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Original Article

Survival and Neurodevelopmental Outcomes of Very Low Birth Weight Infants in a Regional Core Hospital in Kochi, Japan

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We sought to clarify the survival and neurodevelopmental outcomes of very low birth weight infants (VLBWIs) and to identify risk factors for death or neurodevelopmental impairment (NDI) in VLBWIs at our hospital. The total study population was 217 infants born in 2005-2012 weighing ≤1,500 g. We compared their outcomes with those from previous reports analyzed the causes of death. Risk factors for death after discharge or NDI were evaluated by a multivariate logistic regression analysis. The incidences of death or NDI reported revealed in this study and the database of Neonatal Research Network of Japan were 25.3% and 19.6% (p = 0.039), respectively. The main causes of death before discharge were intraventricular hemorrhage, sepsis, and persistent pulmonary hypertension of the newborn. The significant risk factors for death after discharge or NDI were early gestational age (weeks) and periventricular leukomalacia (adjusted odds ratio [95% confidence interval, p-value], 0.72 [0.54-0.94, 0.017] and 6.90 [1.35-38.25, 0.021], respectively). These factors must be addressed in order to improve treatment strategies for VLBWIs.

Key words: intraventricular hemorrhage, periventricular leukomalacia, persistent pulmonary hypertension of the newborn, sepsis, very low birth weight infants

Treatments for preterm infants has improved, and key parameters such as survival rates and neurodevelopmental outcomes have been evaluated [1-6]. In 2003, a database of very low birth weight infants (VLBWIs) was established in Japan (the Neonatal Research Network of Japan [NRNJ]) and the results of several analyses of the database have been reported [6,7]. Since opening in 2005, our hospital has provided care for nearly half of all VLBWIs born in Kochi prefecture, Japan. As such, we feel that creating our own prefecture-wide VLBWIs database and comparing our analysis results with those of other studies would be useful.

In the present study, we attempted to clarify survival and neurodevelopmental outcomes and identify risk factors for death or neurodevelopmental impairment (NDI) in VLBWIs.

Materials and Methods

Data for our retrospective analyses were obtained from the medical records of all surviving infants who were born weighing ≤1,500 g at the Kochi Health Sciences Center in Kochi, Japan between March 2005 and March 2012. The cases of infants were excluded if the infants had any chromosomal abnormalities, multiple anomalies, congenital infection or disease with a poor prognosis.

Confounding factors. We adjusted the data

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for the following confounding factors: maternal age, primiparity, maternal diabetes, pregnancy-induced hypertension, clinical chorioamnionitis, premature rupture of membrane (PROM), antenatal corticosteroid use, cesarean section, sex, gestational age (GA), birth weight (BW), Apgar score (AS) at 1 and 5 min, respiratory distress syndrome (RDS), chronic lung disease (CLD), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), sepsis, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and periventricular leukomalacia (PVL) [8–11]. Clinical chorioamnionitis was diagnosed based on clinical findings such as maternal fever, leukocytosis, or local pain during pregnancy, labor or delivery [12]. Antenatal corticosteroid use was defined as the administration of at least one dose of corticosteroid to the mother at any time before delivery to accelerate fetal lung maturity. The GA was determined by the best estimate based on an early prenatal ultrasound examination, the last menstrual period, and the physical examination of the infant at birth. Small for gestational age (SGA) was defined as a BW less than the 10th percentile of the standard BW for GA as published by the Japan Pediatric Society [13]. RDS was defined as that diagnosed by clinical and radiographic findings. CLD was defined as requiring oxygen at 36 weeks (corrected age). PDA was defined as receiving indomethacin treatment. NEC was defined by a Bell classification of stage II or greater [14]. Sepsis was diagnosed by blood culture. The grade of IVH was diagnosed by cranial echography according to the classification of Papile, with grades III and IV corresponding to severe IVH [15]. ROP was defined as being treated with laser coagulation.

