Acta Med. Okayama, 2013
Vol. 67, No. 4, pp. 219–225

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Thrombocytopenia at Birth Is a Predictor of Cholestasis in Infants with Small for Gestational Age

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Cholestasis and thrombocytopenia are complications that affect infants born small for gestational age (SGA). In SGA infants, other vital organs develop at the expense of the liver, and the thrombopoietin produced by the liver is low, often resulting in cholestasis. We hypothesized that thrombocytopenia at birth can be used to predict cholestasis in very-low-birth-weight infants (VLBWIs) with SGA. This retrospective cohort study enrolled VLBWIs with SGA admitted to a tertiary neonatal intensive care unit. A platelet cutoff value predictive of cholestasis was determined using receiver operating characteristic analysis. Multivariate logistic regression analysis was performed to evaluate the platelet cutoff value, and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Regarding the onset of cholestasis, survival analysis was performed by calculating the adjusted hazard ratios (HRs) and 95% CIs. A total of 87 infants were evaluated, and the platelet cutoff value was determined as 88×10^3 cells/μl. The adjusted OR for this platelet cutoff value was 10.52 (95% CI 2.26–55.93, $p = 0.003$), and the adjusted HR was 7.76 (95% CI 2.51–23.50, $p = 0.0006$). Thrombocytopenia is a useful predictor for cholestasis in VLBWIs with SGA.

Key words: cholestasis, platelet, small for gestational age, thrombocytopenia, very low birth weight

Cholestasis is one of many complications observed in infants born small for gestational age (SGA) and is associated with an increased risk of mortality [1]. The etiology of neonatal cholestasis is multifactorial, and includes asphyxia, total parenteral nutrition, sepsis, necrotizing enterocolitis, gastrointestinal surgery, and fasting [2–9].

Thrombocytopenia is another complication in SGA infants [10]. Platelet counts in SGA infants are typically $100–150 \times 10^3$ cells/μl at birth, followed by a nadir at day 4–5, which resolves by day 7–10 ($>150 \times 10^3$ cells/μl) [11]. Intrauterine hypoxia is thought to account for the impaired thrombopoiesis in SGA infants [12]. SGA infants with intrauterine hypoxia-induced thrombocytopenia have low thrombopoietin (TPO) blood levels [13]. The production of TPO, which promotes thrombopoiesis by increasing platelet counts, is normally triggered in the liver by thrombocytopenia [14]. However, TPO is not typically activated in SGA infants because of liver damage. However, few clinical reports have shown that thrombocytopenia is associated with cholestasis. In this study, we tested the hypothesis that thrombocytopenia at birth predicts cholestasis in very low birth weight infants (VLBWIs) who are born SGA.

Received August 8, 2012; accepted February 1, 2013.
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Materials and Methods

A retrospective cohort study of patients with thrombocytopenia and cholestasis was conducted in singleton VLBWIs born SGA who were admitted into the tertiary neonatal intensive care unit at Okayama Medical Center from January 1, 2003 to December 31, 2010. SGA was defined as having a weight below the 10th percentile for normal birth weight according to standard values published by the Japan Pediatric Society [15]. Exclusion criteria included maternal idiopathic thrombocytopenic purpura, multiple anomalies, chromosomal abnormalities, congenital infections, and neonatal autoimmune thrombocytopenia [2, 12].

Perinatal and neonatal data collected at and after birth included birth characteristics (sex, gestational age (GA), birth weight (BW), height, head circumference, and Apgar scores), cholestasis-related factors (presence or absence, date of onset, date of cure, disease duration, and direct bilirubin (DBIL) concentration), discharge information (transfer, discharge, or death), total parenteral nutrition, sepsis, necrotizing enterocolitis (NEC), gastrointestinal surgery, fasting, maternal diseases during pregnancy (pregnancy-induced hypertension and diabetes mellitus), complete blood count, and blood gas values (pH, pCO_2, and base excess). Sepsis was diagnosed by blood culture. We defined fasting as the discontinuation of enteral feeding. DBIL concentration was measured once a week, and cholestasis was defined as DBIL concentration >2.0 mg/dl [2]. Date of onset was defined as the day DBIL concentration exceeded 2.0 mg/dl, and date of cure was defined as the day DBIL concentration was ≤ 2.0 mg/dl after onset.

