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Prevalence and association of early onset severe hyperbilirubinemia in newborn in the East China region

Retrospective medical record analyses

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Abstract

Research on the prevalence and association of hyperbilirubinemia is controversial because of different cultures, demographics, and clinical conditions. The etiology of hyperbilirubinemia is affected by the environment and other factors in the newborn. The World Health Organization recommended a 1-day hospital stay after uncomplicated delivery, jaundice assessment before discharge, and screening on 3rd and 7th days after birth for hyperbilirubinemia. However, the implementation of these recommendations is difficult in China. The objective of this study was to evaluate the prevalence and association of early onset severe hyperbilirubinemia in newborns in East China. Retrospective medical record analyses for 250 cesarean sections or vaginal deliveries, ≥2 kg body weight, and negative for Hepatitis B surface antigen by birth newborns were performed. A biochemical analyzer, quantitative assay, and quantitative polymerase chain reaction were used to evaluate total serum bilirubin, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and gene variant phenotyping, respectively. A total in 33 (13%) newborns were reported with early onset severe hyperbilirubinemia (according to the American Academy of Pediatrics, total serum bilirubin ≥ 342 μmol/L within 6 hours of birth). All newborns with severe hyperbilirubinemia were hospitalized and underwent phototherapy. The mothers of all newborns had a gestational age ≥ 35 weeks. Hospitalization included artificial feeding, and breastfeeding was rare ($P < .0001$). ABO incompatibility ("O" blood type for mother and either "A" or "AB" or "B" blood type for newborn, $P = .0411$), G6PD deficiency (G6PD/6-phosphogluconate dehydrogenase ≤ 1.0 in quantitative assay, $P = .0422$), Rh incompatibility (the mother's blood type was Rh negative and newborn blood type was Rh positive, $P = .0416$), fewer genotype rs4149056 frequencies ($P = .0452$), higher genotype rs2306283 frequencies ($P = .0461$), and higher genotype rs1805173 frequencies ($P = .0471$) were independent parameter for early onset severe hyperbilirubinemia of newborns. The prevalence of early onset severe hyperbilirubinemia in Chinese newborns is 13% in the East China region. Blood incompatibility, G6PD deficiency, fewer genotype rs4149056 frequencies, higher genotype rs2306283 frequencies, and higher genotype rs1805173 frequencies were independent predictors of early onset severe hyperbilirubinemia among newborns in the East China region (Level of Evidence: IV; Technical Efficacy: Stage 5).

Abbreviations: ANOVA = analysis of variance, CI = confidence interval, Early onset severe hyperbilirubinemia = total serum bilirubin ≥ 342 μmol/L within 6 hours of birth, G6PD = glucose-6-phosphate dehydrogenase, non-severe hyperbilirubinemia = total serum bilirubin < 342 μmol/L, qPCR = quantitative polymerase chain reaction, SD = standard deviation, χ^2-test = Chi-square test.

Keywords: artificial feeding, blood incompatibility, breastfeeding, G6PD deficiency, gestational age, hyperbilirubinemia, newborn

1. Introduction

Hyperbilirubinemia in newborns is most common now.[1] Phototherapy is generally the preferred treatment for severe neonatal hyperbilirubinemia.[2] Hyperbilirubinemia mainly results in an imbalance between the production and elimination of bilirubin in newborns.[3] The detection and association of hyperbilirubinemia is important for the early treatment of hyperbilirubinemia in newborns because hyperbilirubinemia causes autism, jaundice, encephalopathy, life-long disabilities, or death of newborns.[4]

The research on the prevalence and association of hyperbilirubinemia is controversial; for example, the prevalence of

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severe hyperbilirubinemia in eastern Guangdong, China is 32%, and neonatal hemolysis and infection are the main predictors of severe hyperbilirubinemia in eastern Guangdong, China.[3] However, mutations in the G211 gene, ABO incompatibility, and glucose-6-phosphate dehydrogenase (G6PD) deficiency are the main predictors of severe hyperbilirubinemia in Fujian, Southeastern China.[5] G6PD and UGT1A1 deficiencies are the main predictors of severe hyperbilirubinemia in Shanghai, China.[6] The etiology of hyperbilirubinemia is affected by the environment and other factors in newborns.[3] The contradictory results among Chinese newborns are due to different cultures and demographic and clinical conditions.[4]

