analysis of high risk factors

Risk factor	df	P value	95% C.I for Exp Lower	Upper
Gestational diabetes	1	**0.006**	1.656	20.297
Mechanical ventilation >5 days	1	**0.004**	0.053	0.579
Hyperbilirubinemia with exchange transfusion	1	**0.003**	0.032	0.491
Hypoglycemia	1	**0.006**	0.087	0.669
Duration of NICU stay > 5 days	1	**0.000**	0.018	0.116

4. Discussion:

4.1. The present study was undertaken to predict the risk factors responsible for hearing loss in neonates and analyze their profiles.

The incidence of hearing impairment in high risk neonates according to different studies is 1-40.3 % [12, 13, 14]. In this study, the incidence is 24.2 % which is similar to other studies.

264 high risk neonates were subjected to OAE testing, out of which 92(34.8%)neonates referred after the first screening. Majority of the referred neonates were having multiple risk factors. During second OAE screening4(4.3%) neonates weredropped out. Out of remaining 88 infants 10(11.3%) passed the second screening by OAE, while 78 (88.6 %0) failed. These infants were plannedBERA at 12 weeks of age. 6(7.6%) babies out of 78 were lost to follow up during BERA evaluation. Total number of infants subjected to BERA were 72 out of which 64(88.8%) were failed and diagnosed as hearing impaired. All 64 babies havingprofound hearingloss werereferred to Audiologist for earlyintervention. In the present study out of 264 high risk neonates enrolled, 64(24.2%)had hearing impairment.

Majority of the neonates were between 32 to 40 weeks of gestational age withmean gestational age of 35.97 weeks in high risk neonates and 36.66weeks in neonates with hearing impairment, with p value 0.882 which was statistically insignificant.

Mean age at which initial screening done was 14.19 days in all high-risk neonates while it was 20.2 days in neonates with hearing loss. Mean age at which hearing loss was confirmed was 96.4 days (around 14 weeks). This result is consistent with the 1-3-6 benchmark of EHDI guidelines.

Mean birth weight in all high risk neonates was 2480 grams while 2560grams in neonates with hearing loss. Gender analysis revealed, out of all high risk neonates 141 (53.4%) were male and 123(46.5%) were female and among hearing impaired infants 29 (22%) were male and 35 (26.5%) were female having p value 0.389 which is statistically insignificant indicating no gender association with hearing loss.

In this study the analysis of antenatal risk factors revealed that Gestational Diabetes has p value 0.002 indicating significant association with hearing impairment in neonates. This is consistent with the findings of Li et al 2020[15]. The high incidence can be explained as infant of diabetic mother(IDM) are macrosomic and more prone to birth asphyxia, hypoglycemic brain injury and association with occuloauriculo vertebral spectrum (OAVS). Other antenatal risk factors like consanguinity among parents, gestational hypertension and hypothyroidism in mother showed no significant association with hearing loss in neonates.

In our study family history of hearing impairment had no significant statistical association with neonatal hearing loss which is consistent with the inference of Jowel John et al[16]

Regina M et al[10], John et al[16] and Gouri et al[17]concluded that low birth weight is a significant risk factor for hearing impairment but present study did not find any statistical significance between them, though 29.2%(n=21) of

hearing impaired babies were VLBW(birth weight <1500 gram) and 26.7 %(n=4) were ELBW(birth weight <1000 gram)butp value was 0.253 and 0.822 respectively indicating no statistical significance. VLBW and ELBW were not specifically listed as a risk factors in the position statements of JCIH in 2000 and 2007. This indicates the growing understanding that low birth weight itselfdoes not cause hearing loss; but when associated with other concomitant risk factors may precipitate hearing impairment.

In the present study 40.7%(n=37) neonates with moderate to severe HIE were found to have hearing impairment which is statistically significant(p<0.05) andsimilar to study conducted by Misra et al[18] in which43% new born with birth asphyxia were hearing impaired. In our study we included neonates with moderate to severe birth asphyxia defined by Levene et al[19],while study conducted by Sayed et al[20] included only severe asphyxiated neonates with an incidence of hearing impairment 100%. So it can be inferred that more severe the hypoxic insult, more is the hearing impairment.