Continuous data are expressed as means $\pm$ standard deviations (SDs) and compared by Student's *t*-test. Binary or categorical data are expressed as frequencies and percentages. Binary data were compared by chi-square test and Fisher's exact test. In addition, risk ratios (RRs), mean difference (MD), 95% confident intervals (CIs), and *p*-values were calculated. Thrombocytopenia is clinically defined as platelet count $<150\times10^3$ cells/μl [11]. In this study, receiver operating characteristic (ROC) analysis was used to determine a cutoff value predictive of cholestasis. Sensitivity, specificity, positive likelihood ratio, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) were calculated.

Univariate and multivariate logistic regression analysis were performed to evaluate the platelet cutoff value, and the odds ratios (ORs) and corresponding 95% CIs were calculated. Kaplan-Meier survival curves were generated to estimate the risk of cholestasis. Also, hazard ratios (HR), corresponding 95% CIs, and *p*-values were calculated using univariate and multivariate Cox regression analysis. The following potential confounding factors for the platelet cutoff value at birth were used in multivariate logistic regression analysis: 5-min Apgar score, severe SGA, hemoglobin (Hb), and platelet count. The 5-min Apgar score was used to assess asphyxia [4, 9]. A previous report showed that infants with severe SGA were at an increased risk of cholestasis [1]. Severe SGA was defined in this study as follows: GA $\geq$35 wk and $<$40 wk and BW $<$1,500 g; GA $\geq$33 wk and $<$35 wk, and BW $<$1,250 g; GA $\geq$31 wk and $<$33 wk, and BW $<$1,000 g; GA $\geq$29 wk and $<$31 wk, and BW $<$750 g; or GA $\geq$27 wk and $<$29 wk and BW $<$500 g. Hb levels were selected as a potential confounding factor, because Hb levels are associated with liver function in SGA infants [16, 17]. Hb/5 was used a value divided Hb by 5 for the analysis. All statistical analyses were performed using JMP 7.0.1 (SAS Institute, Inc., Cary, NC, USA). This study was approved by the Okayama Medical Center ethics committee.

Results

A total of 87 infants were evaluated in this study. Forty infants exhibited thrombocytopenia (platelet count $<150\times10^3$ cells/μl; mean GA, 31.7 ± 3.3 week; mean BW, 966 ± 334 g), and 47 infants did not exhibit thrombocytopenia (platelet count $\geq150\times10^3$ cells/μl; mean GA, 31.6 ± 2.9 week; mean BW, $1{,}069\pm267$ g; Table 1). The thrombocytopenia group had a lower Apgar score (1 min), lower birth weight, higher WBC, and greater numbers of TPN and fasting cases than the non-thrombocytopenia group. Cholestasis was observed in 9 infants (23%) with thrombocytopenia and 4 infants (8.5%) without thrombocytopenia, with RR 2.64, 95% CI 0.88–7.94, $p=0.079$, sensitivity 0.69, specificity 0.58 (1-specificity = 0.42), positive likelihood ratio 1.65, PPV 0.23 and NPV 0.91.

The platelet concentration of $<88\times10^3$ cells/μl

Table 1 Clinical characteristics and laboratory data (platelet cutoff value: 150×10^3 cells/μl)

