Effects of season of birth and meteorological parameters on serum bilirubin levels during the early neonatal period: a retrospective chart review

Shigeo Iijima (✉ sige_pd@yahoo.co.jp)

Hamamatsu University School of Medicine <https://orcid.org/0000-0003-3391-3757>

Toru Baba

Hamamatsu University School of Medicine

Miyuki Kondo

Hamamatsu University School of Medicine

Tomoka Fujita

Hamamatsu University School of Medicine

Akira Ohishi

Hamamatsu University School of Medicine

Research article

Keywords: neonatal jaundice, bilirubin, season, temperature, sex

Posted Date: October 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-88016/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at International Journal of Environmental Research and Public Health on March 9th, 2021. See the published version at <https://doi.org/10.3390/ijerph18052763>.

Abstract

Background: Neonatal jaundice can be influenced by many factors. Several studies have suggested that the severity of neonatal jaundice may vary with the season, but conclusive data on this issue are currently lacking. The aim of the present study was to establish whether serum bilirubin levels vary in healthy term neonates according to seasonal variation and meteorological factors.

Methods: We retrospectively studied 3,344 healthy term neonates born between 2013 and 2018. Using the capillary technique, total serum bilirubin (TSB) levels were measured on the fourth day after birth. The monthly and seasonal variations in TSB levels and clinical and meteorological effects on TSB levels were assessed.

Results: In the enrolled neonates, the median gestational age was 39.4 weeks, median birthweight was 3,025 g, and median TSB level was 195 $\mu\text{mol/L}$. The TSB level peaked in December and was the lowest in July, but the variation was not statistically significant. The TSB level was significantly higher in the cold season (October to March) than in the warm season (April to September; $p=0.01$). Comparing the seasonal differences according to sex, TSB levels were significantly higher in the cold season in male infants ($p=0.001$), whereas no significant difference was observed in female infants. In only the male population did a weakly negative but significant association exist between TSB levels and daily mean air temperature ($r=-0.07$, $p=0.007$); in the female population, no significant correlation was found between TSB levels and meteorological parameters.

Conclusions: Season of birth appears to be an etiological factor in neonatal jaundice, with an additional influence of sex. However, the contradictions observed in various studies highlight the need for further research on this topic.

Background

The majority of neonates develop physiological jaundice as a result of increased bilirubin levels in the blood, which is due to the combined effect of high red cell turnover, immature hepatic conjugation, and enhanced resorption of bilirubin by the enterohepatic circulation [1]. Neonatal hyperbilirubinemia is associated with a variety of conditions and manifests in approximately 60% of full-term neonates and almost all preterm neonates, with a prevalence greater than 80% [1]. The severity of jaundice varies between infants and may be associated with factors such as race, sex, nutrition, eating habits, hormones, and genetic factors [1–4].

In addition, clinical experience suggests that seasonal variation influences the occurrence and severity of neonatal hyperbilirubinemia. The relationship between the season of birth and physical parameters may depend on environmental effects during the critical periods of an infant's development [5]. An important event occurring soon after birth is the steady increase in serum bilirubin level, with recent studies suggesting that bilirubin has protective effect against secondary oxidants that the neonate is exposed to at birth [2,6]. Several previous studies have found that the development of neonatal jaundice and hyperbilirubinemia depend on the season of the neonate's birth [7–14]. However, there is no consensus on the influence of season of birth on the risk of developing neonatal jaundice.

The purpose of this study was to identify differences in neonatal jaundice according to sex and season of birth. We conducted a retrospective review of data collected from a large population over a long time period and analyzed the total serum bilirubin (TSB) levels in 4-day-old healthy term neonates to determine the presence of monthly and seasonal variations in TSB levels, as well as the association with meteorological parameters.