In the present study hearing impairment was 78.6%(n=22)among neonates having meningitis proven by CSF analysis andwas statistically significant (p<0.05). Ourresultis very high as compared to Jewel John et al 2007 and Vaghasiya et al 2016[21] where 50% of neonatal meningitis cases were diagnosed as hearing impaired. High occupancy in our NICU necessitating early discharge prior to completion of full course of antibiotic and poor patient compliance to follow up may be a contributing factor. AL HarbiMet al[22], KY Chan et al[23] opined thatmeningitis is a significant factor for hearing loss due to vasculitis of inner ear or adhesions comprising eighth cranial nerve.

In a study conducted by Pourarian S et al 2012[24] revealed that 32% of neonatal sepsis cases became hearing impaired, but this was statistically not significant. In the present study hearing impairment in neonates havingculture positive sepsis was 35%(n=21)and statistically significant (p value 0.027) probably due to high number of meningitis cases among sepsis(46.6%).

The use of ototoxic medication to be an important risk factor (p =0.036) for deafness in neonatal period in the current study is similar to Giesel M et al 2006[25] and Hernandez et al 2007[26]. It may be noted that the drugs of choice for treatment of Gram negative organisms at our institute is Gentamycin and Amikacin andstrict control of these drugs is an important risk factor for preventing ototoxicity.

Biswas A K et al 2012[27] concluded that TORCH infection is a significant risk factor in determining neonatal hearing loss. In our studyneonates having TORCH infection proven by serum Ig M assay 68.8%(n=22) were hearing impaired and was statistically significant(p<0.05).

In the present study out of all neonates treated with mechanical ventilation for more than 5 days 29 (72.5%) became hearing impaired. Studies conducted by Ashok et al 2012[27] and Patel et al 2015[4] revealed 41% and 45% of neonates had hearing impairment on mechanical ventilation for more than 5 days respectively. In our study such high association may be due to middle ear effusion secondary toprolonged mechanical ventilation and non titration of oxygen therapy.

Hyperbilirubinemia requiring exchange transfusion is an important risk factor for hearing impairmentin neonatesinferredin the presentstudy is consistent with reports from Sayed et al 2004[20] andNam G S et al 2019[28]. Our study reported 18 (69.2%) hearing impaired neonates who undergone exchange transfusion for jaundice which is quite high as compared to the similar studies. It can be explained as most of the jaundice neonates at our institute were preterm, associated with co morbidities like sepsis and hypoxia and delayed referral from other hospitals after bilirubin induced auditory neuropathy has initiated.

About 17(35.4%) neonates with RDS became hearing impaired in our studyhaving statistical significance. This is consistent with the study conducted by KeihaniDoust Z et al 2018[29].

The present study revealed significant association of Shock and Hypoglycemia during early neonatal period with hearing impairment on later age. None of these risk factors were taken into consideration in current similar studies. Shock

and Hypoglycemia are the usual manifestations of common neonatal illness like birth asphyxia, prematurity, sepsis and infant of diabetic mother. They induce neuronal swelling and necrosis, atrophy of gyrus and white matter myelination causing long term impairment of cognitive function including hearing loss [30,31].

According to the diseaseseverity somehigh risk neonates included in this study had abnormal residual neurological finding at the time of discharge. So we included Neurological deficit at the time of discharge as a risk factor and on analysis obtained 29(54.7%) infants with neurological deficithad hearing impairment during follow up which was statistically significant. None of the current studies have considered this as a risk factor, while Boudewyns A et al revealed that, out of all high risk neonates with Auditory Neuropathy Spectrum Disorder, 50% had abnormalities in magnetic resonance imaging suggestive of neurological dysfunction [32].

The duration of NICU stay which reflects the average age of diagnosis of hearing impairmentto be an important risk factor in the present study is similar to Chang J et al [33].

The overall analysis of the risk factors revealed that gestational diabetes, culture positive sepsis, CSF proven meningitis, TORCH infection, ototoxic medication, shock during hospitalization, RDS, hypoglycemia, hyperbilirubinemia requiring exchange transfusion, residual neurological deficit ,mechanical ventilation for more than 5 days and duration of hospitalization for than 5 days had significant association with hearing impairment. As most of the neonates were having multiple risk factors, multivariate logistic regression analysis of these significant risk factors revealed gestational diabetes, hypoglycemia during hospital stay, mechanical ventilation for more than 5 days, hyperbilirubinemia requiring exchange transfusion and duration of hospitalization more than 5 days were statistically significant independent risk factors.