The etiology of hyperbilirubinemia is complex.[3] The World Health Organization recommends a 1-day hospital stay after uncomplicated delivery, jaundice assessment before discharge, and screening at 3rd day and 7th day after birth for hyperbilirubinemia.[7] However, the implementation of these guidelines is difficult in Chinese institutes because of comparatively fewer facilities and the health care burden on families. Under such conditions, the current study was performed to guide authorities regarding the prevalence and association of early onset severe hyperbilirubinemia in newborns in East China.

The objective of this study was to evaluate the prevalence and association of early onset severe hyperbilirubinemia in newborns available at institutes in East China.

2. Materials and methods

2.1. Ethics approval and consent to participate

The protocol was designed by the authors and approved by the Human Ethics Committee of the First Affiliated Hospital of Ningbo University and the Chinese Neonatal Network (approval no. 15147AHNU, dated February 16, 2022). The study followed the law of China and the v2008 Declarations of Helsinki. As this was a retrospective medical record analysis of neonates, informed consent to participate was waived by the human ethics committee of the First Affiliated Hospital of Ningbo University.

2.2. Inclusion criteria

Cesarean section or vaginally delivered newborns in the institutes were included in the analyses.

2.3. Exclusion criteria

Newborns with incomplete records from institutes were excluded from the study. Newborns <2 kg in body weight and positive for Hepatitis B surface antigen by birth were excluded from the analysis.

2.4. Early onset severe hyperbilirubinemia in newborns

According to the American Academy of Pediatrics, newborns with a total bilirubin of more than 95 % percentile and total serum bilirubin 342 μmol/L or more within 6 hours of birth were considered early onset severe hyperbilirubinemia in newborns.[3]

2.5. Non-severe hyperbilirubinemia in newborns

Newborns with a serum bilirubin level < 342 μmol/L within 6 hours of birth were considered to have non-severe hyperbilirubinemia.[3]

2.6. ABO incompatibility

"O" blood type for the mother and either "A," or "AB," or "B" blood type for the newborn was considered as ABO incompatibility.[8] Cord blood test and a complete blood count were performed for detection of ABO incompatibility.

2.7. G6PD deficiency

Heel capillary blood samples were collected from the newborns. A G6PD nitroblue tetrazolium Quantification Ratio Kit (Fenghua China Guangzhou Co., Ltd., Guangdong, China) was used for the quantitative assay of G6PD. A ratio of G6PD/6-phosphogluconate dehydrogenase 1.0 or less was considered a G6PD deficiency.[9]

2.8. Rh incompatibility

Rh incompatibility was defined as Rh-negative for the mother's blood type and Rh-positive for the newborn blood type.[10]

2.9. Pathological evaluation of total serum bilirubin

Blood samples were collected from empty stomachs. A biochemical analyzer (Trivitron Healthcare, Mumbai, Maharashtra, India) was used to evaluate total serum bilirubin.

2.10. Exclusive breastfeeding

Newborns feed only breast milk, except for oral rehydration solution or any other drops or syrups (prescribed by a pediatrician).[11]

2.11. Quantitative polymerase chain reactions

Venous blood (3 mL) was collected in EDTA tubes (KS Medical, Yeoksamdong, Seoul, Korea). A high-purity Genomic DNA isolation kit (Sigma-Aldrich Solutions, St. Louis, MI) was used to isolate genomic DNA from the blood. Genomic DNA was stored at –20°C until further experiments.

The rs4148323, rs2306283, and rs4149056 gene variants were subjected to quantitative polymerase chain reaction (qPCR) using the primers presented in Table 1. All primers were purchased from Sigma-Aldrich solution (St. Louis, MI).