Methods

Subjects and data collection

We conducted a retrospective chart review of consecutive healthy term neonates who were born in Hamamatsu University Hospital between January 1, 2013 and December 31, 2018. Only Japanese people were included in our study, in order to minimize the effects of confounding variables. To evaluate the TSB levels in healthy neonates, we excluded neonates with a low birthweight ($< 2,500$ g), macrosomia ($\geq 4,000$ g), those delivered preterm (< 37 weeks) or post-term (≥ 42 weeks), and those admitted to the neonatal intensive care unit (NICU). In addition, we excluded neonates with underlying conditions likely to cause hyperbilirubinemia, such as blood type incompatibility, glucose-6-phosphate dehydrogenase deficiency, intrauterine infection (toxoplasma, rubella, cytomegalovirus, herpes, syphilis, and human immunodeficiency virus), major congenital malformations, clinical syndromes, and chromosomal abnormalities. Based on the findings from previous studies [3,10,15], data on sex, birthweight, gestational age, delivery mode, perinatal asphyxia, nutrition, and weight loss in the first 4 days after birth were obtained as potential predictors of TSB levels.

The design and conduct of the present study were in accordance with the general principles outlined in the Declaration of Helsinki and were approved by the ethics committee of Hamamatsu University School of Medicine (Approval Number: 19–103). The need for informed consent was waived because of the retrospective nature of the study.

Blood sampling and serum total bilirubin measurements

Capillary whole blood samples for the measurement of TSB levels were routinely obtained from a heel prick during the 4-day-old check-up. After the physical examination, a single heel prick was performed and a whole blood sample (approximately 40 μ L) was collected in a heparinized capillary tube for the measurement of TSB levels. The blood samples were transported to the laboratory several meters away from the newborn nursery at room temperature, and the TSB level was measured within several minutes after blood sampling by the optical density method using Bilmeter F (Mochida-Siemens, Tokyo, Japan); the measurement error of the device was $\pm$ 3% according to the manufacturer's report. Blood sampling and bilirubin measurements were conducted by six experienced neonatologists who had received training in the use of Bilmeter F.

In our hospital, every neonate received care in the newborn nursery, which was air-conditioned at approximately 26°C throughout the day. All evaluations began at 10:00am and were performed in the newborn nursery.

Collection of seasonal data and meteorological parameters

Japan is an island country running from north to south along East Asia's Pacific coast, and Hamamatsu city is located in the central region (latitude 34.7° north). The climate is relatively mild with an annual average temperature of 16.6°C. In this study, seasons were divided into a warm season (April to September) and a cold season (October to March). The meteorological data on the day the neonates were born were obtained from the Japan Meteorological Agency website [16] and included mean air temperature, mean relative humidity, mean barometric pressure, total precipitation amount, and sunshine duration. These data were collected at the Hamamatsu Local Meteorological Observatory, which is located approximately 1 mile from the hospital.

Statistical analysis

Data are presented as medians with interquartile ranges or as means $\pm$ standard deviations for continuous variables and as counts and percentages for categorical variables. Non-parametric methods (Spearman correlation coefficient, Kruskal-Wallis test, and the Mann-Whitney U test) were used to assess the influence of clinical, seasonal, and meteorological parameters on TSB levels. A linear regression model was built using TSB levels and meteorological parameters with significant seasonal variation as dependent and independent variables, respectively. Data were analyzed using the Statistical Package for Social Sciences (SPSS version 25, Tokyo, Japan). All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

Samples

During the study period, a total of 4,772 neonates were born in our hospital. After excluding those meeting the exclusion criteria and those with missing or unreliable data, 3,344 neonates were included in our study for analysis (Fig. 1). In the enrolled neonates (male/female ratio, 1,685:1,659), the median birthweight was 3,025 g and the median gestational age was 39.4 weeks. The median TSB level was 195 μ mol/L (interquartile range, 168–227 μ mol/L). Overall, 1,698 neonates were delivered during the warm season and 1,646 were delivered during the cold season. There were no significant differences in the birthweight, gestational age, delivery mode, 1-min and 5-min Apgar scores, or nutrition between those born in the warm and cold seasons (Table 1). Sex was associated with significant differences in birthweight ($p = 0.03$), gestational age ($p = 0.04$), nutrition ($p < 0.001$), and weight loss in the first 4 days after birth ($p < 0.001$; Table 1). TSB levels were slightly higher in male infants than in female infants, although the difference was not statistically significant.

