Outcomes of outborn very-low-birth-weight infants in Japan

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ABSTRACT

Background Outcomes of prenatal covariate-adjusted outborn very-low-birth-weight infants (VLBWIs) (≤1500 g) remain uncertain.

Objective To compare morbidity and mortality between outborn and inborn VLBWIs.

Design Observational cohort study using inverse-probability-of-treatment weighting.

Setting Neonatal Research Network of Japan.

Patients Singleton VLBWIs with no major anomalies admitted to a neonatal intensive care unit from 2012 to 2016.

Methods Inverse-probability-of-treatment weighting with propensity scores was used to reduce imbalances in prenatal covariates (gestational age (GA), birth weight, small for GA, sex, maternal age, premature rupture of membranes, chorioamnionitis, preeclampsia, maternal diabetes mellitus, antenatal steroids and caesarean section). The primary outcome was severe intraventricular haemorrhage (IVH). The secondary outcomes were outcomes at resuscitation, other neonatal morbidities and mortality.

Results The full cohort comprised 15 842 VLBWIs (668 outborns). The median (IQR) GA and birth weight were 28.9 (26.4–31.0) weeks and 1128 (862–1351) g for outborns and 28.7 (26.3–30.9) weeks and 1042 (758–1295) g for inborns. Outborn VLBWIs had a higher incidence of severe IVH (8.2% vs 4.1%; OR, 3.45; 95% CI 1.16 to 10.3) and pulmonary haemorrhage (3.7% vs 2.8%; OR, 5.21; 95% CI 1.41 to 19.2). There were no significant differences in Apgar scores, oxygen rates at delivery, intubation ratio at delivery, persistent pulmonary hypertension of the newborn, IVH of any grade, periventricular leukomalacia, chronic lung disease, oxygen at discharge, patent ductus arteriosus, retinopathy of prematurity, necrotising enterocolitis, sepsis or mortality.

Conclusion Outborn delivery of VLBWIs was associated with an increased risk of severe IVH.

What is already known on this topic?

- Although the incidence of outborn very-low-birth-weight infants (VLBWIs) has been decreasing in Japan during the past decade, postnatal transport of neonatal patients cannot be totally avoided.
- Mortality and major morbidity rates are higher among outborn VLBWIs than among their inborn peers.
- However, outcomes of prenatal covariate-adjusted outborn VLBWIs remain uncertain.

What this study adds?

- Using inverse-probability-of-treatment weighting to reduce the imbalance in covariates determined immediately after birth, outborn delivery was found to be associated with severe intraventricular haemorrhage.

INTRODUCTION

Progress in perinatal management[1–4] and centralisation of perinatal care[5–10] have improved outcomes in preterm infants. However, complications associated with premature birth still exist; in particular, intraventricular haemorrhage (IVH) greatly impacts the outcome of very-low-birth-weight infants (VLBWIs) (≤1500 g).[11] Severe IVH is associated with increased mortality and long-term developmental impairment, which impacts the quality of life of patients and families and also introduces a significant socioeconomic burden.[12] While the aetiology of IVH is multifactorial,[13] several retrospective studies have revealed that outborn birth and interhospital transport are risk factors for IVH in VLBWIs.[14–22]

A major problem of evaluating outcomes of outborn preterm infants is that perinatal characteristics (maternal illnesses, pregnancy complications, delivery mode and antenatal steroid exposure) are significantly different between inborn and outborn preterm neonates.[14–22] Several previous reports used traditional covariate adjustment in regression models for risk adjustment of the differences in outcomes between inborn and outborn neonates. However, when large differences in important prognostic characteristics are present, adjusting for these differences with conventional multivariable techniques may not adequately balance the groups.[23] The propensity score (PS), defined as the conditional probability of exposure given a set of observed covariates, has been shown to effectively balance measured covariates between two groups in comparative observational studies.[24]

This study was performed to compare the risk of mortality and morbidity between outborn and inborn VLBWIs in Japan by inverse-probability-of-treatment weighting (IPTW) analysis using PSs.[25] We hypothesised that the incidence of severe IVH, other morbidities and mortality is higher in outborn than inborn VLBWIs.