Outcomes. Outcomes included death before or after discharge, transfer before or after discharge, NDI, no NDI and lost to follow-up (LTF). Death or transfer after discharge and NDI were evaluated ≥ 3 years (*i.e.*, 36–42 months). NDI was defined as any of the following: cerebral palsy, unilateral or bilateral blindness, severe hearing impairment, or developmental delay. Developmental delay was defined as a developmental quotient (DQ) < 70 on the Kyoto Scale of Psychological Development (KSPD) test, or as determined by the physicians of infants who did not undergo this test [4,16].

Statistical analysis. After the exclusions were made, we divided our study population was divided into groups according to BW (every 250 g) and GA (every 2 weeks). We then compared the rates of death or NDI and other parameters between the present study and that by Kono *et al.*, which was based on NRNJ [4].

We divided the evaluated cases into 2 groups based on their clinical characteristics of evaluated cases were divided into 2 groups (no NDI vs. death after discharge or NDI). We compared the groups by performing a univariate logistic regression analysis, and we used a simple descriptive analysis to calculate mean differences, risk ratios, and 95% confidence intervals (95%CIs). For death after discharge or NDI, a multivariate logistic regression analyses was performed to adjust for confounding factors including primiparity, pregnancy-induced hypertension, clinical chorioamnionitis, antenatal corticosteroid use, male sex, GA, AS at 5 min < 7, RDS, CLD, PDA, NEC, sepsis, severe IVH, ROP and PVL, all of which have been found to affect neurodevelopmental outcomes in VLBWIs [5,9,17]. GA but not BW was included in the models because the two measurements are colinear [5]. We also calculated the adjusted odds ratios (AORs) and their 95%CIs were also calculated.

Among the infants with KSPD, we analyzed the DQ scores from the KSPD test for risk factors by using the least-squares method. Lastly, we compared the results of our evaluations of the cases involving LTF and transfer after discharge.

All statistical analyses were performed using JMP 10.0.2 software (SAS Institute, Cary, NC, USA), with p-values < 0.05 indicating statistical significance. The present study protocol was approved by the Ethics Review Committee of the Kochi Health Sciences Center.

Results

The data from 217 of the 225 infants born during the specified period were used for our analysis (Fig. 1); the eight remaining cases were excluded for reasons including lung sequestration, cerebral arteriovenous malformation, right lung agenesis with esophageal atresia, double outlet right ventricle with hydrocephalus, holoprosencephaly, congenital cytomegalovirus infection, congenital muscular dystrophy, and trisomy 13.

The evaluated cases included infants with no NDI

(n＝117), NDI (n＝38; 1 infant with cerebral palsy, 2 with visual impairment, and 35 with developmental delays: 18 with DQ ＜70 and 17 as determined by physicians), and those who died (n＝2). Infants, who were diagnosed with developmental delays, were clinically judged and unable to take the test. Of the 155 surviving infants (with or without NDI), 92 had undergone the KSPD test.