A total of 4 μL of PCR master mix and 1 μL of DNA template were processed at 94°C for 5 minutes, followed by 45 cycles of 94°C for 20 seconds, 56°C for 30 seconds, 72°C for 60 seconds, and 72°C for 180 seconds. The final material was processed with shrimp alkaline phosphatase (Sigma-Aldrich Solutions, St. Louis, MI) to remove free deoxynucleoside triphosphates. The reaction was performed with primers through a single-base extension reaction at 94°C for 30 seconds, followed by 40 cycles at 94°C for 5 seconds, 5 cycles at 52°C for 5 seconds, 80°C for 5 seconds, and finally 72°C for 180 seconds. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (Sigma-Aldrich, St. Louis, MO) was performed for the final product.

The rs8175347 and rs1805173 gene variants were subjected to PCR followed by ABI 3730xl DNA Sequencer (Thermo Fisher Scientific, Waltham, MA) and electrophoresis (Thermo Fisher Scientific, Waltham, MA).

2.12. Statistical analysis

InStat 3.01 GraphPad Software (San Diego, CA) was used for the statistical analysis. Categorical variables are presented as frequencies, with percentages in parentheses. Continuous normal variables are presented as mean ± standard deviation (SD). Continuous non-normal variables are depicted as medians with Q3–Q1 in parentheses. The Kolmogorov-Smirnov

Table 1

Primers used in quantitative polymerase chain reactions.

Gene	Loci	The sequence of quantitative polymerase chain reactions primers (5'–3')	Sequences of single-base extension primers
OAP1B1	rs2306283	Forward: ACGTTGGATGGATGTTCTTACAGTTACAGG Reverse: ACGTTGGATGACAAGTGGATAAGGTCGATG	CGATGTTGAATTTTCTGATGAAT
	rs4149056	Forward: ACGTTGGATGAATCTGGGTCATACATGTGG Reverse: ACGTTGGATGCCAATGGTACTATGGGAGTC	CCAAGCATATTACCCATGAAC
UGT1A1	rs4148323	Forward: ACGTTGGATGCTGACGCCTCGTTGTACATC Reverse: ACGTTGGATGCACATCCTCCCTTTGGAATG	GACTTCTTCAAGGTGTAAAATGCTC
HO-1	rs8175347	Forward: AACTCCCTGCTACCTTTGTGG Reverse: ATGGCACAGGGTACGTCTTC	
	rs1805173	Forward: AGAGCCTGCAGCTTCTCAGA Reverse: ACAAAGTCTGGCCATAGGAC	

method was used to determine the normality of continuous variables. One-way analysis of variance (ANOVA) was used for the statistical analysis of continuous normal variables. The Mann–Whitney test was used for non-normal continuous variables. The Kruskal–Wallis' test (nonparametric ANOVA) was used for non-normal continuous variables. Tukey (for normal variables) or Dann multiple comparison tests (for non-normal variables) were used for post hoc analysis. Fisher exact test or chi-square test (χ^2-test, when the sample size in the 2 × 2 table was > 40) was used for categorical variables for statistical analysis. Multivariate logistic regression analysis was performed to evaluate independent parameters for severe hyperbilirubinemia in newborns. All results were considered significant if *P* value was <.05 at the 95% confidence interval (Cl).

3. Results

3.1. Study population

From September 1, 2021, to December 15, 2022, 275 cesarean sections or vaginally delivered newborns were available at the First Affiliated Hospital of Ningbo University, Zhejiang, China, and the First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui, China. Among them, 5 newborns had incomplete records in the institutes, 7 newborns weighed <2 kg, and 13 newborns were positive for Hepatitis B surface antigen by birth. Therefore, data from these newborns (25 newborns) were excluded from the analysis. Demographic and clinical conditions, ABO incompatibility and G6PD deficiency status, total serum bilirubin level, and gene variant qPCR analyses of 250 newborns were included in the study. A summary chart of the retrospective medical record analyses of newborns is presented in Figure 1.

3.2. Demographic and clinical parameters

The mothers of all newborns had a gestational age ≥35 weeks. A total of 68% of newborns are male and 32% were female. A total of 33 (13 %) newborns out of 250 newborns were reported early onset severe hyperbilirubinemia condition (according to the American Academy of Pediatrics, total serum bilirubin ≥ 342 μmol/L within 6 hours of birth). All newborns with early onset severe hyperbilirubinemia were hospitalized and underwent phototherapy. Sex, body weight, gestational age, age of newborns, and nature of delivery were comparable between newborns with early onset severe hyperbilirubinemia (total serum bilirubin ≥ 342 μmol/L) and non-severe hyperbilirubinemia newborns (total serum bilirubin < 342 μmol/L, *P* > .05 for all). Hospitalization included artificial feeding, and breastfeeding was rare. The demographic and clinical parameters of the newborns are presented in Table 2.

