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Neonatal Intensive Care for Preterm Very Low-Birth-Weight Infants at a Medical School-Affiliated Neonatal Intensive Care Unit

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Background: The standard of care in Japan for preterm very low-birth-weight (VLBW) infants has long been at the highest level internationally, owing to advances in technology and the perinatal medical system throughout the country.

Methods: To identify issues for further improvement of outcomes for preterm VLBW infants in our neonatal intensive care unit (NICU), perinatal care practice was reviewed by analyzing data from medical records on pregnancy complications and management and infant mortality and morbidity.

Results: Data from 250 preterm VLBW infants, excluding those with severe congenital anomalies, were analyzed. There were 49 cases (19.6%) of cumulative morbidity, including infants who died before discharge and those who had major complications such as bronchopulmonary dysplasia, intraventricular hemorrhage/periventricular leukomalacia, and retinopathy of prematurity. The prevalence remained constant throughout the study period. Infants born via medically indicated preterm birth had a higher cumulative morbidity rate than those born via spontaneous preterm birth. Small-for-gestational-age status was the only factor significantly associated with cumulative morbidity in multivariate analysis. Of all the infants, 69 (47.3%) completed a course of antenatal corticosteroids (ACS).

Conclusions: The quality of neonatal intensive care for preterm VLBW infants in our NICU was consistent with outcomes for top-ranked NICUs in Japan. Critical issues in improving outcomes for these infants include determining the optimal timing of delivery by comprehensively assessing fetal well-being and promoting ACS. (J Nippon Med Sch 2025; 92: 262–267)

Key words: neonatal intensive care, very low-birth-weight infant, preterm birth, perinatal medical system

Introduction

Japan has long maintained the highest level of neonatal care among developed countries[1]. The significantly lower mortality and morbidity rates for preterm and low-birth-weight infants are attributed both to technological advances and to a well-organized perinatal health care system in which women with high-risk pregnancies are transferred to a regional perinatal medical center with a neonatal intensive care unit (NICU) before delivery and multidisciplinary management is initiated[2–4]. This system provides integrated care for pregnant women, even those with complications unrelated to pregnancy, and their fetus and provides neonatal intensive care after birth in a hospital on a regional basis.

NICUs are being established in regional core hospitals across the country, thus contributing to one of the highest survival rates for very low-birth-weight (VLBW) infants worldwide. Nevertheless, preterm VLBW remains an important issue in perinatal medicine because of the burden on healthcare resources, including the care of sur-

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viving infants with long-term complications[5]. The management and treatment of preterm VLBW infants is a specialized area of medicine requiring the highest level of expertise and is therefore a good indicator of the quality of care provided in the NICU[1,3,6]. Our NICU was set up by reorganizing the departments in a medical school hospital and started operations as a regional perinatal medical center in Kanagawa Prefecture[7].

We retrospectively analyzed the status of neonatal intensive care for preterm VLBW infants in our NICU and reviewed standard practice to identify areas for future improvement.

Methods

The Institutional Review Board of Nippon Medical School Musashi Kosugi Hospital approved the study (Approval No. D-2024-008).

This retrospective cohort study analyzed medical record data for preterm VLBW infants (gestational age <37 weeks and birth weight <1,500 g) admitted to our NICU from its opening in April 2013 to December 2023. Infants with chromosomal abnormalities, genetic disorders, or severe congenital malformations requiring surgery immediately after birth were excluded from the analysis. Infants who were transferred from other NICUs after their acute clinical problems had resolved and stabilized were also excluded. Data retrieved from medical records included maternal information [hypertensive disorders of pregnancy (HDP), chorioamnionitis (CAM), premature rupture of the membranes (PROM), hyperglycemic disorders in pregnancy, antenatal corticosteroid (ACS) use, complications unrelated to pregnancy, and advanced maternal age] and neonatal information [gestational age at birth, birth weight, small for gestational age (SGA), and death or major morbidity before discharge from the NICU, including bronchopulmonary dysplasia (BPD), intraventricular hemorrhage and/or cystic periventricular leukomalacia (IVH/PVL), and retinopathy of prematurity (ROP)].