Table 1
Seasonal and sex differences in the characteristics of the study population and meteorological parameters

	Season			Sex		
	Warm season	Cold season	P-	Male	Female	P-
	n = 1698	n = 1646	value	n = 1685	n = 1659	value
Clinical parameters						
Birthweight, g	3022 (2810–3256)	3030 (2824–3280)	0.27	3034 (2836–3280)	3018 (2800–3251)	0.03
Gestational age, weeks	39.3 (38.4–40.1)	39.4 (38.4–40.3)	0.06	39.3 (38.4–40.1)	39.4 (38.4–40.2)	0.04
Male sex, (%)	848 (49.9)	837 (50.8)	0.60	-	-	-
Warm season, (%)	-	-	-	848 (50.3)	850 (51.2)	0.60
Delivery mode (vaginal delivery:cesarean section), (%)	1348:350 (79:21)	1338:308 (81:19)	0.90	1351:334 (80:20)	1335:324 (80:20)	0.08
Apgar score at 1 min	8 (8–9)	8 (8–9)	0.87	8 (8–9)	8 (8–9)	0.57
Apgar score at 5 min	9 (9–9)	9 (9–9)	0.89	9 (9–9)	9 (9–9)	0.88
Nutrition (breast:mix:formula), (%)	181:1478:39 (11:87:2)	162:1459:25 (10:89:1)	0.93	241:1400:44 (14:83:3)	102:1537:20 (6:93:1)	< 0.001
Weight loss in the first 4 days after birth, (%)	2.6 (1.0–4.1)	2.6 (1.0–4.3)	0.38	2.4 (1.0–4.1)	2.7 (1.1–4.3)	0.04
Total serum bilirubin level, $\mu\text{mol/L}$	193 (166–226)	197 (169–231)	0.01	195 (169–229)	193 (166–227)	0.05
Meteorological parameters						
Daily mean air temperature, $^{\circ}\text{C}$	23.3 (20.2–26.9)	10.4 (6.9–15.5)	< 0.001	18.4 (10.5–23.6)	18.4 (10.1–23.5)	0.42
Daily mean relative humidity, %	75 (68–83)	60 (51–72)	< 0.001	70 (58–79)	70 (57–79)	0.77
Daily mean barometric pressure, hPa	1006 (1002–1009)	1012 (1008–1016)	< 0.001	1008 (1004–1013)	1008 (1004–1013)	0.75
Daily total precipitation amount, mm	6.8 $\pm$ 17.2	4.0 $\pm$ 12.5	< 0.001	5.5 $\pm$ 16.3	5.3 $\pm$ 13.8	0.74
Daily sunshine duration, h	6.6 (1.6–10.7)	7.7 (2.6–9.5)	0.06	7.0 (2.0–9.8)	7.3 (1.9–9.8)	0.67
Categorical variables are expressed with number (%) and continuous variables with mean $\pm$ standard deviation or median (interquartile range).						

Monthly and seasonal variations in the meteorological parameters

The mean daily air temperature was lowest in January (median, 6.0 $^{\circ}\text{C}$) and peaked in August (median, 28.0 $^{\circ}\text{C}$). The mean daily relative humidity peaked in July (median, 76.0%) and was the lowest in February (median, 51.5%). The mean daily barometric pressure was lowest in August (median, 1,002.6 hPa) and peaked in December (median, 1,012.6 hPa). The total daily precipitation amount peaked in September (mean, 11.9 mm) and was lowest in January (mean, 1.7 mm). The daily duration of sunshine was lowest in September (median, 4.2 h) and peaked in May (median, 8.9 h). A comparison of the climate variables between the warm and cold seasons indicated that the air temperature, relative humidity, and levels of precipitation were significantly higher in the warm season

(all p s < 0.001). In contrast, the barometric pressure was significantly lower in the warm season (p < 0.001). The duration of sunshine was slightly higher in the warm season than in the cold season, but this difference was not statistically significant.

Monthly and seasonal variations in total serum bilirubin levels

On a monthly basis, the TSB level peaked in December (median, 202 $\mu\text{mol/L}$) and was lowest in July (median, 190 $\mu\text{mol/L}$; Fig. 2), although the variation was not statistically significant. In male infants, the TSB level was highest in December (median, 209 $\mu\text{mol/L}$) and lowest in July (median, 190 $\mu\text{mol/L}$); which was a significant difference (p = 0.04). Conversely, in female infants, the TSB level was highest in March (median, 200 $\mu\text{mol/L}$) and lowest in May (median, 188 $\mu\text{mol/L}$), but without significant variation. The TSB levels were significantly higher in the cold season than in the warm season (p = 0.01; Table 1). Comparing the seasonal differences according to sex, TSB levels were significantly higher in the cold season in male infants (p = 0.001), whereas the difference was not significant in female infants (Table 2).