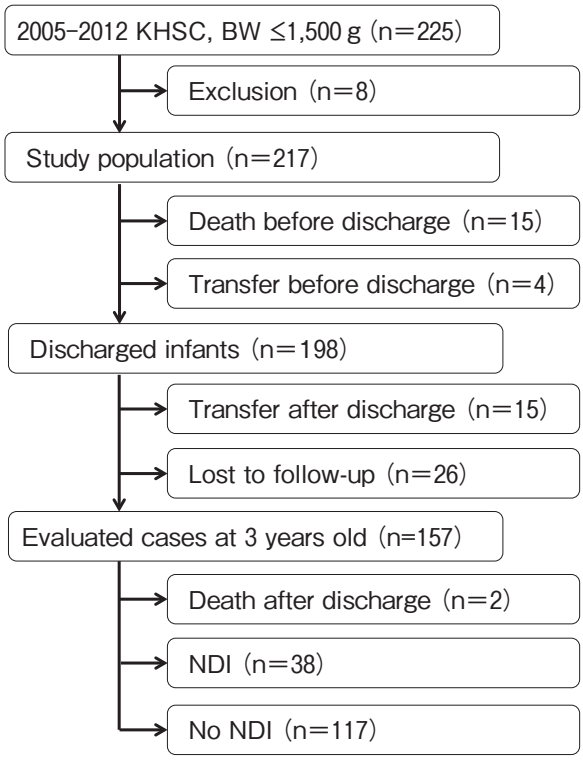

Fig. 1 Flow chart of the recruitment of very low birth weight infants born at the Kochi Health Sciences Center in Kochi, Japan between March 2005 and March 2012.

Neonatal outcomes by BW group are shown in Fig. 2 and Table 1. The numbers(%) of each group were 2 (0.9) for infants weighing ≤500 g, 39 (18.0) for those weighing 501–750 g, 47 (21.7) for 751–1,000 g, 67 (30.9) for 1,001–1,250 g, and 62 (28.6) for 1,251–1,500 g. The comparison of our present findings to those of Kono *et al.* [4] revealed the following: the rates of death before discharge in the two studies were 6.9% versus 7.6% ($p＝0.722$): the rate of death after discharge was 0.9% versus 0.7% ($p＝0.642$: , the rate of death plus NDI was 25.3% versus 19.6% ($p＝0.039$): and the rate of no NDI was 53.9% versus 47.6% ($p＝0.125$), respectively. The rate of death or NDI in each BW group is shown in Table 2. The death/NDI rate for the 751–1,000 g BW group and that of the total population in the present study were significantly higher than the corre-

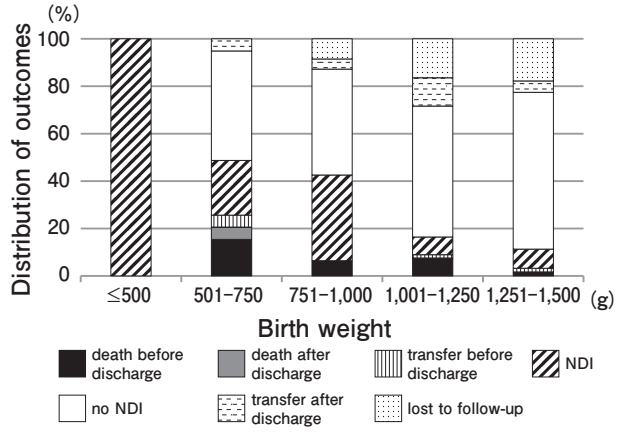

Fig. 2 Neonatal outcomes of the study infants (n＝217) by birth weight (every 250 g). Black, death before discharge; gray, death after discharge; vertical stripes, transfer before discharge; diagonal lines, NDI; white, no NDI; wave, transfer after discharge; dotted, lost to follow-up.

Table 1 Outcomes by birth weight group (every 250 g)

Outcome		≤500 g (n＝2)	501–750 g (n＝39)	751–1,000 g (n＝47)	1,001–1,250 g (n＝67)	1,251–1,500 g (n＝62)	Total (n＝217)
Death BD	n (%)	0 (0)	6 (15.4)	3 (6.4)	5 (7.5)	1 (1.6)	15 (6.9)
Death AD	n (%)	0 (0)	2 (5.1)	0 (0)	0 (0)	0 (0)	2 (0.9)
NDI	n (%)	2 (100)	9 (23.1)	17 (36.2)	5 (7.5)	5 (8.1)	38 (17.5)
No NDI	n (%)	0 (0)	18 (46.2)	21 (44.7)	37 (55.2)	41 (66.1)	117 (53.9)
Transfer BD	n (%)	0 (0)	2 (5.1)	0 (0)	1 (2.1)	1 (1.6)	4 (1.8)
Transfer AD	n (%)	0 (0)	2 (5.1)	2 (4.3)	8 (11.9)	3 (4.8)	15 (6.9)
LTF	n (%)	0 (0)	0 (0)	4 (8.5)	11 (16.4)	11 (17.7)	26 (12.0)