		Platelet count		RR or MD (95% CI)	*p*-value
		$<150 \times 10^3$ cells/μl (n = 40)	$\geq 150 \times 10^3$ cells/μl (n = 47)		
At birth	Primiparity	20 (50%)	25 (53%)	0.94 (0.62–1.42)	0.767
	Maternal PIH	15 (38%)	12 (26%)	1.47 (0.78–2.76)	0.229
	Maternal DM	0 (0%)	0 (0%)	–	–
	Male gender	20 (50%)	18 (38%)	1.31 (0.81–2.10)	0.273
	Apgar score (1 min)	5.8 (2.5)	7.2 (1.4)	−1.40 (−2.24–−0.55)	0.001
	Apgar score (5 min)	7.5 (2.3)	8.3 (1.3)	−0.75 (−1.53–0.02)	0.057
	Gestational age (wk)	31.7 (3.3)	31.6 (2.9)	0.12 (−1.21–1.45)	0.853
	Birth weight (g)	966 (334)	1,069 (267)	−104 (−231–25)	0.112
	Birth weight (SD)	−3.2 (1.0)	−2.6 (0.9)	−0.60 (−1.00–−0.19)	0.004
	Severe SGA	20 (50%)	15 (32%)	1.57 (0.93–2.64)	0.086
	Birth height (cm)*	34.2 (4.7)	35.3 (3.4)	−1.09 (−2.84–0.65)	0.216
	Birth height (SD)*	−2.7 (1.3)	−2.3 (0.9)	−0.39 (−0.86–0.08)	0.104
	Birth head circumference (cm)*	26.2 (3.2)	26.1 (3.3)	0.10 (−1.28–1.49)	0.882
	Birth head circumference (SD)*	−1.4 (1.6)	−1.4 (1.0)	0.10 (−0.48–0.67)	0.741
	pH	7.246 (0.120)	7.287 (0.113)	−0.041 (−0.091–0.009)	0.103
	pCO_2 (mm Hg)	51.9 (14.0)	51.0 (9.9)	0.97 (−4.16–6.09)	0.709
	Base excess (mmol/l)	−6.2 (5.5)	−4.3 (3.8)	−1.95 (−3.94–0.05)	0.056
	WBC ($\times 10^3$ cells/μl)	18.5 (13.6)	14.5 (14.3)	4.01 (−1.97–10.00)	0.186
	Hb (g/dl)	17.0 (3.0)	16.6 (3.5)	0.47 (−0.92–1.86)	0.503
	Platelet ($\times 10^3$ cells/μl)	106 (33)	226 (74)	−120 (−145–−95)	<0.0001
After birth	Cholestasis	9 (23%)	4 (8.5%)	2.64 (0.88–7.94)	0.079
	Onset of cholestasis (day)	15.4 (17)	17.8 (26.2)	−2.31 (−28.30–23.69)	0.849
	Cure of cholestasis (day)	36.9 (10.3)	45.5 (15.5)	−8.61 (−49.67–32.45)	0.653
	TPN	24 (60%)	17 (36%)	1.66 (1.05–2.62)	0.027
	Sepsis	3 (7.5%)	3 (6.4%)	1.18 (0.25–5.50)	1.000
	NEC	0 (0%)	1 (2.1%)	0 (–)	1.000
	Gastrointestinal surgery	2 (5.0%)	2 (4.3%)	1.18 (0.17–7.97)	1.000
	Fasting	7 (17.5%)	3 (6.4%)	2.74 (0.76–9.91)	0.176

Data are expressed as means (± standard deviations) or numbers of cases (percent).
RR, risk ratio; MD, mean difference; CI, confidence interval; PIH, pregnancy-induced hypertension; DM, diabetes mellitus; WBC, white blood cell; Hb, hemoglobin; TPN, total parenteral nutrition; NEC, necrotizing enterocolitis.
*Indicates cases lacking birth height and head circumference data.

was chosen as the cutoff value for predicting cholestasis (sensitivity 0.46, specificity 0.91 (1-specificity = 0.09), positive likelihood ratio 4.88, PPV 0.46, NPV 0.91 and AUC 0.67). This cutoff value identified 13 infants with thrombocytopenia (mean GA, 32.6 ± 4.3 wk; mean BW, $1,032 \pm 443$ g) and 74 infants without thrombocytopenia (mean GA, 31.5 ± 2.8 wk; mean BW, $1,020 \pm 274$ g) (Table 2). Six infants (46%) exhibited both thrombocytopenia and cholestasis, and 7 infants (9.5%) exhibited cholestasis but not thrombocytopenia (RR 4.88, 95% CI 1.95–12.21, $p = 0.0006$).

The results for cholestasis-predictive factors were as follows: platelet counts $<150 \times 10^3$ cells/μl, OR = 2.64, 95% CI = 0.88–7.94, $p = 0.079$ and adjusted OR = 4.33, 95% CI = 1.13–20.26, $p = 0.032$, for platelet counts $<88 \times 10^3$ cells/μl, OR = 4.88, 95% CI = 1.95–12.21, $p = 0.0006$ and adjusted OR = 10.52, 95% CI = 2.26–55.93, $p = 0.003$ (Table 3).