Table 2
Seasonal differences in characteristics of the study population and meteorological parameters according to sex

	Male				Female			
	Total n = 1685	Warm season n = 848	Cold season n = 837	P- value	Total n = 1659	Warm season n = 850	Cold season n = 809	P- value
Clinical parameters								
Birthweight, g	3034 (2836– 3280)	3022 (2830– 3270)	3044 (2840– 3290)	0.37	3018 (2800– 3251)	3022 (2792– 3232)	3016 (2810– 3266)	0.53
Gestational age, weeks	39.3 (38.4– 40.1)	39.3 (38.4– 40.0)	39.4 (38.4– 40.1)	0.13	39.4 (38.4– 40.2)	39.4 (38.4– 40.1)	39.4 (38.4– 40.3)	0.26
Delivery mode (vaginal delivery:cesarean section), (%)	1351:334 (80:20)	673:175 (79:21)	678:159 (81:19)	0.14	1335:324 (80:20)	675:175 (79:21)	660:149 (82:18)	0.08
Apgar score at 1 min	8 (8–9)	8 (8–9)	8 (8–9)	0.49	8 (8–9)	8 (8–9)	8 (8–9)	0.34
Apgar score at 5 min	9 (9–9)	9 (9–9)	9 (9–9)	0.83	9 (9–9)	9 (9–9)	9 (9–9)	0.67
Nutrition (breast:mix:formula), (%)	241:1400:44 (14:83:3)	126:694:28 (15:82:3)	115:706:16 (14:84:2)	0.96	102:1537:20 (6:93:1)	55:784:11 (7:92:1)	47:753:9 (6:93:1)	0.71
Weight loss in the first 4 days after birth, (%)	2.4 (1.0– 4.1)	2.4 (0.9– 4.1)	2.5 (1.0– 4.1)	0.22	2.7 (1.1– 4.3)	2.7 (1.1– 4.2)	2.7 (1.1– 4.4)	0.98
Total serum bilirubin level, $\mu\text{mol/L}$	195 (169– 229)	191 (166– 224)	200 (174– 233)	0.001	193 (166– 227)	193 (166– 227)	195 (166– 227)	0.75
Meteorological parameters								
Daily mean air temperature, $^{\circ}\text{C}$	18.4 (10.5– 23.6)	23.4 (20.5– 26.9)	10.5 (6.9– 15.6)	< 0.001	18.4 (10.1– 23.5)	23.2 (19.7– 26.9)	10.0 (6.8– 15.2)	< 0.001
Daily mean relative humidity, %	70 (58–79)	75 (67–82)	60 (52–72)	< 0.001	70 (57–79)	75 (68– 83)	60 (51– 71)	< 0.001
Daily mean barometric pressure, hPa	1008 (1004– 1012)	1005 (1002– 1009)	1012 (1008– 1016)	< 0.001	1008 (1004– 1013)	1006 (1002– 1009)	1012 (1008– 1015)	< 0.001
Daily total precipitation amount, mm	5.5 $\pm$ 16.3	6.9 $\pm$ 19.2	4.1 $\pm$ 12.6	< 0.001	5.3 $\pm$ 13.8	6.6 $\pm$ 15.0	3.8 $\pm$ 12.3	< 0.001
Daily sunshine duration, h	7.0 (2.0– 9.8)	6.2 (1.8– 10.6)	7.6 (2.5– 9.5)	0.30	7.3 (1.9– 9.8)	6.8 (1.3– 10.8)	7.7 (2.9– 9.5)	0.10
Categorical variables are expressed with number (%) and continuous variables with mean $\pm$ standard deviation or median (interquartile range).								