AD, after discharge; BD, before discharge; LTF, lost to follow-up; NDI, neurodevelopmental impairment.

sponding rates observed by Kono *et al.*

Neonatal outcomes according to GA group are shown in Fig. 3 and Table 3. The rates of death or NDI in each GA group were 50.0%, 59.3%, 42.9%, 24.0%, 3.4%, 13.3%, 0%, 0%, and 100% at 22–23, 24–25, 26–27, 28-29, 30–31, 32–33, 34–35, 36–37, and 38–39 gestational weeks, respectively.

The characteristics of the infants who died or were transferred before discharge are shown in Table 4.

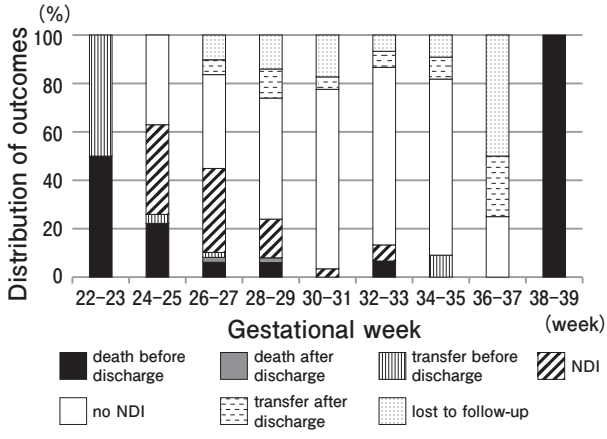

Fig. 3 Neonatal outcomes of thestudy infants (n = 217) by gestational week (every 2 weeks). Black, death before discharge; gray, death after discharge; vertical stripes, transfer before discharge; diagonal lines, NDI; white, no NDI; wave, transfer after discharge; dotted, lost to follow-up.

The main causes of death were IVH (n = 6), sepsis (n = 4), and persistent pulmonary hypertension of the newborn (n = 3).

The univariate logistic regression analysis for the evaluated cases (no NDI vs. death after discharge or NDI) (Table 5) revealed that the characteristics of the infants who died after discharge or had NDI were early GA, low BW, low AS at 1 min, RDS, CLD, PDA, ROP, and PVL.

We performed a multivariate logistic regression analysis to assess death after discharge or NDI in the evaluated cases. As shown in Table 6, the significant risk factors included early GA (weeks) (AOR [95% CI, *p*-value], 0.72 [0.54–0.94, 0.017]) and PVL (6.90 [1.35–38.25, 0.021]).

Our analysis of the DQ scores on the KSPD test (n = 92) revealed that the significant risk factors for low DQ were early GA, severe IVH, ROP and PVL ($p = 0.017$, 0.021, 0.019 and 0.014, respectively) (Table 7).

Lastly, we compared the evaluated cases versus those that were either transferred after discharge or LTF (Table 8). The characteristics of the LTF and transfer after discharge cases were late GA, high BW, high AS at 1 min, and less ROP.

Table 2 Rates of death or NDI by birth weight group for the present study versus that by Kono *et al.* [4].

(%)	≤500 g	501–750 g	751–1,000 g*	1,001–1,250 g	1,251–1,500 g	Total*
Present study (%)	100	43.6	42.6	14.9	9.7	25.3
Kono *et al.* (%)	65.6	40.1	20.8	9.8	8.5	19.6
p-value	0.308	0.668	0.0005	0.184	0.739	0.039

NDI, neurodevelopmental impairment. *$p < 0.05$ for the difference between the two studies' data.