3.3. Risk factors

A total of 30 (12 %) newborns had ABO incompatibility and 10 (4%) newborns had G6PD deficiency. A higher number of newborns had ABO incompatibility, Rh incompatibility, C-reactive protein, and G6PD deficiency if they had early onset severe hyperbilirubinemia (*P* < .05 for all, Fisher exact test). Infection(s) in newborns due to any cause was comparable between newborns with early onset severe hyperbilirubinemia and newborns with non-severe hyperbilirubinemia (*P* > .05, Fisher exact test). The univariate analyses for details of the risk factors for early onset severe hyperbilirubinemia in newborns are presented in Table 3.

3.3.1. Quantitative polymerase chain reactions. All gene variants of early onset severe hyperbilirubinemia and non-severe hyperbilirubinemia newborns followed by the Weinberg equilibrium. Frequencies of genotype rs4149056 (*P* = .0421, Fisher exact test) were lower and those of rs2306283 (*P* = .042, Fisher exact test) and rs1805173 (*P* = .032, Fisher exact test) were higher among newborns with early onset severe hyperbilirubinemia than among newborns without early onset severe hyperbilirubinemia.

3.3.2. Multivariate logistic regression analysis for risk factor. Multivariate logistic regression analysis revealed that ABO incompatibility, G6PD deficiency, Rh incompatibility, lower genotype rs4149056 frequencies, higher genotype rs2306283 frequencies, and higher genotype rs1805173 frequencies were independent parameters for early onset severe hyperbilirubinemia in newborns. Details of the multivariate logistic regression analysis are presented in Table 4.

4. Discussion

The current study reported a 13% prevalence of early onset severe hyperbilirubinemia condition among newborns in the East China region. The prevalence of early onset severe hyperbilirubinemia in the current study is consistent with that of available studies on African neonates[12] but is not consistent with a retrospective analysis of neonatal severe hyperbilirubinemia in eastern Guangdong, China.[3] Its prevalence is affected by environmental factors.[3] Hyperbilirubinemia in newborns is a global issue that requires identifying its cause and etiology.

The current study reported that ABO and Rh incompatibility are associated with early onset severe hyperbilirubinemia in newborns. The results of blood incompatibility predictors for early onset severe hyperbilirubinemia in newborns of the current study are consistent with those of a case-control study on neonatal severe hyperbilirubinemia in Southeastern China,[5] a meta-analysis,[4] a retrospective analysis of neonatal severe hyperbilirubinemia in eastern Guangdong, China,[3] and studies on Indian neonatal hyperbilirubinemia.[13,14] The antigen-antibody reaction between red blood cells in the mother and newborn leads to hemolysis and hyperbilirubinemia.[14]