Kaplan-Meier analysis revealed an increased risk for cholestasis among infants with thrombocytopenia (platelet count $<150 \times 10^3$ cells/μl or 88×10^3 cells/μl) (Fig. 1). Cox regression analysis of platelet cutoff values yielded an HR of 2.48 (95% CI, 0.88–7.97, $p = 0.086$) and adjusted HR of 3.35 (95% CI, 1.12–11.30, $p = 0.031$) for 150×10^3 cells/μl, and an HR of 7.09 (95% CI, 2.46–20.04, $p = 0.0006$) and adjusted

Table 2 Clinical characteristics and laboratory data (platelet cutoff value: 88×10^3 cells/μl)

		Platelet count		RR or MD (95% CI)	*p*-value
		$<88 \times 10^3$ cells/μl (n = 13)	$\geq 88 \times 10^3$ cells/μl (n = 74)		
At birth	Primiparity	9 (69%)	36 (49%)	1.42 (0.92–2.19)	0.233
	Maternal PIH	6 (46%)	21 (28%)	1.63 (0.82–3.24)	0.201
	Maternal DM	0 (0%)	0 (0%)	–	–
	Male	3 (23%)	35 (47%)	0.49 (0.18–1.35)	0.135
	Apgar score (1 min)	5.3 (2.8)	6.7 (1.9)	−1.44 (−2.65–−0.22)	0.021
	Apgar score (5 min)	7.2 (2.4)	8.1 (1.7)	−0.91 (−2.00–0.18)	0.099
	Gestational age (wk)	32.6 (4.3)	31.5 (2.8)	1.13 (−0.72–2.97)	0.228
	Birth weight (g)	1,032 (443)	1,020 (274)	12 (−169–194)	0.894
	Birth weight (SD)	−3.4 (1.0)	−2.8 (1.0)	−0.64 (−1.22–−0.06)	0.031
	Severe SGA	8 (62%)	27 (36%)	1.69 (0.998–2.85)	0.089
	Birth height (cm)*	34.3 (6.8)	34.9 (3.4)	−0.59 (−3.04–1.86)	0.633
	Birth height (SD)*	−3.0 (1.1)	−2.4 (1.1)	−0.54 (−1.19–−0.12)	0.107
	Birth head circumference (cm)*	26.9 (4.6)	26.0 (2.9)	0.92 (−1.00–2.84)	0.344
	Birth head circumference (SD)*	−1.2 (2.4)	−1.4 (1.1)	0.20 (−0.60–0.99)	0.620
	pH	7.250 (0.079)	7.271 (0.123)	−0.021 (−0.092–0.049)	0.551
	pCO_2 (mm Hg)	50.9 (12.6)	51.5 (11.9)	−0.53 (−7.70–6.63)	0.882
	Base excess (mmol/l)	−6.4 (2.9)	−4.9 (5.0)	−1.45 (−4.28–1.38)	0.312
	WBC ($\times 10^3$ cells/μl)	25.4 (16.6)	14.8 (13.1)	10.60 (2.46–18.74)	0.011
	Hb (g/dl)	15.9 (3.8)	16.9 (3.1)	−1.03 (−2.97–0.90)	0.292
	Platelet ($\times 10^3$ cells/μl)	65 (15)	190 (77)	−124 (−167–−81)	<0.0001
After birth	Cholestasis	6 (46%)	7 (9.5%)	4.88 (1.95–12.21)	0.0006
	Onset of cholestasis (day)	6.5 (4.1)	24.4 (22.9)	−17.93 (−38.90–3.04)	0.087
	Cure of cholestasis (day)	32.0 (30.0)	46.0 (30.9)	−14.00 (−51.24–23.24)	0.426
	TPN	6 (46%)	35 (47%)	0.98 (0.52–1.84)	0.939
	Sepsis	1 (7.7%)	5 (6.8%)	1.14 (0.14–8.97)	1.000
	NEC	0 (0%)	1 (1.4%)	0 (–)	1.000
	Gastrointestinal surgery	1 (7.7%)	3 (4.1%)	1.90 (0.21–16.87)	0.483
	Fasting	5 (38%)	5 (6.8%)	5.69 (1.91–16.94)	0.0009

Data are expressed as means (± standard deviations) or numbers of cases (percents).
RR, risk ratio; MD, mean difference; CI, confidence interval; PIH, pregnancy-induced hypertension; DM, diabetes mellitus; WBC, white blood cell; Hb, hemoglobin; TPN, total parenteral nutrition; NEC, necrotizing enterocolitis.
*Indicates cases lacking birth height and head circumference data.