Preterm births were classified a spontaneous preterm birth, defined as a delivery that did not respond to tocolytic treatment, or a medically indicated preterm birth, i.e., a delivery precipitated by fetal or maternal indications before labor onset.

To evaluate changes in infant outcomes over time, the study period was divided into three terms. Definitions of maternal and neonatal morbidities were as follows: HDP was a blood pressure of ≥140/90 mm Hg emerging after 20 weeks of gestation[8]. CAM was diagnosed histopathologically on the basis of grade II or III placental inflammation, according to the Blanc classification[9]. PROM was defined as an interval from onset to delivery longer than 24 h. Hyperglycemic disorders in pregnancy are diagnosed based on blood glucose levels and include gestational diabetes mellitus, overt diabetes in pregnancy, and pregestational diabetes mellitus[10].

ACS use was defined as maternal receipt of at least one dose of betamethasone intramuscularly before delivery. A complete course of ACS therapy was defined as delivery occurring at least 24 h but no later than 7 days after the administration of a full dose (24 mg) of betamethasone. Advanced maternal age was defined as a birth at age 35 years or older. SGA was defined as weight and height below the 10th percentile for the standard for gestational age at birth. BPD was defined as infant dependence on any form of respiratory support or supplemental oxygen at 36 weeks of corrected gestational age[11]. Diagnosis of IVH/PVL was based on cranial ultrasonography findings of grade III or IV on Papaille's classification[12]. ROP was diagnosed when laser photocoagulation therapy deemed necessary for the infant[13].

Statistical Analysis

Continuous variables are presented as means and standard deviations and categorical variables as frequencies (percentages). The Pearson chi-square test was used to compare categorical variables. Student's t-test was used to compare continuous variables. Logistic regression was used in multivariate analyses to examine risk factors for cumulative morbidity, after adjustment for gestational age. Results were considered significant at a P-value of <0.05.

Results

During the study period, 293 infants were admitted to our NICU. Of these infants, 43 were excluded: 31 were transferred from other NICUs after acute care had been completed and their condition had stabilized, and 12 had congenital anomalies or conditions requiring surgical intervention immediately after birth. The remaining 250 infants were admitted directly to our NICU at birth and included in the study. Only two infants were born in other hospitals and were admitted to our NICU by neonatal transfer. Of the remaining 248 infants, 125 (50.4%) were born to mothers with high-risk pregnancies who had been transferred to our hospital by ambulance. The mean gestational age and birth weight of the 250 preterm VLBW infants were 28.9 ± 2.6 (22-35) weeks and 1,096 ± 273 (353-1,499) g, respectively. The smallest infant

Table 1 Outcomes of the infants according to gestational age

Gestational age (weeks)	Total	-27	28-31	32-36
Number of infants	250	75	130	45
SGA**	117 (46.8%)	23 (30.6%)	50 (38.5%)	44 (97.8%)
BPD**	31 (12.4%)	21 (28%)	10 (7.7%)	0
IVH**	12 (4.8%)	11 (14.7%)	1 (0.8%)	0
ROP**	12 (4.8%)	12 (16%)	0	0
Died before discharge**	7 (2.8%)	4 (5.3%)	3 (2.3%)	0
Cumulative morbidity**	49 (19.6%)	35 (46.7%)	14 (10.8%)	0