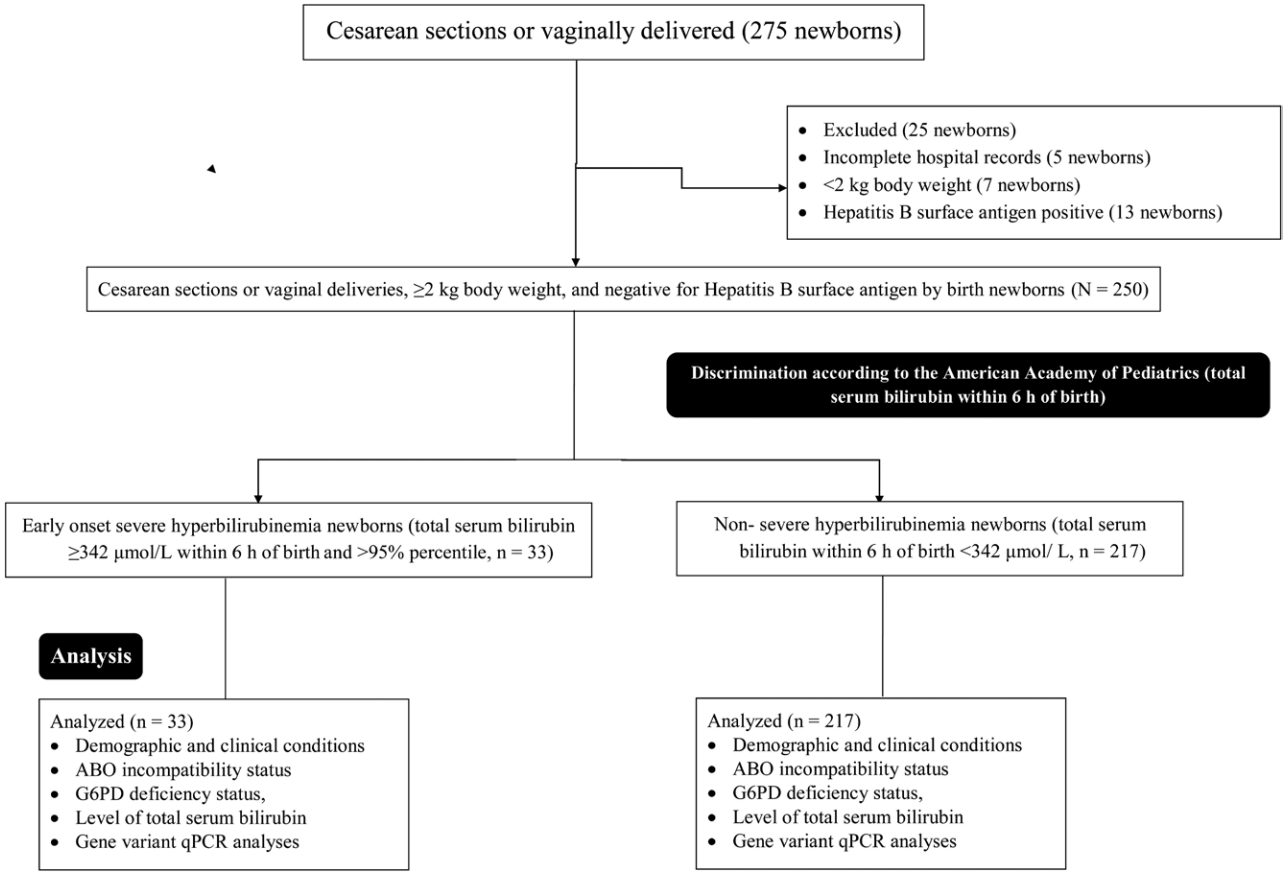

Figure 1. The summary chart of retrospective medical record analyses of newborns. G6PD = glucose-6-phosphate dehydrogenase, qPCR = quantitative polymerase chain reaction.

Table 2

Demographic and clinical parameters of newborns.

Parameters	Newborns			Comparisons between newborns with early onset severe hyperbilirubinemia and those with non-severe hyperbilirubinemia		
	Total	Early onset severe hyperbilirubinemia	Non-severe hyperbilirubinemia			
Numbers of newborns	**250**	**33**	**217**	***P* value**	**Test value**	**95% CI**
Gender						
Male	169 (68)	23 (70)	146 (67)	.8443 (Fisher exact test)	1.102	0.5509 to 2.206
Female	81 (32)	10 (30)	71 (33)			
Body weight (g)	2907 (3047–2742)	2839 (3012–2673)	2941 (3047–2742)	.288 (Mann–Whitney test)	3093.5	N/A
Gestational age (weeks)	37 (37.5–36.5)	37 (37–36)	37 (37.5–36.5)	.0681 (Mann–Whitney test)	2875.5	N/A
Age of newborns (days)	2 (3–2)	2 (3–1)	2 (3–2)	.0595 (Mann–Whitney test)	2853.5	N/A
Nature of delivery						
Cesarean section	65 (26)	8 (24)	57 (27)	.9999 (Fisher exact test)	0.9108	0.4326 to 1.917
Vaginal	185 (74)	25 (76)	160 (73)			
Total serum bilirubin (μmol/L)	267 (272–262)	350 (354.5–348)	265 (270–261)	<.001 (Kruskal-Wallis' test/Dann test)	85.993	N/A
Feeding						
Artificial feeding	33 (13%)	33 (100)	0 (0)	<.0001 (Fisher exact test)	Infinity	-Infinity to Infinity
Breastfeeding	217 (87%)	0 (0)	217 (100)			