Table 3 Multivariate logistic regression analysis of platelet concentration as a predictor of cholestasis

	Adjusted OR	95% CI	*p* value
Apgar score (5 min)	1.40	0.95–2.55	0.102
Severe SGA	1.85	0.50–7.17	0.357
Hb/5	0.30	0.10–0.82	0.018
Platelet $<150 \times 10^3/\mu$l	4.33	1.13–20.26	0.032
	Adjusted OR	95% CI	*p* value
Apgar score (5 min)	1.53	0.99–2.97	0.060
Severe SGA	1.74	0.44–7.11	0.425
Hb/5	0.39	0.13–1.08	0.069
Platelet $<88 \times 10^3/\mu$l	10.52	2.26–55.93	0.003

OR, odds ratio; CI, confidence interval.

HR of 7.76 (95% CI, 2.51–23.50, $p = 0.0006$) for 88 $\times 10^3$ cells/μl (Table 4). Increased DBIL concentrations were associated with both platelet cutoff values. DBIL concentrations were very high in some infants with thrombocytopenia (Fig. 2). Maximum DBIL level of infants with platelet count ≥ 88 and $< 150 \times 10^3$ cells/μl became almost 1 mg/dl.

Discussion

In this study, we tested whether thrombocytopenia ($< 150 \times 10^3$ cells/μl) was a useful predictive factor for cholestasis. In univariate analysis, the incidences of cholestasis in the thrombocytopenia group were higher in the setting of both cutoff values; 150 and 88 $\times 10^3$ cells/μl. In multivariate analysis, adjusted OR and adjusted HR were 4.33 and 3.35, respectively, which were high. In addition, when using the new cutoff value of 88×10^3 cells/μl, the adjusted OR and adjusted HR rose to 10.52 and 7.76, respectively. Thus, thrombocytopenia would be useful for predicting cholestasis. Though NPVs for both cut-off values were high, over 0.9, the PPV for 88×10^3 cells/μl was 0.46, which was twice as high as PPV for 150×10^3 cells/μl. But, because the value of PPV was not high relatively, we might need to investigate the new cutoff value more precisely in a future study. The high NPV showed that patients without thrombocytopenia were not likely to have cholestasis. This

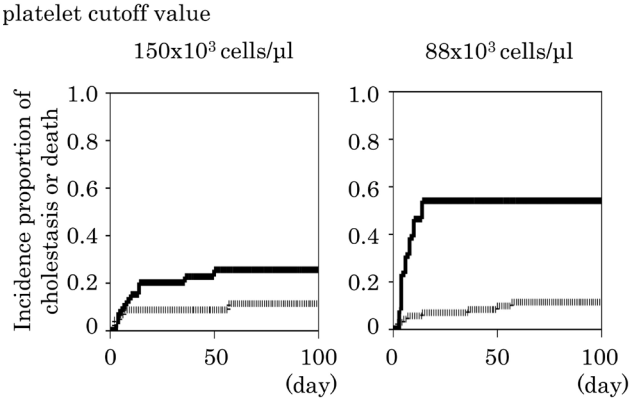

Fig. 1 Kaplan-Meier survival analysis for cholestasis or death. Solid line represents infants with thrombocytopenia, and the dashed line represents those without thrombocytopenia. Platelet cutoff values are 150×10^3 cells/μl (left) and 88×10^3 cells/μl (right). Infants with thrombocytopenia were at higher risk for cholestasis or death.

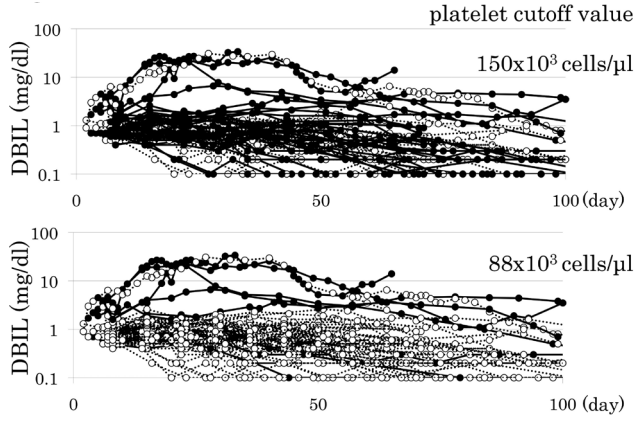

Fig. 2 Platelet cutoff values are 150×10^3 cells/μl (upper) and 88×10^3 cells/μl (lower). Filled markers represent infants with thrombocytopenia, and open markers represent those without thrombocytopenia. DBIL concentrations were very high in some infants with thrombocytopenia. Maximum DBIL level of infants with platelet count ≥ 88 and $< 150 \times 10^3$ cells/μl became almost 1 mg/dl.

