

ORIGINAL ARTICLE

Neonatal Outcomes of Extremely Preterm Infants from Taiwan: Comparison with Canada, Japan, and the USA



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Key Words

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Background: This study compared the current trend in survival rates and morbidity for very low birth weight (VLBW) infants in five Medical Training Centers of Prematurity for the Premature Baby Foundation of Taiwan (PBFT), with the outcomes from the USA, National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN), the Canadian Neonatal Network (CNN), and the Neonatal Research Network of Japan (NRNJ).

Methods: The survival rates of VLBW infants according to gestational age (GA) and major morbidities were compared between networks (Taiwan, USA, Canada, and Japan). Taiwanese data for VLBW infants of GA ≤ 28 weeks between 2007 and 2012 were obtained from the "PBFT Annual Conferences of Premature Care" reports defining survival rate as neonates that survived to the time of discharge. Major morbidities included severe neurological injury (Grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia), bronchopulmonary dysplasia, severe retinopathy of prematurity, necrotizing enterocolitis, late-onset sepsis, and patent ductus arteriosus.

Results: The survival rates of VLBW infants of GA ≤ 28 weeks from the PBFT (Taiwan), NICHD NRN (USA), CNN (Canada), and NRNJ (Japan) were 77% (1323/1718), 72% (6859/9575), 82%

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(2353/2872), and 89% (4489/5069), respectively. The annual survival rates in Taiwan from 2007 to 2012 were 72%, 76%, 76%, 74%, 77%, and 78%, respectively. When GA from ≤ 23 weeks to 28 weeks was assessed in Taiwan, the survival rates of VLBW infants according to each week were 22%, 50%, 70%, 80%, 88%, and 92%, respectively. The survival rate, especially at lower GAs, was highest in the NRNJ (Japan). The major difference between Taiwan and Japan was attributed to the lower survival rates at lower GA (≤ 26 weeks) in Taiwan. Japan had the lowest rates of major morbidities among the four countries.

Conclusion: The survival rate of VLBW infants has improved over the past 6 years in Taiwan. It is higher than the USA, but lower than Canada and Japan. However, the results from Taiwan are from five Medical Training Centers for the PBFT rather than from a population-based study. It is crucial to have a nationwide neonatal research network to develop new practical approaches for VLBW infants in Taiwan.

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1. Introduction

The introduction of neonatal intensive care units (NICUs) has resulted in substantial improvements in outcomes for very low birth weight (VLBW, <1.5 kg) infants during the past four decades in Taiwan. Our previous reports have separately monitored morbidity and mortality rates among VLBW infants.^{1–5} Increased VLBW infant survival rates have paralleled improvements in prenatal, obstetric, and neonatal care. However, previous reports have presented patient characteristics and outcomes according to birth weight (BW). Such BW-specific data may be skewed by more mature infants with growth restriction.

The Premature Baby Foundation of Taiwan (PBFT) and five Medical Centers jointly founded the Program of Medical Training Center of Prematurity in 1998.⁶ The purpose of this report was to present the survival rates and morbidity for VLBW infants according to gestational age (GA) ≤ 28 weeks in these five centers from 2007 to 2012, and to compare with the current outcomes from the USA, National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN),⁷ the Canadian Neonatal Network (CNN), and the Neonatal Research Network of Japan (NRNJ).⁸

2. Materials and methods

Anonymized data for VLBW infants of GA ≤ 28 weeks between 2007 and 2012 were obtained in Taiwan from the reports of the PBFT Annual Conferences of Premature Care (not published). The collection of patient data for the PBFT was approved by the Institutional Review Boards of each hospital.

The survival rate was defined as neonates that survived to the time of discharge. The major morbidities included severe neurological injury [defined as Grade 3 or Grade 4 intraventricular hemorrhage (IVH), or periventricular leukomalacia (PVL)], bronchopulmonary dysplasia (BPD, defined as supplemental oxygen use at a postmenstrual age of 36 weeks), severe retinopathy of prematurity (ROP, defined as Stage III or above according to international classification and received treatment), and necrotizing

enterocolitis (NEC, Stage ≥ 2 of Bell's criteria). These morbidities were considered for this study because they have been reported to have an impact on developmental outcome between 18 months and 24 months.⁹ Late-onset sepsis (positive blood culture performed >72 hours after birth in the presence of clinical signs of infection) can influence mortality, and management of patent ductus arteriosus (PDA, treated with pharmacological closure or/and ligation) may reduce severe IVH, therefore, both were also included in the comparison of morbidities.^{1,10,11}