Categorical variables are depicted as the frequencies with percentages in parenthesis. Continuous non-normal variables are depicted as medians with Q3–Q1 in parenthesis. All results were considered significant if the *P* value was <.05. Test value (relative risk for Fisher exact test, Mann–Whitney *U*-statics for Mann-Whitney test, Kruskal–Wallis' statics for Kruskal–Wallis' test).
CI = confidence interval (using the approximation of Katz), N/A = not applicable.

Blood transfusion could be a possible solution to ABO and Rh incompatibilities.

The current study reported that G6PD deficiency was associated with early onset severe hyperbilirubinemia in newborns. The results of the association of enzyme deficiency predictors with early onset severe hyperbilirubinemia in newborns of the current study are consistent with those of a case-control study on neonatal severe hyperbilirubinemia in Southeastern China,[5] a meta-analysis,[4] and a retrospective analysis of neonatal severe hyperbilirubinemia in eastern Guangdong,

Table 3

The univariate analyses for details of risk factors for early onset severe hyperbilirubinemia condition of newborns

Parameters	Newborns			Comparisons between newborns with early onset severe hyperbilirubinemia and those with non-severe hyperbilirubinemia		
	Total	Early onset severe hyperbilirubinemia	Non-severe hyperbilirubinemia			
Total serum bilirubin	–	≥342 μmol/L	<342 μmol/L			
Numbers of newborns	250	33	217	*P* value	Relative risk	95% CI
ABO incompatibility*	30 (12)	8 (24)	22 (10)	.0381	2.347	1.167–4.721
Glucose-6-phosphate dehydrogenase deficiency†	10 (4)	6 (18)	4 (2)	.0005	5.333	2.873–9.900
Infection(s)	15 (6)	3 (9)	12 (6)	.4275	1.567	0.5395–4.550
Rh incompatibility‡	17 (7)	6 (18)	11 (5)	.0143	3.046	1.460–6.352
C-reactive protein (≥10 mg/dL)	19 (8)	7 (21)	12 (6)	.0059	3.237	1.640–6.535

Variables are depicted as the frequencies with percentages in parenthesis. Fisher exact test was used for statistical analysis. All results were considered significant if the *P* value was <.05.

CI = confidence interval (using the approximation of Katz).

*"O" blood type for a mother and either "A" or "AB," or "B" blood type for a newborn.

†G6PD/6-phosphogluconate dehydrogenase ≤ 1.0 in the quantitative assay.

‡The mother's blood type was Rh negative and the newborn blood type was Rh positive.

Table 4

Multivariate logistic regression analysis

Parameters	Odd ratio	95% CI	*P* value
ABO incompatibility (*present vs absent)	1.1852	1.1251–1.4521	.0411
G6PD deficiency (*present vs absent)	1.2911	1.1511–1.4522	.0422
Genotype rs4149056 frequencies (*fewer vs normal)	1.1321	1.0524–1.1892	.0452
Genotype rs2306283 frequencies (*higher vs normal)	1.1821	1.0921–1.2921	.0461
Genotype rs1805173 frequencies (*higher vs normal)	1.3101	1.2101–1.4122	.0471
Rh incompatibility (*present vs absent)	1.0112	1.0001–1.2211	.0416
C-reactive protein (≥10 mg/dL vs <10 mg/dL)	0.9351	0.8522–0.9851	.0527
Feeding (artificial feeding vs breastfeeding)	0.9211	0.8851–0.9952	.0611

An odd ratio > 1 and *P* value <.05 was considered significant.

CI = confidence interval.

*Significant parameter for early onset severe hyperbilirubinemia condition of newborns.

China.[3] G6PD deficiency and ABO and Rh incompatibilities are associated with severe hyperbilirubinemia in newborns.[5] This (G6PD deficiency) is a hereditary genetic defect in hyperbilirubinemia.