Table 4 Multivariate Cox regression analysis of platelet concentration as a predictor of cholestasis

	Adjusted HR	95% CI	*p value*
Apgar score (5 min)	1.12	0.88–1.52	0.386
Severe SGA	1.36	0.46–3.95	0.565
Hb/5	0.33	0.16–0.74	0.008
Platelet $< 150 \times 10^3/\mu$l	3.35	1.12–11.30	0.031
	Adjusted HR	95% CI	*p value*
Apgar score (5 min)	1.16	0.91–1.58	0.250
Severe SGA	1.25	0.41–3.79	0.693
Hb/5	0.44	0.21–0.93	0.032
Platelet $< 88 \times 10^3/\mu$l	7.76	2.51–23.50	0.0006

HR, hazard ratio; CI, confidence interval.

finding might also be useful in the clinical setting. In this study, we analyzed the platelet count only at birth, because we wanted to check whether thrombocytopenia at birth could predict cholestasis.

Onset of cholestasis was about 2–3 weeks after birth. The onset of the thrombocytopenia cases (platelet $<88\times10^3$ cells/μl) was very early (6.5 ± 4.1 day). The cholestasis was resolved at 32.0 ± 30.0 and 46.0 ± 30.9 days in the thrombocytopenia and non-thrombocytopenia groups, respectively. But the DBIL of the thrombocytopenia group remained high, even at day 100 (Fig. 2). The characteristic of thrombocytopenia group shows a quick and sustained elevation of DBIL to rather high levels.

Asphyxia was related with cholestasis in a previous report [9]. In our study, the Apgar score (5 min) was low in the thrombocytopenia group. However, it did not have a statistically significant OR or HR in multivariate analysis. Therefore, the association is unclear.

There was no difference in Hb between the thrombocytopenia and non-thrombocytopenia groups. But the aOR and aHR of Hb/5 were less than 1. This means that low Hb leads to cholestasis. Erythropoietin, which activates erythrocyte production, is produced in the liver [18]. And erythropoiesis occurs in the liver at the second trimester [19]. There might be relationship between Hb and cholestasis.

As potential causes of cholestasis, the TPN, sepsis, NEC, gastrointestinal surgery and fasting were checked. Only fasting had higher incidence in the thrombocytopenia group. These 5 factors were not added to multivariate analysis from the point of the time course, because this study's aim was to determine whether thrombocytopenia at birth predicted cholestasis.

The incidence of severe SGA was higher in the thrombocytopenia group. Severe SGA was expected to have high OR and HR, because SGA was one of the causes of cholestasis. However, the aOR and aHR of severe SGA were 1.74 and 1.25 respectively, which were lower than those of thrombocytopenia. Then, the impact of SGA for the thrombocytopenia was still unclear in the study.

From the pathophysiological view, various factors (maternal, placental or fetal factors) appear to cause SGA, which leads to thrombocytopenia and cholestasis. In the SGA infant, the development of the liver and intestine is sacrificed through diving reflex. The liver has various functions. One of them is TPO production. Decreased TPO production would cause thrombocytopenia. On the other hand, if bile acid secretion of hepatocytes decreases temporarily, cholestasis would occur. Thus, both thrombocytopenia and cholestasis would be derived from liver damage. This study also showed that every SGA infant did not have thrombocytopenia or cholestasis; in other words, SGA is a heterogeneous condition. The possibility of predicting cholestasis by thrombocytopenia might reveal the presence of one subgroup of SGA, which easily had liver damage. In this study, we excluded chromosomal anomalies. We could not analyze the cause of SGA because of the small number of cases. In the future, the relationship among the causes of SGA, thrombocytopenia and cholestasis should be clarified with a larger dataset.

One limitation of this study is that it is based on retrospective data collected from a single tertiary neonatal intensive care unit. Prospective multicenter studies are needed to confirm our results. In addition, we could not check acquired cytomegalovirus infection in all patients with cholestasis.

Our study shows that thrombocytopenia can be used to predict cholestasis in VLBWIs who are born SGA. We determined that the platelet cutoff value of 88×10^3 cells/μl is useful.