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PATIENTS AND METHODS

Study setting and population

In Japan, approximately 50% of deliveries are managed at birth centres or level I hospitals for maternal care. In 2015 in Japan, the preterm birth rate was 5.6% and the stillbirth rate was 2.1 per 1000 total births. The Ministry of Health, Labour and Welfare (MHLW) of Japan formulated guidelines that pertain to the maintenance of perinatal medical systems; specifically, prefectural government bodies are required to designate tertiary perinatal medical centres (which provide high-level intensive neonatal care and high-level obstetric maternal–fetal care) and regional perinatal medical centres based on the care level required by patients.[26] The proportion of neonatal transport among VLBWIs in Japan decreased from 12% in 2003 to 6% in 2011 and plateaued through 2015.[26] The Neonatal Research Network of Japan (NRNJ), which was created with a grant from the MHLW of Japan, established a network database of VLBWIs across perinatal medical centres in Japan. In total, 192 facilities (including 83 tertiary centres) were registered in the NRNJ in 2012, and the population coverage of VLBWIs was approximately 70% in 2012.[4] The NRNJ has been collecting maternal and infant clinical data of VLBWIs during their stay at the neonatal intensive care units (NICUs) and follow-up visits.[26]

VLBWIs registered in the NRNJ database who were born and admitted to a NICU from 1 January 2012 to 31 December 2016 were included in the present study. To reduce immeasurable variables that might affect the outcomes, we excluded infants with a non-singleton birth status, major congenital anomalies (defined as any structural abnormalities of surgical, medical or cosmetic importance), gestational age (GA) of <22 weeks or uncertain GA and uncertain birth weight (BW) as well as outborn infants who were transported to a NICU after 3 days of life. Stillborn infants and infants who were unable to be transported to tertiary centres and died were not included in the study. Additionally, we excluded infants without primary outcome (severe IVH) data and without prenatal confounder data. This study was approved by the internal review board of Tokyo Women's Medical University and registered as a prospective observational study with the University Hospital Medical Information Network clinical registration system in Japan (UMIN000006961). The data collection of all infants in the NRNJ database was approved by the infants' parents or guardians.

Definitions of patient characteristics and outcomes

Maternal and neonatal characteristics were obtained from the NRNJ database. GA was determined based on ultrasound examination during the first trimester and the date of the last menstrual period. Infants with a BW below the 10th percentile of the mean of the Japanese birth size standard data were classified as small for GA (SGA). Antenatal steroids were defined as the administration of corticosteroids to the mother at any time before delivery. Premature rupture of membranes (PROM) was defined as rupture of membranes before labour onset. Maternal diabetes mellitus (DM) was defined as impaired glucose tolerance of the mother, including gestational DM. Persistent pulmonary hypertension of the newborn and pulmonary haemorrhage were diagnosed clinically. IVH was classified according to the grading scale established by Papile *et al*.[27] Severe IVH was defined as grade III and IV. In Japanese NICUs, brain ultrasounds of VLBWIs with a high risk of IVH are frequently undertaken during the initial 72 hours after birth, and weekly follow-up is usually performed thereafter.[26] Periventricular leukomalacia (PVL) was defined as periventricular hyperintensity, cerebral white matter atrophy predominantly in the peritrigonal region and ventriculomegaly with an irregular ventricular wall on MRI. Chronic lung disease (CLD) was defined as the requirement for supplemental oxygen or pressure-supported ventilation at 36 weeks' corrected postmenstrual age. Patent ductus arteriosus (PDA) was diagnosed clinically or by echocardiography. Surgical intervention was performed when hemodynamically significant symptoms remained despite repeated courses of medication (indomethacin or ibuprofen). Necrotising enterocolitis (NEC) was defined according to radiological or operative evidence and the criteria established by Bell *et al* (stage II or greater). Retinopathy of prematurity (ROP) was diagnosed and treated according to the criteria proposed by the task force of the MHLW of Japan. Sepsis was diagnosed by positive blood culture results. Neonatal mortality was defined as death of an infant before hospital discharge.