The results of neonatal outcomes of extremely preterm infants in the USA were obtained from the NICHD NRN study.⁷ This was the first NICHD NRN study to report outcomes on the basis of GA-specific information; a total of 9575 infants of GAs of 22–28 weeks and BWs of 401–1500 g were included in this study. The data from Canada and Japan were taken from a recent report that compared outcomes of VLBW infants between the CNN (Canada) and NRNJ (Japan).⁸ A total of 15,153 VLBW infants, 5341 from Canada and 9812 from Japan, formed the study population. Among these infants, 2872 (53.8%) in the CNN (Canada) and 5069 (51.7%) in the NRNJ (Japan) of GA ≤ 28 weeks were included in our study. These two reports were selected for our study because GA-based outcomes were used in their methods.

The survival rate of VLBW infants according to GA and the major morbidities were compared among networks from Taiwan, USA, Canada, and Japan. Statistical significance for unadjusted comparisons was determined using χ^2 or Fisher's exact tests. A significance level of $p < 0.05$ was used without multiple comparison adjustments.

3. Results

3.1. Neonatal survival rates of VLBW infants in Taiwan from five training centers between 2007 and 2012

A total of 1718 VLBW infants of GA ≤ 28 weeks were admitted to five centers for the PBFT between January 1, 2007 and December 31, 2012, and were included in this study. The overall survival rate was 77% (1323/1718). The

survival rates in each year from 2007 to 2012 were 72%, 76%, 76%, 74%, 77%, and 78%, respectively (Figure 1). The survival rates of VLBW infants according to each week of GA from ≤ 23 weeks to 28 weeks were 22%, 50%, 70%, 80%, 88%, and 92%, respectively (Figure 2). Survival rates up until discharge increased with increasing GA, and the majority of infants of GAs ≥ 25 weeks survived.

3.2. Comparison of survival rates of VLBW infants in Taiwan with those in the USA, Canada, and Japan

Survival rates have improved significantly in the past decade in the USA and Japan. The overall survival rates of VLBW infants of GA ≤ 28 weeks in the NICHD NRN (USA), CNN (Canada), and NRNJ (Japan) were 72% (6859/9575),⁷ 82% (2353/2872),⁸ and 89% (4489/5069),⁸ respectively (Figure 3). The survival rates according to GA for VLBW infants in the PBFT, NICHD NRN, CNN, and NRNJ are summarized in Table 1. The survival rates of VLBW infants of GA ≤ 28 weeks in the PBFT (Taiwan) was significantly higher than in the NICHD NRN (USA) ($p < 0.0001$), but was lower than the CNN (Canada) and NRNJ (Japan) ($p < 0.0001$). The survival rate, especially at lower GAs, was highest in the NRNJ (Japan). The major difference between Taiwan and Japan was attributed to the lower survival rates at lower GAs (≤ 26 weeks) in Taiwan.

3.3. Comparison of major morbidities of VLBW Infants in Taiwan with those in the USA, Canada, and Japan

A comparison of major morbidities including severe neurological injury (IVH Grade ≥ 3 or PVL), BPD, severe ROP, NEC, late-onset sepsis, PDA with indomethacin treatment or surgical ligation, and length of stay among the four networks is summarized in Table 2. The NICHD NRN (USA) study involved a total of 9575 VLBW infants of GA ≤ 28 weeks. The proportion of all infants who survived >12 hours ($n = 8515$) was used to calculate the rates of morbidity, except for BPD, which used the proportion of infants who survived to a postmenstrual age of 36 weeks ($n = 7023$), and for ROP, which used the number of infants who

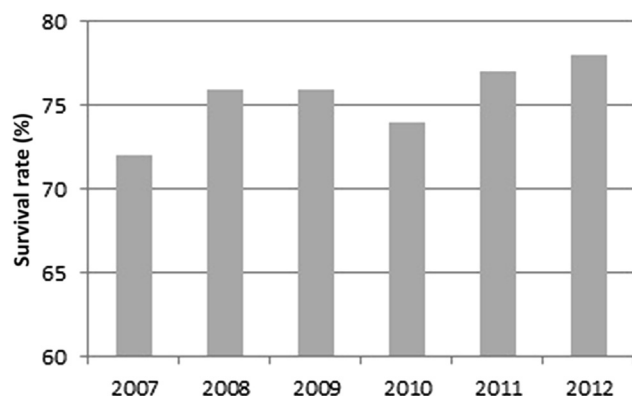


Figure 1 Survival rates in each year among 1718 very low birth weight infants of gestational age ≤ 28 weeks admitted to five training centers for the Premature Baby Foundation of Taiwan from 2007 to 2012.