** p<.01

Table 2 Pregnancy complications and management according to gestational age

Gestational age (weeks)	Total	-27	28-31	32-36
Number of infants	250	75	130	45
HDP	57 (22.8%)	13 (17.3%)	32 (24.6%)	12 (21.0%)
CAM**	47 (18.8%)	25 (33.3%)	22 (16.9%)	0
PROM	29 (11.6%)	11 (14.7%)	15 (11.5%)	3 (7.7%)
Hyperglycemic disorders in pregnancy	9 (3.6%)	3 (4.0%)	4 (3.1%)	2 (4.4%)
Advanced maternal age	107 (42.8%)	33 (44.0%)	55 (42.3%)	19 (42.2%)
ACS	146 (58.3%)	41 (54.7%)	84 (64.6%)	21 (46.7%)
ACS complete/attempt	69/146 (47.3%)	15/41 (36.6%)	43/84 (51.2%)	11/21 (52.4%)

** p<.01

weighed 353 g. Seventy-five infants were born at ≤27 weeks (extremely preterm), 130 infants at 28-31 weeks (very preterm), and 45 infants at 32-36 weeks (moderately and late preterm). Of the total, 117 (46.8%) infants were SGA. There were 194 singletons and 56 multiples, namely, 31 pairs of twins (49 infants) and 4 sets of triplets (7 infants). During the study period, 27 infants were transferred to other NICUs: 9 required more complex management, such as cardiac surgery, and 18 were returned to community hospitals near their family residence after their condition had been stabilized. The remaining 223 infants were discharged to their homes.

The clinical outcomes of the infants are shown in **Table 1**. Seven infants (2.8%) died: four were extremely preterm and three were very preterm. The rates of BPD, IVH/PVL, and ROP were 31 (12.4%), 12 (4.8%), and 12 (4.8%), respectively. Cumulative morbidity, defined as the occurrence of these serious complications or death before discharge, was observed in 49 (19.6%) cases, exclusively among infants with a gestational age of <32 weeks.

The pregnancy complications and management are shown in **Table 2**. The rates of HDP, CAM, PROM, hyperglycemic disorders in pregnancy, and advanced maternal age were 57 (22.8%), 47 (18.8%), 29 (11.6%), 9 (3.6%), and 107 (42.8%), respectively. In total, 146 (58.3%) infants received at least one dose of ACS. Of these infants, 69 (47.3%) received the full course of treatment. Moreover, 108 (43%) infants were born via spontaneous preterm birth, and 142 (57%) were born through medically indicated preterm birth. A comparison of these two groups is presented in **Table 3**. Gestational age was significantly earlier in infants born via spontaneous preterm birth, as was the prevalence of CAM. Conversely, rates of HDP and SGA were higher in infants born via medically indicated preterm birth. The prevalence of major neonatal morbidities in each group was as follows: in the spontaneous preterm birth group, BPD, IVH/PVL, and ROP were observed in 11 (10.2%), 6 (5.6%), and 6 (5.6%) cases, respectively, while in the medically indicated preterm birth group, the corresponding numbers were 20 (14.1%), 6 (4.2%), and 6 (4.2%) (with overlap among these conditions). Additionally, three infants died before discharge in the spontaneous preterm birth group and four died in the medically indicated preterm birth group. The cumulative morbidity rate was lower in infants born via spontaneous preterm birth; however, the difference was not statistically significant.

The reasons for medically indicated preterm birth and maternal complications unrelated to pregnancy are shown in **Table 4, 5**. The main indications for interventional preterm birth were maternal HDP and nonreassuring fetal status (NRFS). Thyroid disorder was the most

Table 3 Comparison by the type of preterm births

	Spontaneous preterm birth	Medically indicated preterm birth
Number of infants	108	142
Gestational age (weeks) **	28.3±2.4	29.5±2.6
SGA**	26 (24.1%)	91 (64.1%)
HDP**	6 (5.6%)	51 (35.9%)
CAM**	38 (35.2%)	9 (6.3%)
Cumulative morbidity	18 (15.8%)	31 (22.8%)

** p<.01

Table 4 Reasons for medically indicated preterm birth

HDP	51 (35.9%)
NRFS	42 (29.6%)
Fetal growth arrest	25 (17.6%)
Placental abruption	9 (6.3%)
Bleeding from placenta previa	7 (4.9%)

* includes some duplication

Table 5 Maternal complications unrelated to pregnancy

Thyroid disorder	8
Epileptic disorder	2
Inflammatory bowel disease	2
Sjogren's syndrome	2
Cushing syndrome	1
Postoperative congenital heart disease	2
Malignant tumor	2

* includes some duplication

prevalent complication unrelated to pregnancy.