Correlation between total serum bilirubin levels and meteorological parameters at birth

Simple linear regression analysis showed that there were no significant correlations between TSB levels and mean daily air temperature ($p = 0.23$), mean daily relative humidity ($p = 0.17$), mean daily barometric pressure ($p = 0.08$), daily total precipitation amount ($p = 0.06$), and daily duration of sunshine ($p = 0.06$). In only the male population were there weakly negative but significant

correlations between TSB levels and daily mean air temperature ($r=-0.07$, $p = 0.007$); in addition, the TSB level had a weakly positive but significant correlation with daily mean barometric pressure ($r = 0.06$, $p = 0.01$) and daily total precipitation amount ($r = 0.07$, $p = 0.008$). Stepwise multiple linear regression analysis was conducted to evaluate the impact of the independent variables (mean daily air temperature, mean daily barometric pressure, and total daily precipitation amount) on TSB levels. Only the mean daily air temperature was found to significantly influence the TSB levels ($p = 0.04$). When analyzing only the female population, simple linear regression analysis showed no significant correlation between TSB levels and any of the climatic parameters.

Discussion

In the present study, TSB levels were significantly higher in infants born during the cold season (October to March), and only in the male population, the bilirubin level was found to have a weak but significant negative correlation with mean daily air temperature at birth. Therefore, season of birth appears to be an etiological factor in neonatal jaundice. Furthermore, there also appears to be an influence of sex.

In 1969, Milby et al. described seasonal variations in the incidence of neonatal hyperbilirubinemia for the first time [7]. In their study, the incidence of neonatal unconjugated hyperbilirubinemia was significantly high during the fourth quarter of each year. However, climatic information was not described, and the cause of the seasonal fluctuation was unclear. Subsequently, eight other studies have been conducted to investigate the possible impact of the season of birth on serum bilirubin levels of neonates or pathological hyperbilirubinemia [8–14,17] (Table 3). Two of these studies demonstrated that TSB levels were higher in the cold season, as shown in the present study [8,17], although the study by Hojat et al. did not confirm the presence of a statistically significant difference. Anttolainen et al. suggested that the short duration of daylight experienced during the cold season could increase the incidence of hyperbilirubinemia [8]. Sunlight can prevent hyperbilirubinemia [18] because the sun emits blue-green light in the spectrum needed to most effectively convert bilirubin to its water-soluble isomers for excretion. Hojat et al. also described that there is less sunlight in the winter and the decomposition of bilirubin decreases during this time [17]. In addition, they suggested that parents often increase a baby's room temperature to prevent hypothermia in winter, and this can cause dehydration and increase serum bilirubin levels. In the present study, there was no statistical significance in the seasonal and monthly variations of sunshine duration, and no significant correlation between serum bilirubin level and sunshine duration was found. On the other hand, six previous studies have demonstrated that serum bilirubin levels and the incidence of pathologic hyperbilirubinemia were significantly higher in warm seasons [9–14] (Table 3); González et al. suggested that high temperatures during the summer and the associated higher dehydration rate may be the main cause [9]. Additionally, they suggested that the seasonal differences could be due to breast milk jaundice. Ahmady et al. also suggested that, during the summer season, increased temperature led to increased breastfeeding rates to compensate for dehydration and elevated bilirubin levels [13]. Breastfeeding has been recognized as a contributing factor for the development of neonatal hyperbilirubinemia, as the breastmilk of some women contains a metabolite of progesterone called $3\alpha,20\beta$ -pregnanediol, which inhibits UDP-glucuronosyltransferase (UGT) bilirubin glucuronidation activity [4]. Moreover, breastfed babies, particularly those who have difficulty nursing or getting enough nutrition from breastfeeding, are at a higher risk of jaundice. Besides dehydration, a low caloric intake through inadequate levels of breast feeding may contribute to the onset of jaundice. In the present study, room temperature was not included in the evaluated environmental factors and daily feeding volume was also not investigated. However, weight loss rate in the first 4 days after birth was not significantly different between the warm and cold seasons. Therefore, dehydration of the newborn during the warm season is unlikely. Our previously published paper reported that room temperature in the neonatal ward was unchanged throughout the year [19]. Moreover, in the present study, the rate of breastfed neonates was not different between those born in the warm and cold seasons.