Table 3 Outcomes by gestational age groups (every 2 weeks)

Outcome		22–23w (n = 2)	24–25w (n = 27)	26–27w (n = 49)	28–29w (n = 50)	30–31w (n = 58)	32–33w (n = 15)	34–35w (n = 11)	36–37w (n = 4)	38–39w (n = 1)	Total (n = 217)
Death BD	n (%)	1 (50.0)	6 (22.2)	3 (6.1)	3 (6.0)	0 (0)	1 (6.7)	0 (0)	0 (0)	1 (100)	15 (6.9)
Death AD	n (%)	0 (0)	0 (0)	1 (2.0)	1 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.9)
NDI	n (%)	0 (0)	10 (37.0)	17 (34.7)	8 (16.0)	2 (3.4)	1 (6.7)	0 (0)	0 (0)	0 (0)	38 (17.5)
No NDI	n (%)	0 (0)	10 (37.0)	19 (38.8)	25 (50.0)	43 (74.1)	11 (73.3)	8 (72.7)	1 (25.0)	0 (0)	117 (53.9)
Transfer BD	n (%)	1 (50.0)	1 (3.7)	1 (2.0)	0 (0)	0 (0)	0 (0)	1 (9.0)	0 (0)	0 (0)	4 (1.8)
Transfer AD	n (%)	0 (0)	0 (0)	3 (6.1)	6 (12.0)	3 (5.2)	1 (6.7)	1 (9.0)	1 (25.0)	0 (0)	15 (6.9)
LTF	n (%)	0 (0)	0 (0)	5 (10.2)	7 (14.0)	10 (17.2)	1 (6.7)	1 (9.0)	2 (50.0)	0 (0)	26 (12.0)

AD, after discharge; BD, before discharge; LTF, lost to follow-up; NDI, neurodevelopmental impairment.

Table 4 Characteristics of infants who either died (n = 15) or were transferred before discharge (n = 4)

No.	Death/Transfer	GA (weeks)	BW (g)	Length of NICU stay	Cause
1	D	23	506	0	Asphyxia
2	D	24	661	371	CAM, CLD
3	D	24	676	4	IVH 4
4	D	24	808	1	CAM, PPHN
5	D	25	558	9	IVH 3, Sepsis
6	D	25	592	6	PPHN, IVH 4
7	D	25	652	27	Sepsis
8	D	26	880	8	IVH 4
9	D	26	1,032	9	TTTS, PA, IVH 4
10	D	27	852	3	IVH 4
11	D	28	1,186	0	Hydrops
12	D	29	1,070	52	Ileus, Sepsis
13	D	29	1,152	27	Sepsis
14	D	33	1,404	30	Congenital intestinal obstruction
15	D	38	1,184	50	PPHN
16	T	23	610	116	ROP
17	T	25	696	106	ROP
18	T	27	1,090	25	PDA
19	T	34	1,440	71	PA

BW, birth weight; CAM, chorioamnionitis; CLD, chronic lung disease; GA, gestational age; IVH, intraventricular hemorrhage; PA, pulmonary atresia; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of the newborn; ROP, retinopathy of prematurity; TTTS, twin-to-twin transfusion syndrome.

Table 5 Characteristics of evaluated cases (n = 157)