5. Conclusion:

Early screening and recognition of hearing impairment during the neonatal period is the fundamental step to reduce the negative consequences on a child's psychosocial, scholastic, and social-emotional development. The two staged screening protocols with OAE and confirmation by BERA were found to be useful tools in detecting hearing loss in high-risk neonates and were quite beneficial and justified in terms of scientific and economic principles that significantly reduced further costs to the patient. Moreover, the study highlights the relevance of neonatal screening and antenatal factors assessment in our country where it is not performed routinely in all healthcare centers.

6. Limitation:

As it is a hospital-based study in a tertiary care center with limited resources the universal screening of hearing loss among neonates could not be performed. As it is a single-center study, the results are not devoid of confounders and interactions despite our relentless effort. More of our study was done in tertiary care centers; so didn't project the hearing impact on the whole population.

7. Recommendation:

Universal newborn screening for hearing loss in high-risk neonates and early identification of risk factors and exposure reduction should be done, so that the devastating effects of hearing impairment could be prevented before it starts. We recommend further longitudinal case-control studies and randomized controlled trials to be conducted to evaluate the predictors of hearing loss and their profiles in neonates so that prevention of exposure, early diagnosis, and timely intervention could be performed to manage long-term language and cognitive complications.

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9. Author's Contribution:

All authors were involved in research design, data analysis, and manuscript preparation and editing.

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None

11. Abbreviations :

AAP - American Academy of Pediatrics
ABR - Auditory Brainstem Response
BAEP - Brainstem Associated Evoked Potential
BERA - Brainstem Evoked ResponseAudiometry
CI - Confidence Interval
CSF - Cerebro Spinal Fluid
df - Degree of freedom
EHDI - Early Hearing Detection and Intervention
ELBW - Extreme Low Birth Weight
HIE - Hypoxic Ischemic Encephalopathy
HRR - High Risk Register
JCIH - Joint Committee on Infant Hearing
NICU - Neonatal Intensive Care Unit
NI H - National Institute of Health
NPPCD - National Programme for Prevention and Control of Deafness
OAVS - Oculo-Auriculo Vertebral Spectrum
OR - Odds Ratio
RDS - Respiratory Distress Syndrome
SD - Standard Deviation
TOAE - Transient Oto Acoustic Emission
TORCH - Toxoplasma Rubella Cytomegalovirus Herpes
VLBW - Very Low Birth Weight
VIMSAR - Veer SurendraSai Institute of Medical Sciences and Research

12. Operational deftnitions:

1. Neonates- Babies of age from birth up to 28 days of life.
2. Premature neonates: Neonates having gesta- tional age less than 37 weeks.
3. VLBW neonates: Neonates having birth weight in between 1500 grams to 1000 grams.
4. ELBW neonates: Neonates having birth weight less than 1000grams.
5. Hypoxic IschemicEncephalopathy: Grades of hypoxic ischemic encephalopathy were defined as per Leveneclassification.
6. Pregnancy Induced Hypertension: Defined as Hypertensionwith or without proteinuria after 20 weeks of gestation.
7. Gestational Hypothyroidism: Defined as abnormal Serum thyroid stimulating hormone (TSH), tri-iodothyronin (T3), tetra-iodothyronin(T4) levels of mother duringor before pregnancy.
8. Gestational Diabetes mellitus: Defined as ab- normal Fasting blood glucose and oral glucose tol- erance test during pregnancy.
9. Sepsis: Defined as microbiologically confirmed blood culture samples taken from clinically suspected cases.
10. Meningitis: Defined as cytological, biochem- ical and microbiological characteristics proven CSF analysis obtained fromclinically suspected cases.
11. TORCH infection: Defined as congenital-Toxoplasma, Rubella, Cytomegalovirus, Herpes virus infection proved by serological positive titer of Immunoglobulin M[64].
12. Respiratory Distress Syndrome: Defined as Silverman Anderson score of more than 4 in preterm term neonates .
13. Shock: Defined as inability to maintain the peripheral perfusion due to multiple factors.
14. Hypoglycemia: Defined as random plasma glucose less than 45 mg/dl and blood glucose less than 40 mg/dl.
15. Neurological deficit: Defined as abnormal neurological examinationat the time of discharge.

Data Analysis: Continuous data were expressed in mean ±SD; categorical data were expressed in

proportions. Data normalcy testing of continuous data was done and no transformation was required. All the descriptive statistics were done by SPSS v 25(IBM, New York) .For all statistical purposes p value < 0.05 was considered significant.

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