Table 3
Reported articles investigating seasonal variation of serum bilirubin levels in neonates or neonatal hyperbilirubinemia

Study and country	Study type	Inclusion criteria	Sample size	Age at study	Seasonality	Sex difference	Summary
Milby et al., 1969, USA [7]	R	Serum indirect bilirubin, > 171 µmol/L	170	Unknown	Yes	Yes	Incidence of hyperbilirubinemia was high during the fourth quarter of each year. Elevated bilirubin levels were more frequent in male infants.
Anttolainen et al., 1975, Finland [8]	P	BW, < 2500 g	76	0–10 d	Yes	NA	Total bilirubin levels were lower from March to August than from September to February.
González et al., 1996, Spain [9]	P	Serum total bilirubin, > 274 µmol/L	161	Unknown	Yes	NA	Pathologic hyperbilirubinemia was commoner in fall and less common in winter (not a statistically significant difference). Pathologic hyperbilirubinemia due to breastmilk jaundice was significantly commoner in summer.
Bottini et al., 2000, Italy [10]	P	Unknown	343	23–25 h	Yes	Yes	The rise of serum bilirubin was minimal in autumn (September–November). The rise of serum bilirubin showed a tendency to decrease from winter to autumn. The rise of serum bilirubin level in spring and summer was significantly higher in female infants than in male infants.
Bottini et al., 2003, Italy [11]	P	Unknown	5540	Unknown	Yes	Yes	The maximum incidence of phototherapy was observed from May to August. The proportion of infants undergoing phototherapy was lower in female infants.
Cerna et al., 2010, Czech [12]	R	Healthy, term	565	Unknown	Yes	NA	The incidence of hyperbilirubinemia was higher in summer. The frequency of phototherapy use was higher during summer.
Ahmady et al., 2015, Egypt [13]	P	GA, 37 weeks	500	Unknown	Yes	Yes	Total and unconjugated bilirubin were higher in newborns born in summer. Increased unconjugated bilirubin was more common in male infants born in summer. Total and unconjugated bilirubin in female infants were significantly raised in summer. Conjugated bilirubin was elevated in winter.
Bala et al., 2016, India [14]	P	GA, 37 weeks	1000	Unknown	Yes	Yes	Total and indirect bilirubin were higher in summer. Indirect bilirubin level was higher in male infants in summer. In female infants, total and indirect bilirubin were significantly raised in winter. Direct bilirubin level was raised in winter.
Hojat et al., 2018, Iran [17]	P	GA, 38–42 weeks BW, 2500–3400 g	400	7 d	No	NA	The highest bilirubin level was observed in winter (not statistically significant).
R, retrospective study; P, prospective study; GA, gestational age; BW, birthweight; NA, not analyzed							

Regarding sex differences, five of nine studies refer to a role of sex in seasonal variation of bilirubin levels [7,10,11,13,14] (Table 3). Four of them reported that serum bilirubin levels or the incidence of pathological hyperbilirubinemia were higher in male infants [7,11,13,14]. Meanwhile, Bottini et al. reported that the rise of serum bilirubin levels in the warm season was significantly higher in

female infants, whereas in the cold season, no significant differences between male infants and female infants were observed [10]. In addition, two studies reported that conjugated bilirubin was more common in female infants [13,14]. Sex divergent glucuronidation rates were observed in humans, and sex differences in UGT mRNA have also been observed in animal studies [20,21]. Sex hormones may be an important regulator of conjugation. In a previous study, the phenomenon of protection from oxidative stress was shown to be much more marked in male than in female newborn infants [10].

Several other clinical factors may influence neonatal hyperbilirubinemia. As bilirubin has a protective effect against secondary oxidative stress [2,6], seasonal variation of birth stress may influence bilirubin levels during the first few days of life [10]. In one study, the highest number of births leading to cerebral palsy occurred in spring, with the lowest number occurring in winter [22]. Low birthweight and prematurity are well-recognized as being major risk factors for exaggerated hyperbilirubinemia [1]. Seasonal patterns of low birthweight and preterm births have been found [23]. As pregnant women are particularly sensitive to meteorological conditions and environmental exposure [5], the period before delivery could be a critical window influencing fetal growth when high or low ambient temperature exposure occurs [23]. In summer, heat stress can damage antioxidant defense systems and lead to increased oxytocin secretion [24]. In winter, decreased sunlight exposure may lead to lower levels of vitamin D [25], which is essential for normal placental function and fetal growth [26]. The mode of delivery may also influence the jaundice risk. In previous studies, lower bilirubin levels were observed after cesarean section (CS) and this is supposedly explained by placental transfusion or the timing of cord clamping [27,28]. However, other studies comparing CS with vaginal delivery did not show a difference in hyperbilirubinemia risk [15,29]. In the present study, birthweight, gestational age, 1-min and 5-min Apgar scores (as an indicator of birth stress), and delivery mode were not associated with significant seasonal variations.