The primary outcome was severe IVH (grade III or IV). Secondary outcomes were the Apgar score at 5 min, oxygen treatment at delivery, intubation at delivery, persistent pulmonary hypertension of the newborn and other neonatal morbidities such as IVH of any grade (grade I–IV), PVL, CLD, oxygen at discharge, pulmonary haemorrhage, PDA requiring ligation, ROP requiring treatment, NEC and in-hospital mortality.

Statistical analysis

We compared the baseline characteristics and outcomes between the inborn and outborn groups. Missing data were defined as blank answers. Unknown data were defined as an answer of 'unknown', which we did not exclude from the analysis. Fisher's exact test was used to examine differences between groups for categorical variables, while the Mann-Whitney non-parametric U-test was used to examine continuous variables. IPTW-adjusted regression analysis using PSs was performed to model the impact of outborn birth on severe IVH, outcomes at resuscitation, other neonatal morbidities and mortality, while adjusting for the baseline maternal and prenatal characteristics and reweighting the data to account for the unbalanced nature of observational data.[25] PSs were estimated using a logistic regression model that include all possible prenatal confounders likely to have affected the neonatal outcomes, including GA, BW, SGA, sex, maternal age, PROM, chorioamnionitis, preeclampsia, maternal DM, antenatal steroids and caesarean section delivery.[28 29] Weights of patients in the outborn group were the inverse of the PS, and weights of patients in the inborn group were the inverse of (1−PS).

Data management and statistical analyses were performed using R statistical software, V.3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria). IPTW was conducted using the packages Matching (V.4.9–7) and survey (V.3.37). All reported p values are two-sided, and values of $p<0.05$ were considered statistically significant. Data are presented as median (IQR) or number (%).

RESULTS

Population characteristics

In total, 25 373 VLBWIs were registered in the NRNJ database from 2012 to 2016. Among them, infants with non-singleton birth (n=5715), congenital anomalies (n=1430), GA of <22 weeks or incomplete data (n=28), incomplete BW data (n=724) and outborn neonates transported on day >3 of life (n=221) were excluded. Among the resulting analysis cohort of 17 255 VLBWIs, 1105 (6.4%; 1004 inborns and 101 outborns) were excluded because of missing primary