Acknowledgments. We would like to thank our colleagues at the Okayama Medical Center, including Shigehiro Mori, Hirosuke Morita, Akihito Takeuchi, Eiko Toda, Yoko Yamabe, and Kazue Nakamura for their important contributions to this study.

References

1. Robinson DT and Ehrenkranz RA: Parenteral nutrition-associated cholestasis in small for gestational age infants. J Pediatr (2008) 152: 59–62.
2. Costa S, Maggio L, Sindico P, Cota F, De Carolis MP and Romagnoli C: Preterm small for gestational age infants are not at higher risk for parenteral nutrition-associated cholestasis. J Pediatr (2010) 156: 575–579.
3. Drongowski RA and Coran AG: An analysis of factors contributing to the development of total parenteral nutrition-induced cholestasis. JPEN J Parenter Enteral Nutr (1989) 13: 586–589.
4. Jacquemin E, Lykavieris P, Chaoui N, Hadchouel M and Bernard O: Transient neonatal cholestasis: origin and outcome. J Pediatr (1998) 133: 563–567.
5. Kaufman SS, Gondolesi GE and Fishbein TM: Parenteral nutrition associated liver disease. Semin Neonatol (2003) 8: 375–381.
6. Kelly DA: Liver complications of pediatric parenteral nutrition--epidemiology. Nutrition (1998) 14: 153–157.

7. Moss RL, Das JB and Raffensperger JG: Necrotizing enterocolitis and total parenteral nutrition-associated cholestasis. Nutrition (1996) 12: 340–343.
8. Tufano M, Nicastro E, Giliberti P, Vegnente A, Raimondi F and Iorio R: Cholestasis in neonatal intensive care unit: incidence, aetiology and management. Acta Paediatr (2009) 98: 1756–1761.
9. Vajro P, Amelio A, Stagni A, Paludetto R, Genovese E, Giuffre M and DeCurtis M: Cholestasis in newborn infants with perinatal asphyxia. Acta Paediatr (1997) 86: 895–898.
10. Salonvaara M, Riikonen P, Kekomaki R, Vahtera E, Mahlamaki E, Halonen P and Heinonen K: Effects of gestational age and prenatal and perinatal events on the coagulation status in premature infants. Arch Dis Child Fetal Neonatal Ed (2003) 88: F319–323.
11. Castle V, Andrew M, Kelton J, Giron D, Johnston M and Carter C: Frequency and mechanism of neonatal thrombocytopenia. J Pediatr (1986) 108: 749–755.
12. Maruyama H, Shinozuka M, Kondoh Y, Akahori Y, Matsuda M, Inoue S, Sumida Y and Morishima T: Thrombocytopenia in preterm infants with intrauterine growth restriction. Acta Med Okayama (2008) 62: 313–317.
13. Sola-Visner M, Sallmon H and Brown R: New insights into the mechanisms of nonimmune thrombocytopenia in neonates. Semin Perinatol (2009) 33: 43–51.
14. Kaushansky K: Determinants of platelet number and regulation of thrombopoiesis. Hematology Am Soc Hematol Educ Program (2009): 147–152.
15. Itabashi K, Fujimura M, Kusuda S, Tamura M, Hayashi T, Takahashi T, Goishi K, Nimura M, Takahashi Y, Isobe K, Iida K, Uetani Y, Kondo Y, Shirahata S, Sugiura M, Takahashi N, Funato M, Horiuchi K and Yamaguchi S: New standard of birth constitution classified by gestational age in Japan [author translated, in Japanese]. Journal of Japan Pediatric Society (2010) 114: 1271–1293.
16. Snijders RJ, Abbas A, Melby O, Ireland RM and Nicolaides KH: Fetal plasma erythropoietin concentration in severe growth retardation. Am J Obstet Gynecol (1993) 168: 615–619.
17. Stallmach T, Karolyi L, Lichtlen P, Maurer M, Hebisch G, Joller H, Marti HH and Gassmann M: Fetuses from preeclamptic mothers show reduced hepatic erythropoiesis. Pediatr Res (1998) 43: 349–354.
18. Ebert BL and Bunn HF: Regulation of the erythropoietin gene. Blood (1999) 94: 1864–1877.
19. Ohls RK, Li Y, Abdel-Mageed A, Buchanan G Jr., Mandell L and Christensen RD: Neutrophil pool sizes and granulocyte colony-stimulating factor production in human mid-trimester fetuses. Pediatr Res (1995) 37: 806–811.