The present study has limitations. First, the retrospective study design restricted the appropriate assessment of potential confounders. Second, the meteorological data used for the statistical analyses were not available at the time that the neonate was born or the blood was sampled. In addition, data on the indoor temperature in the maternity ward were not available. For mothers, personal exposure to meteorological indicators may be modified by the duration of time spent indoors before delivery. Actual exposure of individuals to meteorological conditions might not always be the same as the recorded data of a specific geographical region. As a result, this may lead to some degree of evaluation error.

The present study also has strengths. Information about seasonal variation in neonatal jaundice is limited because most other studies are based on a small sample size, a limited number of variables, and a short study period. Unlike previous studies, this study evaluated the association between serum bilirubin levels and meteorological data in early neonatal period with a relatively large sample size.

Conclusions

The present study has evaluated the relationship between season of birth and neonatal jaundice, and the hypothesis that such a relationship is mediated at least in part by meteorological factors and sex. Our study findings suggest that season of birth is an etiological factor in neonatal jaundice, with an additional influence of sex. However, the contradictions observed in various studies and the mechanisms of seasonal fluctuation in serum bilirubin levels remain unclear. Further large, prospective studies are required to address this important issue.

Abbreviations

TSB, total serum bilirubin; NICU, neonatal intensive care unit; UGT, UDP-glucuronosyltransferase; CS, cesarean section

Declarations

Ethics approval and consent to participate

The present study protocol was designed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Hamamatsu University School of Medicine (Approval Number: 19–103). The need for informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

SI conceived the study and was responsible for data collection. SI performed data analysis, interpreted the data, and prepared the first draft of the manuscript. TB, MK, TF, and AO made substantial contributions to acquisition of data. All authors reviewed and contributed to revisions of the manuscript.

Acknowledgements

The authors would like to extend their gratitude to the midwives and nurses at the perinatal center of Hamamatsu University Hospital.

References

1. Shaughnessy EE, Goyal NK. Jaundice and hyperbilirubinemia in the newborn. In: Kliegman RM, St. Geme III JW, editors. Nelson textbook of pediatrics 21st ed. Philadelphia: Elsevier; 2019. p. 953-7.
2. Bélanger S, Lavoie JC, Chessex P. Influence of bilirubin on the antioxidant capacity of plasma in newborn infants. *Biol Neonate*. 1997;71:233-8.
3. Tioseco JA, Aly H, Milner J, Patel K, El-Mohandes AA. Does gender affect neonatal hyperbilirubinemia in low-birth-weight infants? *Pediatr Crit Care Med*. 2005;6:171-4.
4. Maruo Y, Morioka Y, Fujito H, Nakahara S, Yanagi T, Matsui K, et al. Bilirubin uridine diphosphate-glucuronosyltransferase variation is a genetic basis of breast milk jaundice. *J Pediatr*. 2014;165:36-41.e1.
5. Balbus JM, Malina C. Identifying vulnerable subpopulation for climate change health effects in the United States. *J Occup Environ Med*. 2009;51:33-7.
6. Minetti M, Mallozzi C, Di Stasi AM, Pietraforte D. Bilirubin is an effective antioxidant of peroxynitrite-mediated protein oxidation in human blood plasma. *Arch Biochem Biophys*. 1998;352:165-74.
7. Milby TH, Mitchell JE, Freeman TS. Seasonal neonatal hyperbilirubinemia. *Pediatrics*. 1969;43:601-5.
8. Anttolainen I, Similä S, Wallgren EI. Effect of seasonal variation in daylight on bilirubin level in premature infants. *Arch Dis Child*. 1975;50:156-7.
9. González de Dios J, Moya Benavent M, Sirvent Mayor MC, Durá Travé T. Diferencias estacionales en la ictericia neonatal [Seasonal differences in neonatal jaundice]. *An Esp Pediatr*. 1996;45:403-8.
10. Bottini N, Dituri F, Bottini FG. Season of birth and early neonatal events. The rise of serum bilirubin. *Biol Rhythm Res*. 2000;31:50-5.
11. Bottini M, Meloni GF, Gloria-Bottini F. Seasonal pattern of phototherapy: A study in the Sardinian population. *Biol Rhythm Res*. 2003;34:13-21.
12. Cerna M, Vitek L, Mala K, Konickova R. Seasonal nature of neonatal jaundice. *Pediatr Res*. 2010;68:586.
13. Armady MM, El-Sayed SAM, Ali YF, Baraka AM. Effect of fetal sex and seasonal variation on the level of neonatal hyperbilirubinemia. *Curr Sci Int*. 2015;4:708-13.