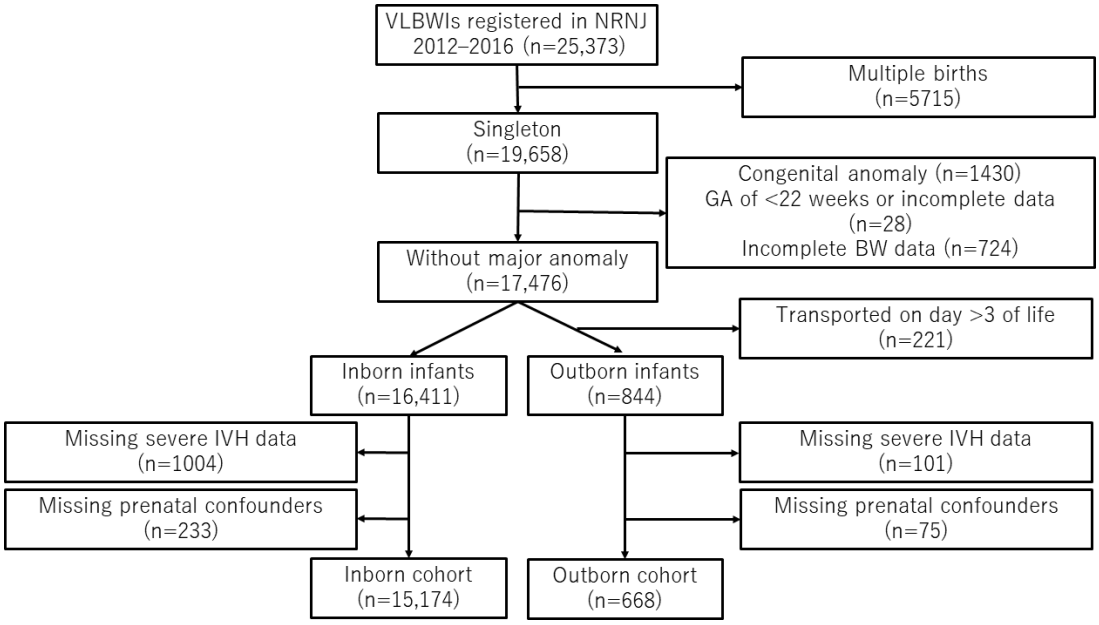

Figure 1 Flow of patient enrolment in this study. BW, birth weight; GA, gestational age; IVH, intraventricular haemorrhage; NRNJ, Neonatal Research Network of Japan; VLBWI, very-low-birth-weight infant.

outcome (severe IVH) data and 308 (1.8%; 233 inborns and 75 outborns) were excluded because of incomplete prenatal confounder data. Finally, we analysed 15 842 VLBWIs, among whom 668 were outborn and transported within 3 days of life and the remaining 15 174 were inborn controls (figure 1). Compared with the study cohort, VLBWIs who were excluded had a higher GA (29.0 (26.4–31.3) vs 28.7 (26.3–30.9), p=0.01), higher incidence of PROM (40.1% vs 30.7%, p<0.001) and clinical chorioamnionitis (26.1% vs 20.1%, p<0.001), and lower incidence of antenatal steroids (53.9% vs 58.8%, p=0.02) and caesarean section (72.6% vs 78.2%, p<0.001) (online supplementary file data 1).

The baseline maternal and prenatal characteristics of the analysis cohort are shown in table 1. In the study cohort, the outborn VLBWIs had a heavier BW (1128 (862–1351) vs 1042 (758–1295) g, p<0.001), younger maternal age (32 (27-36) vs 33 (29-36) years, p<0.001) and lower incidence of SGA (20.7% vs 30.2%, p<0.001), PROM (19.5% vs 31.2%, p<0.001), clinical chorioamnionitis (11.8% vs 19.5%, p<0.001), preeclampsia (14.7% vs 27.5%, p<0.001), maternal DM (2.1% vs 4.6%, p=0.001), antenatal steroids (16.5% vs 59.9%, p<0.001) and caesarean section (49.4% vs 79.4%, p<0.001). No significant difference in the ratio of umbilical cord milking was found between the groups (68.6% vs 69.3%, p=0.69).

Outcomes at resuscitation and neonatal morbidity in outborn VLBWIs using IPTW analysis with PSs

The outborn VLBWIs showed no significant differences in the Apgar scores, oxygen ratio at delivery, intubation ratio at delivery or persistent pulmonary hypertension of the newborn (table 2).

The outborn VLBWIs had more cases of severe IVH (8.2% vs 4.1%; OR, 3.45; 95% CI 1.16 to 10.3) and pulmonary haemorrhage (3.7% vs 2.8%; OR, 5.21; 95% CI 1.41 to 19.2). No significant differences in mortality or other morbidities (IVH of any grade, PVL, CLD, oxygen at discharge, PDA requiring ligation, ROP requiring treatment, NEC or sepsis) were found between the groups (table 3).

Table 1 Baseline characteristics

	Outborn (n=668)	Inborn (n=15 174)	P value	Unknown
Gestational age, weeks	28.9 (26.4–31.0)	28.7 (26.3–30.9)	0.43	–
Birth weight, g	1128 (862–1351)	1042 (758–1295)	<0.001	–
SGA	138 (20.7)	4577 (30.2)	<0.001	–
Male	358 (50.8)	7715 (53.6)	0.167	–
Maternal age, years	32 (27–36)	33 (29–36)	<0.001	–
PROM	130 (19.5)	4734 (31.2)	<0.001	–
Clinical chorioamnionitis	79 (11.8)	2952 (19.5)	<0.001	737
Preeclampsia	98 (14.7)	4177 (27.5)	<0.001	103
Maternal DM	14 (2.1)	699 (4.6)	<0.001	197
Antenatal steroids	110 (16.5)	9088 (59.9)	<0.001	192
Caesarean section	330 (49.4)	12 054 (79.4)	<0.001	–

Data are expressed as median (IQR) or number (%).
DM, diabetes mellitus; PROM, premature rupture of membranes; SGA, small for gestational age.