Characteristic		No NDI (n = 117)	Death AD or NDI (n = 40)	MD or RR (95%CI)	*P*-value
Maternal age (years)	Mean (SD)	32.1 (5.3)	30.6 (6.3)	1.5 (−0.5–3.5)	0.145
Primiparity	n (%)	61 (52.1)	23 (57.5)	0.91 (0.66–1.2)	0.557
Diabetes	n (%)	5 (4.3)	0 (0)	–	0.330
PIH	n (%)	32 (27.4)	9 (22.5)	1.2 (0.64–2.3)	0.547
Chorioamnionitis	n (%)	14 (12.0)	4 (10.0)	1.2 (0.42–3.4)	1.000
PROM	n (%)	41 (35.0)	11 (27.5)	1.3 (0.73–2.2)	0.382
ACS	n (%)	68 (58.1)	28 (70.0)	0.83 (0.64–1.1)	0.183
Cesarean section	n (%)	106 (90.6)	36 (90.0)	1.01 (0.89–1.1)	1.000
Male	n (%)	62 (53.0)	18 (45.0)	1.2 (0.80–1.7)	0.383
Gestational age (weeks)*	Mean (SD)	29.8 (2.7)	27.4 (2.0)	2.4 (1.5–3.3)	<.0001
Birth weight (g)*	Mean (SD)	1,096 (264)	886 (266)	210 (115–306)	<.0001
SGA	n (%)	52 (44.4)	11 (27.5)	1.6 (0.94–2.8)	0.059
AS at 1 min < 7*	n (%)	62 (53.0)	30 (75.0)	0.71 (0.55–0.90)	0.015
AS at 5 min < 7	n (%)	28 (23.9)	15 (38.5)	0.62 (0.37–1.0)	0.079
RDS*	n (%)	82 (70.1)	38 (95.0)	0.74 (0.64–0.85)	0.0009
CLD*	n (%)	5 (4.3)	6 (15.0)	0.28 (0.092–0.88)	0.022
PDA*	n (%)	38 (32.5)	23 (57.5)	0.56 (0.39–0.82)	0.005
NEC	n (%)	1 (0.9)	0 (0)	–	1.000
Sepsis	n (%)	1 (0.9)	3 (7.5)	0.11 (0.012–1.1)	0.051
Severe IVH	n (%)	1 (0.9)	2 (5.0)	0.17 (0.016–1.8)	0.160
ROP*	n (%)	18 (15.4)	18 (45.0)	0.34 (0.20–0.59)	0.0001
PVL*	n (%)	4 (3.4)	7 (17.5)	0.20 (0.060–0.63)	0.006

ACS, antenatal corticosteroid use; AD, after discharge; AS, Apgar score; CI, confidence interval; CLD, chronic lung disease; IVH, intraventricular hemorrhage; MD, mean difference; NEC, necrotizing enterocolitis; NDI, neurodevelopmental impairment; PDA, patent ductus arteriosus; PIH, pregnancy-induced hypertension; ROP, retinopathy of prematurity; PROM, premature rupture of the membranes; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; RR, risk ratio; SGA, small for gestational age. *indicates *p*-value < 0.05.

Table 6 Multivariate logistic regression analysis for death after discharge or NDI

Risk factors	AOR	95%CI	*P*-value
Primiparity	1.57	0.64–3.98	0.321
PIH	2.01	0.62–6.56	0.243
Chorioamnionitis	0.58	0.13–2.14	0.422
ACS	1.16	0.42–3.35	0.778
Male	0.88	0.36–2.17	0.775
Gestational age (weeks)*	0.72	0.54–0.94	0.017
AS at 5 min < 7	0.77	0.28–2.05	0.610
RDS	2.46	0.50–18.71	0.283
CLD	1.60	0.29–8.49	0.579
PDA	1.05	0.37–2.95	0.926
NEC	8.97e–8	0–18.84	0.436
Sepsis	2.03	0.17–49.81	0.585
Severe IVH	2.68	0.14–87.31	0.518
ROP	2.17	0.74–6.48	0.156
PVL*	6.90	1.35–38.25	0.021

ACS, antenatal corticosteroid use; AOR, adjusted odds ratio; AS, Apgar score; CI, confidence interval; CLD, chronic lung disease; IVH, intraventricular hemorrhage; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; NDI, neurodevelopmental impairment; PDA, patent ductus arteriosus; PIH, pregnancy-induced hypertension; ROP, retinopathy of prematurity; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome. *indicates p-value < 0.05.