14. Bala J, Agrawal Y, Chugh K, Kumari M, Goyal V, Kumar P. Variation in the serum bilirubin levels in newborns according to gender and seasonal changes. *Arch Med Health Sci.* 2015;3:50-5.
15. Phuapradit W, Chaturachinda K, Aunlamai S. Risk factors for neonatal hyperbilirubinemia. *J Med Assoc Thai.* 1993;76:424-8.
16. Japan Meteorological Agency. Weather, Climate & earthquake information. <http://www.jma.go.jp/jma/indexe.html>. Accessed 7 May 2020.
17. Hojat M, Zarezadeh N, Mogharab V, Rahmanian E. Investigating the relationship between serum bilirubin levels in the first week of life with season of birth. *World Family Medicine.* 2018;16:30-3.
18. Cremer RJ, Perryman PW, Richards DH. Influence of light on the hyperbilirubinaemia of infants. *Lancet.* 1958;1:1094-7.
19. Iijima S, Sekii K, Baba T, Ueno D, Ohishi A. Seasonal variation in the international normalized ratio of neonates and its relationship with ambient temperature. *BMC Pediatr.* 2016;16:97.
20. Buckley DB, Klaassen CD. Mechanism of gender-divergent UDP-glucuronosyltransferase mRNA expression in mouse liver and kidney. *Drug Metab Dispos.* 2009;37:834-40.
21. Muraca M, Fevery J. Influence of sex and sex steroids on bilirubin uridine diphosphate-glucuronosyltransferase activity of rat liver. *Gastroenterology.* 1984;87:308-13.
22. Sienkiewicz D, Paszko-Patej G, Okurowska-Zawada B, Kułak W. Seasonal variations in cerebral palsy births. *Arch Med Res.* 2018;49:114-8.
23. Li S, Wang J, Xu Z, Wang X, Xu G, Zhang J, et al. Exploring associations of maternal exposure to ambient temperature with duration of gestation and birth weight: a prospective study. *BMC Pregnancy Childbirth.* 2018;18:513.
24. Forgati M, Kandalski PK, Herrerias T, Zaleski T, Machado C, Souza MRDP, et al. Effects of heat stress on the renal and branchial carbohydrate metabolism and antioxidant system of Antarctic fish. *J Comp Physiol B.* 2017;187:1137-54.
25. McGrath JJ, Keeping D, Saha S, Chant DC, Lieberman DE, O'Callaghan MJ. Seasonal fluctuations in birth weight and neonatal limb length; does prenatal vitamin D influence neonatal size and shape? *Early Hum Dev.* 2005;81:609-18.
26. Gernand AD, Bodnar LM, Klebanoff MA, Parks WT, Simhan HN. Maternal serum 25-hydroxyvitamin D and placental vascular pathology in a multicenter US cohort. *Am J Clin Nutr.* 2013;98:383-8.
27. Gale R, Seidman DS, Dollberg S, Stevenson DK. Epidemiology of neonatal jaundice in the Jerusalem population. *J Pediatr Gastroenterol Nutr.* 1990;10:82-6.
28. Yamauchi Y, Yamanouchi I. Difference in TcB readings between full term newborn infants born vaginally and by cesarean section. *Acta Paediatr Scand.* 1989;78:824-8.
29. Alkan S, Tiras U, Dallar Y, Sunay D. Effect of anaesthetic agents administered to the mothers on transcutaneous bilirubin levels in the neonates. *Acta Paediatr.* 2010;99:993-6.

Figures

Figure 1

Flow chart of subject recruitment.

Figure 2

Serum bilirubin levels by month of birth Mean and 95% confidence interval for monthly total serum bilirubin level in healthy term neonates at 4 days after birth.