Table 2 Comparison of outcomes at resuscitation between outborn and inborn VLBWIs using IPTW

	Outborn (n=668)	Inborn (n=15 174)	OR (95% CI)
Apgar score of <5–1 min	266 (43.4)	6143 (40.5)	1.44 (0.84 to 2.47)
Missing	55 (8.2)	15 (0.0)	
Apgar score of <5–5 min	119 (19.6)	1561 (10.3)	1.78 (0.85 to 3.72)
Missing	60 (9.0)	53 (0.3)	
Oxygen at delivery	555 (85.9)	13 013 (87.0)	0.79 (0.30 to 2.11)
Missing	22 (3.4)	221 (1.5)	
Intubation at delivery	470 (71.1)	9055 (60.0)	1.57 (0.79 to 3.10)
Missing	7 (1.1)	93 (0.6)	
PPHN	31 (4.7)	973 (6.5)	1.19 (0.30 to 4.75)
Missing	14 (2.1)	95 (0.6)	

Data are expressed as number or number (%).
IPTW, inverse probability of treatment weighting; PPHN, persistent pulmonary hypertension of the newborn; VLBWI, very-low-birth-weight infant.

DISCUSSION

In the present study with a maternal and prenatal baseline-adjusted cohort, an outborn VLBWI status was significantly associated with severe IVH. These results are consistent with previous studies involving traditional covariate adjustment in regression models.[14–22] In the full cohort of the present study, outborn VLBWIs were relatively healthier with a heavier BW and fewer cases of pregnancy-associated complications such as SGA, PROM, chorioamnionitis, preeclampsia and maternal DM compared with inborns. However, outborn VLBWIs had significantly lower rates of antenatal steroids and caesarean section than inborns, which might have adversely affected the outcomes.[30 31]

Table 3 Comparison of neonatal morbidities and mortality between outborn and inborn VLBWIs using IPTW

	Outborn (n=668)	Inborn (n=15 174)	OR (95% CI)
Severe IVH	55 (8.2)	626 (4.1)	3.45 (1.16 to 10.3)
Missing	0 (0.0)	0 (0.0)	
IVH, any grade	129 (19.3)	1977 (13.0)	1.77 (0.80 to 3.88)
Missing	0 (0.0)	0 (0.0)	
PVL	29 (4.5)	405 (2.7)	3.17 (0.59 to 16.9)
Missing	19 (2.8)	101 (0.7)	
CLD	128 (22.1)	3627 (31.4)	1.14 (0.41 to 3.16)
Missing	90 (13.5)	1192 (7.9)	
Oxygen at discharge	43 (7.1)	1123 (7.9)	1.10 (0.28 to 4.38)
Missing	64 (9.6)	900 (5.9)	
Pulmonary haemorrhage	25 (3.7)	430 (2.8)	5.21 (1.41 to 19.2)
Missing	2 (0.0)	71 (0.4)	
PDA requiring ligation	46 (7.0)	990 (6.6)	2.02 (0.55 to 7.42)
Missing	11 (1.6)	95 (0.6)	
ROP requiring treatment	77 (10.0)	2030 (15.2)	2.34 (0.88 to 6.24)
Missing	98 (14.7)	1853 (12.2)	
NEC	13 (2.0)	252 (1.7)	0.56 (0.17 to 1.84)
Missing	15 (2.2)	55 (0.4)	
Sepsis	47 (7.1)	1238 (8.2)	0.81 (0.26 to 2.54)
Missing	7 (1.0)	88 (0.6)	
Mortality	35 (5.2)	621 (4.1)	3.01 (0.91 to 9.96)
Missing	0 (0.0)	17 (0.1)	

Data are expressed as number (%).
CLD, chronic lung disease; IPTW, inverse probability of treatment weighting; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; VLBWI, very-low-birth-weight infant.