Table 7 Risk factor analysis for DQ by KSPD test with least squares method

Risk factors	*t*-value	95%CI	*P*-value
Primiparity	−0.44	−4.43–2.83	0.662
PIH	−0.51	−5.52–3.27	0.612
Chorioamnionitis	0.55	−3.78–6.70	0.581
ACS	1.15	−1.64–6.10	0.254
Male	−0.38	−4.21–2.87	0.706
Gestational age (weeks)*	2.45	0.44–4.29	0.017
AS at 5 min < 7	−0.91	−6.03–2.26	0.368
RDS	0.21	−4.19–5.17	0.836
CLD	−1.29	−12.47–2.68	0.202
PDA	0.79	−2.56–5.95	0.430
NEC	−0.17	−17.60–14.76	0.862
Sepsis	−0.07	−9.84–9.19	0.946
Severe IVH*	−2.36	−35.44–−3.01	0.021
ROP*	−2.40	−10.04–−0.93	0.019
PVL*	−2.52	−16.09–−1.89	0.014

ACS, antenatal corticosteroid use; AS, Apgar score; CI, confidence interval; CLD, chronic lung disease; DQ, developmental quotient; IVH, intraventricular hemorrhage; KSPD, Kyoto Scale of Psychological Development; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; NDI, neurodevelopmental impairment; PDA, patent ductus arteriosus; PIH, pregnancy-induced hypertension; ROP, retinopathy of prematurity; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome. *indicates p-value < 0.05.

Table 8 Evaluated cases vs. those that were LTF and transferred after discharge

Characteristic		Evaluated (n = 157)	LTF, transfer AD (n = 41)	MD or RR (95%CI)	*P*
Maternal age (years)	Mean (SD)	31.7 (5.6)	31.5 (6.0)	0.2 (−1.7–2.2)	0.822
Primiparity	n (%)	84 (53.5)	19 (46.3)	1.2 (0.8–1.7)	0.414
Diabetes	n (%)	5 (3.2)	0 (0)	–	0.586
PIH	n (%)	41 (26.1)	11 (26.8)	0.97 (0.55–1.7)	0.926
Chorioamnionitis	n (%)	18 (11.5)	2 (4.9)	2.4 (0.57–9.7)	0.260
PROM	n (%)	52 (33.1)	11 (26.8)	1.2 (0.71–2.1)	0.441
ACS	n (%)	96 (61.2)	29 (70.7)	0.86 (0.68–1.1)	0.257
Cesarean section	n (%)	142 (90.5)	38 (92.7)	0.98 (0.88–1.1)	1.000
Male	n (%)	80 (51.0)	17 (41.5)	1.2 (0.83–1.8)	0.279
Gestational age (weeks)*	Mean (SD)	29.2 (2.7)	30.3 (2.7)	−1.1 (−2.0–−0.18)	0.020
Birth weight (g)*	Mean (SD)	1,043 (279)	1,165 (212)	−122 (−214–−30)	0.010
SGA	n (%)	63 (40.1)	18 (43.9)	0.91 (0.62–1.4)	0.662
AS at 1 min < 7*	n (%)	92 (58.6)	16 (39.0)	1.5 (1.0–2.3)	0.025
AS at 5 min < 7	n (%)	43 (27.6)	8 (19.5)	1.4 (0.72–2.8)	0.295
RDS	n (%)	120 (76.4)	32 (78.1)	0.98 (0.81–1.2)	0.827
CLD	n (%)	11 (7.0)	2 (4.9)	1.4 (0.33–6.2)	1.000
PDA	n (%)	61 (38.9)	15 (36.6)	1.1 (0.68–1.7)	0.790
NEC	n (%)	1 (0.6)	0 (0)	–	1.000
Sepsis	n (%)	4 (2.6)	2 (4.9)	0.52 (0.10–2.8)	0.606
Severe IVH	n (%)	3 (1.9)	0 (0)	–	1.000
ROP*	n (%)	36 (22.9)	3 (7.3)	3.1 (1.0–9.7)	0.027
PVL	n (%)	11 (7.0)	1 (2.4)	2.9 (0.38–21.6)	0.466

ACS, antenatal corticosteroid use; AD, after discharge; AS, Apgar score; CI, confidence interval; CLD, chronic lung disease; IVH, intraventricular hemorrhage; LTF, lost to follow-up; MD, mean difference; NEC, necrotizing enterocolitis; NDI, neurodevelopmental impairment; PDA, patent ductus arteriosus; PIH, pregnancy-induced hypertension; ROP, retinopathy of prematurity; PROM, premature rupture of the membranes; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; RR, risk ratio; SGA, small for gestational age. *indicates p-value < 0.05.