Table 6 shows changes in clinical features over time. The prevalence of ROP declined, whereas that of HDP increased in recent years. No other significant changes were observed. Because cumulative morbidity was noted only in infants with a gestational age of <32 weeks, a multivariate analysis was conducted after adjusting for gestational weeks at birth, to identify potential risk factors. SGA was the only factor significantly associated with cumulative morbidity (odds ratio, 2.81; 95% confidence interval, 1.14-7.18, p = 0.027, **Fig. 1**).

Discussion

Since the establishment of our NICU, the overall survival rate and survival rate without major morbidity of preterm VLBW infants are 97.2% and 80.4%, respectively, which are comparable with the latest data from top-ranked NICUs in Japan[6]. Nearly all preterm VLBW infants were born in our hospital, and half of these were born to mothers with high-risk pregnancies who had been transferred. This allowed us to initiate appropriate care for very premature infants immediately after birth, which ultimately resulted in favorable outcomes. This also indicates that our NICU functioned effectively within the framework of the regional emergency perinatal medical system.

As shown in **Table 1**, cumulative morbidity was analyzed only for infants with a gestational age of <32 weeks. The gestational age of infants tended to be lower when they were born to mothers with CAM or if they were spontaneously born preterm (**Table 2, 3**). Nevertheless, the cumulative morbidity rate was higher in the medically indicated preterm group, although the difference was not significant. Furthermore, in multivariate analysis, SGA was the only factor associated with cumulative morbidity (**Figure 1**). These observations indicate that infant outcomes can be improved by greater attention to both simple prematurity and intrauterine conditions that affect fetal growth. In fact, the main reasons for medically indicated preterm birth were HDP, NRFS, and fetal growth arrest (**Table 4**). Because these conditions result from chronic deterioration of the intrauterine environment, which adversely affects fetal growth, emergency operative delivery is unavoidable. This acutely imposed stress may also disrupt the normal development of organ systems in SGA infants, potentially leading to a range of complications. BPD, IVH/PVL, and ROP are notable examples of respiratory, central nervous system, and sensory complications, respectively, and serve as critical determinants of long-term outcomes in preterm infants. In addition to these complications, we identified two cases of perforated peritonitis and three cases of culture-proven sepsis. However, the incidences of these complications did not significantly differ between SGA and appropriate for gestational age infants. Medically indicated preterm births account for approximately 30% of all pre-

Table 6 Changes in outcomes and clinical characteristic over time

Characteristics	Total	2013-2016	2017-2019	2020-2023	p-value
Number of infants	250	84	81	85	
Gestational age (weeks)	28.9±2.6	28.5±2.7	28.9±2.4	29.4±2.5	0.571
Birth weight (g)	1,096±273	1,051±289	1,114±272	1,121±251	0.260
SGA	117 (46.8%)	37 (44.0%)	33 (40.7%)	47 (55.3%)	0.141
BPD	31 (12.4%)	11 (13.1%)	9 (11.1%)	11 (12.9%)	0.912
IVH	12 (4.8%)	4 (4.8%)	4 (4.9%)	4 (4.7%)	0.997
ROP*	12 (4.8%)	9 (10.7%)	3 (3.7%)	0	0.042
Death before discharge	7 (2.8%)	3 (3.6%)	2 (2.5%)	2 (2.4%)	0.870
Cumulative morbidity	49 (19.6%)	19 (22.6%)	14 (17.2%)	16 (18.8%)	0.672
HDP*	57 (22.8%)	17 (20.2%)	13 (16.0%)	27 (31.8%)	0.043
CAM	47 (18.8%)	18 (21.4%)	19 (23.5%)	10 (11.8%)	0.117
PROM	29 (11.6%)	12 (14.3%)	10 (12.3%)	7 (8.2%)	0.455
Advanced maternal age	107 (42.8%)	30 (35.7%)	34 (42.0%)	43 (50.6%)	0.146
Antenatal corticosteroids	146 (58.4%)	51 (60.7%)	53 (65.4%)	42 (49.4%)	0.597