In the present study, we used a rigorous IPTW method with PSs to reduce the imbalance of 11 prenatal covariates. Fang *et al*[18] recently evaluated the outcomes of outborn preterm (<30 weeks) neonates in the USA using a PS-matched cohort and reported that when matched for illness severity, an outborn status was associated with lower mortality but a greater risk of severe IVH, NEC, ROP and CLD. The lower outborn mortality in their study may be explained by selection bias; the authors did not include outborns who were selectively retained because they were considered non-viable.[18] Additionally, Helenius *et al*[19] evaluated a PS-matched cohort in England and found that in extremely preterm infants (<28 weeks), birth in a non-tertiary hospital and transfer within 48 hours were associated with an increased risk of severe brain injury when compared with birth in a tertiary setting.

Unlike previous PS-matched analyses,[18 19] we used IPTW methods with PS-adjusted maternal and prenatal, but not neonatal (eg, postnatal respiratory treatment and Apgar scores), baseline covariates to evaluate the effects of neonatal transport and the effects of neonatal resuscitation. However, no significant differences were found in outcomes at resuscitation between inborns and outborns.

The aetiology of severe IVH that develops during neonatal transport remains uncertain. Transport introduces the hazards of noise and vibration, acceleration and deceleration forces and additional handling and temperature fluctuations.[32] Additionally, interhospital transport of VLBWIs may cause deterioration in their physiological status.[33 34] Furthermore, Harrison and McKechnie[35] reported that all infants irrespective of GA showed higher levels of discomfort as demonstrated by increases in premature infant pain profile scores during transport compared with baseline. A longer duration of interhospital transport,[36] or time from birth to neonatal transport,[37] may affect outcomes of ill neonates who require neonatal transport.

Centralisation of very preterm delivery to hospitals with the highest level of neonatal care and the mode and practice of transporting neonates differ by country and region. Centralisation seems difficult to achieve despite considerable efforts.[38] The ratio of neonatal transport of VLBWIs or very preterm infants ranges from about 15% to 20% in England,[39] the USA[18] and Australia.[8] In contrast, Finland has achieved highly centralised perinatal care; the ratio of neonatal transport remains at 2%–4% of all very preterm infants.[7] This success may have been achieved by clinician-driven initiation and adequate staffing and infrastructure.[7] However, although in utero maternal transport in cases of high-risk pregnancy is optimal, postnatal transport of VLBWIs cannot be totally avoided. We need to develop more sophisticated neonatal transport systems and be prepared for outborn delivery of VLBWIs.[40]

This study has several limitations. First, this was a retrospective observational study. Because randomisation was impossible, we adjusted maternal and prenatal covariates available from the NRNJ database using IPTW methods. However, additional unmeasured confounding factors might have affected the outcomes. For example, clinical decisions regarding when and how to terminate pregnancy was difficult to include in the analysis. Additionally, because of the retrospective design, many data were missing, especially for outborns. Second, we excluded stillborn infants as well as infants who were unable to be transported to tertiary centres and died. This may have underestimated the outborn mortality rate. Third, we were unable to account for the

birth hospital volume or duration of transport. Fourth, outborn infants transferred back to smaller neonatal units for continuous non-intensive care were not included in the study. Fifth, the database did not cover the numbers and characteristics of VLBWIs who remained in non-tertiary units in Japan.

The main strength of this study is the large number of patients with precise perinatal data from a national database in Japan. Notwithstanding the above-described limitations, this study indicates a significant risk associated with an outborn VLBWI status, even in a country with a very low incidence of severe IVH.[26]

CONCLUSION

In this large cohort study using nationwide registry data in Japan, outborn delivery of VLBWIs was associated with an increased risk of severe IVH.

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