The current study reported that lower genotype rs4149056 frequencies, higher genotype rs2306283 frequencies, and higher genotype rs1805173 frequencies are associated with early onset severe hyperbilirubinemia in newborns. The results of genetic predictors for early onset severe hyperbilirubinemia in newborns of the current study are consistent with those of a case-control study on neonatal severe hyperbilirubinemia in Southeastern China,[5] a meta-analysis,[4] a retrospective analysis of neonatal severe hyperbilirubinemia in eastern Guangdong, China,[3] and a study on Indian neonatal hyperbilirubinemia.[13] Risk factors should be monitored, and clinicians should predict early onset severe hyperbilirubinemia in newborns and its treatment.

The study reported that infection was not associated with early onset severe hyperbilirubinemia in newborns in the East China region. The results of the current study regarding infection are not consistent with those of a retrospective analysis of neonatal severe hyperbilirubinemia in eastern Guangdong, China.[3] Differences in the time for diagnosis of infection in the current study of newborns and neonates in retrospective analyses[3] are responsible for contradictory results. Generally, infection increases serum bilirubin levels,[15] and hyperbilirubinemia is associated with an increase in bilirubin levels.[3] Early diagnosis of infection in newborns is required to overcome hyperbilirubinemia.

Elevated C-reactive protein levels were not independently associated with early onset severe hyperbilirubinemia in newborns in East China. The results of the current study regarding elevated C-reactive levels are not consistent with those of available studies on African neonates.[12] Prolonged labor, birth asphyxia, and meconium aspiration are responsible for elevated C-reactive protein in newborns.[12] These obstetric parameters, such as the nature of delivery, are not responsible for hyperbilirubinemia in newborns.[16] Worse maternal parameters are not associated with a risk of early onset severe hyperbilirubinemia in newborns in the East China region.

Maternal gestational age was not independently associated with early onset severe hyperbilirubinemia in the newborns. In the current study, the mothers of all newborns had a gestational age of ≥35 weeks. Premature delivery is independently associated with hyperbilirubinemia condition in newborns.[4,16] Mature delivery is not associated with early onset severe hyperbilirubinemia.

Exclusive artificial feeding was not independently associated with early onset severe hyperbilirubinemia in the newborns. All newborns with severe hyperbilirubinemia were on artificially fed. According to World Health Organization recommendations for newborns[7] that, all newborns should be exclusively breastfed. The results of the current study regarding exclusive breastfeeding are not consistent with those of available studies on African neonates[12] and randomized trials on Nepali neonates[17] but are consistent with a meta-analysis.[4] Research on neonatal hyperbilirubinemia regarding artificial feeding and exclusive breastfeeding is controversial.

The limitations of this study are its retrospective design and lack of a dynamic study. The retrospective analysis of medical records introduces the possibility of recall bias and incomplete information. Hyperbilirubinemia is not further divided into significant hyperbilirubinemia, severe hyperbilirubinemia, extreme hyperbilirubinemia, or critical hyperbilirubinemia. Not enough sample size for this kind of retrospective study, especially from China (they generally show the big population data). The other limitations of the study lack of detailed demographic and clinical parameters of neonates. The research only involves newborns from the eastern region of China, which might limit the generalizability of the results to other areas. And the single center (Ningbo city) cannot represent eastern China. The study only assessed the initial conditions of newborns and lacked tracking observations of long-term outcomes and subsequent developments.

5. Conclusions

The prevalence of early onset severe hyperbilirubinemia among newborns is 13 % in the East China region. Hyperbilirubinemia in newborns is a global issue that requires identifying its cause and etiology. ABO and Rh incompatibilities, G6PD deficiency, fewer genotype rs4149056 frequencies, higher genotype rs2306283 frequencies, and higher genotype rs1805173 frequencies were independent predictors of early onset severe hyperbilirubinemia in newborns in the East China region. Worse maternal parameters and exclusive artificial feeding are not associated with a risk of early onset severe hyperbilirubinemia in newborns in the East China region. Further research is needed to validate and refine the results, considering more potential influencing factors and long-term outcomes.

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