* $p<.05$

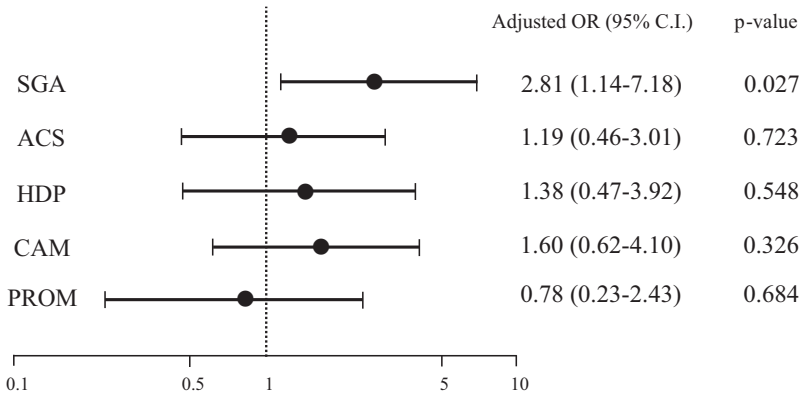

Fig. 1 Risk factors for cumulative morbidity
Multivariate analysis after adjusting for gestational age indicated that small for gestational age (SGA) status was the only factor significantly associated with cumulative morbidity (odds ratio, 2.81; 95% confidence interval, 1.14-7.18; p = 0.027).

term births[14]; however, in this study, the number of such cases exceeded that of spontaneous preterm births. Unsurprisingly, our hospital, as a regional perinatal medical center, has a high proportion of high-risk pregnancies, including those with maternal complications unrelated to pregnancy (**Table 5**). In addition, infants born to mothers of advanced maternal age accounted for 42.8% of the total. This may partially explain the higher rate of SGA (46.8%), as compared with HDP (22.8%), in this study. In the future, the increasing age of pregnant women will inevitably result in more high-risk pregnancies with complications unrelated to pregnancy. In this study, thyroid disorders requiring medication was the most common complication. The management of underlying maternal conditions in close collaboration with a multidisciplinary team of specialists is becoming increasingly important to improve outcomes of preterm VLBW infants.

Regarding serious postnatal complications, the prevalences of BPD and IVH/PVL remained unchanged throughout the study period, whereas that of ROP decreased. This shows that our NICU has provided a consistently high level of care for preterm VLBW infants since its establishment. During this period, the latest technologies have been introduced to provide sensitive care for very small and premature infants. These include lung-protective ventilatory management[15], circulatory control using vasoactive drugs[16], aggressive nutritional supplementation[17], and continuous oxygen saturation monitoring for strategic restrictive management of oxygen supplementation[18]. ACS is another well-regarded in-

tervention for reducing mortality and morbidity in preterm infants[19]. However, multivariate analysis did not show an advantage for ACS, owing to its inadequate implementation, particularly in the lower gestational age group (**Fig. 1**, **Table 2**). Promotion of ACS at an earlier gestational age might further improve outcomes for preterm VLBW infants.

Further improvement of outcomes for preterm VLBW infants requires earlier detection of CAM, which has been discussed for years, determination of optimal timing of delivery based on a comprehensive assessment of fetal growth and well-being, and aggressive use of ACS. Finally, it is essential to establish a follow-up system to verify long-term developmental outcomes for preterm VLBW infants and provide feedback to clinical practice in the NICU.

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