Discussion

In the present study we examined VLBWIs born in 2005–2012 according to their BW. Kono *et al.* has reported the detailed from their database analysis of Japanese infants born in 2003–2004 [4]. Specifically, they found that the percentages of infants weighing ≤500 g, 501–750 g, 751–1,000 g, 1,001–1,250 g, and 1,251–1,500 g were 3.9%, 18.2%, 22.1%, 25.6%, and 30.1%, respectively. At our hospital, infants weighing ≤500 g comprised 0.9% of the total VLBWI population. As such, our VLBWIs would weigh more than those in the study by Kono *et al.* [4]. Our comparison of our results to those of Kono *et al.* revealed that rates of death or NDI among our infants were higher, particularly in the 751–1,000 g BW group. Kusuda *et al.* showed recent improvements of neonatal care during 2003–2008 [6]. Even though the infants in our present analysis were heavier and the study period was later, the neonatal outcomes in the present study appear to be worse. During the study period, there were 6 or 7 pediatricians and a few residents taking care of the patients in the pediatric ward and NICU. Two neonatologists who were among the seven pediatricians were not always available to handle the problems of preterm infants. This shortage of staff could be one of the reasons why the neonatal outcomes of our hospital's VLBWI cases were worse.

In our analysis, the main causes of death before discharge included IVH, sepsis, and PPHN (Table 4). Previous studies have reported these diseases as risk factors for mortality and morbidity [1,5,18]. We observed herein that the risk factors for long-term outcomes were early GA and PVL (Table 6), both of which have already been reported as risk factors [1,5,19]. Our analysis of the DQ scores obtained by the KSPD test with least-squares method showed that ROP was also a risk factor. Our study findings suggest that early GA, IVH, sepsis, PPHN, ROP, and PVL in particular should be monitored closely.

Neonatal treatment strategies must be reevaluated so that the incidence of these diseases can be greatly decreased. In terms of sepsis, infection control is extremely important. Our recent infection control efforts include motivating the medical staff not to spread infections such as methicillin-resistant staphylococcus aureus (MRSA), and reevaluating the procedure used for percutaneously inserted central catheters, because careful fundamental techniques would be the first step to decrease the incidence of sepsis. As for IVH, PPHN, ROP and PVL, early stabilization and maintaining good cardiopulmonary status are essential. We also organized a symposium for improving the respiratory management of extremely low birth weight infants with other adjacent NICUs [20]. Our hospital's weakness in the area of respiratory management was correctly pointed out at the symposium, which led to direct clinical improvement. In the near future we hope to organize another symposium to address circulation.

In the present study and the study of Kono *et al.*, the percentages of infants who were transferred or LTF were 20.7% and 32.9% ($p=0.0001$), respectively [4]. Notably, our study had fewer infants who were both transferred and LTF. The characteristics of these infants included late GA, high BW, high AS at 1 min, and less ROP (Table 8), indicating a lower rate of NDI. For both our study and that by Kono *et al.*, the possibility remains that the rates of death or NDI were overestimated [4].

The present study has several limitations. First, our study population was somewhat small, and we plan to continue these analyses further cases are accumulated. Second, the percentage of infants who were transferred or LTF was fairly high, indicating the need for a closer follow-up of VLBWIs in the future.

In conclusion, our neonatal outcomes seem to be worse than those reported in the NRNJ database. The main causes of death before discharge were IVH, sepsis, and PPHN, whereas the risk factors for death after discharge or NDI were early GA and PVL. Given these findings, improved strategies for treating VLBWIs continue to be necessary.

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