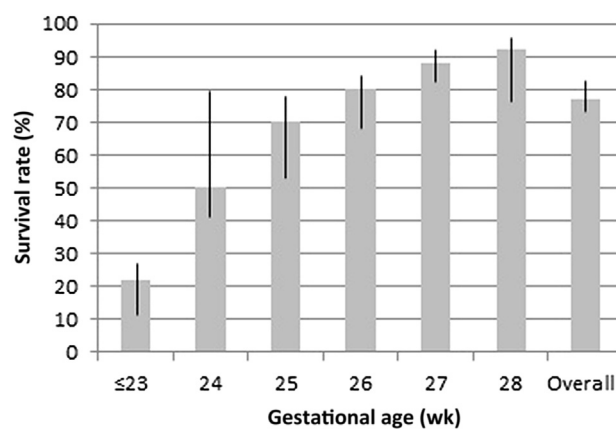


Figure 2 Survival rates according to gestational age (GA) among 1718 very low birth weight infants of GA ≤ 28 weeks admitted to five training centers for the Premature Baby Foundation of Taiwan from 2007 to 2012. The thin lines indicate ranges across centers.

remained in hospital at 28 days ($n = 7313$). By contrast, the CNN (Canada) and NRNJ (Japan) used the number of VLBW infants of GA ≤ 28 weeks to present the rates of all morbidities. For the purpose of this study, the PBFT (Taiwan) also used the number of all eligible infants to present the rates of all morbidities.

Taiwan had higher rates of severe neurologic injury ($p < 0.002$) and late-onset sepsis ($p < 0.0001$) compared with the NRNJ (Japan), but were lower than the NICHD NRN (USA) and CNN (Canada). Taiwan also had the highest rate

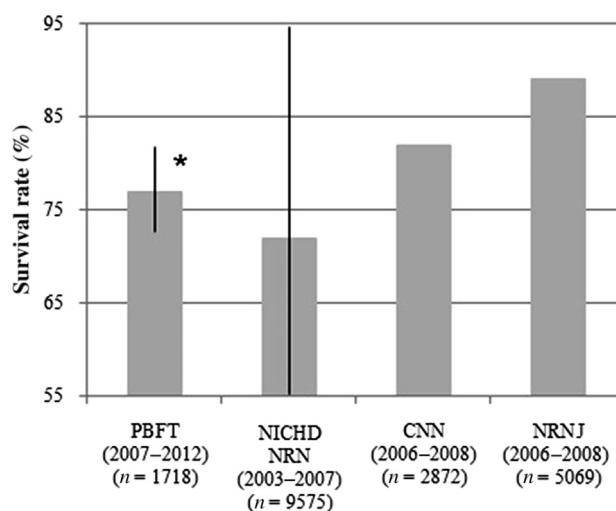


Figure 3 Overall survival rates of very low birth weight infants of gestational age ≤ 28 weeks in four networks from Taiwan (PBFT), the USA (NICHD NRN),⁷ Canada (CNN),⁸ and Japan (NRNJ).⁸ The PBFT was significantly higher than the NICHD NRN ($*p < 0.0001$), but was lower than the CNN and NRNJ ($*p < 0.0001$). The thin lines indicate ranges across centers. No range was available for the data of the CNN and NRNJ. CNN = Canadian Neonatal Network; NICHD NRN = National Institute of Child Health and Human Development Neonatal Research Network; NRNJ = Neonatal Research Network of Japan; PBFT = Premature Baby Foundation of Taiwan.

Table 1 Comparison of survival rates according to gestational age for very low birth weight infants in four networks from Taiwan, the USA, Canada, and Japan.

Network	≤23 wk	24 wk	25 wk	26 wk	27 wk	28 wk	Total
PBFT	22 (11–27)	50 (41–80)	70 (53–79)	80 (69–85)	88 (82–92)	92 (78–95)	77* (73–82)
NICHD NRN ⁷	18 (0–53)	55 (20–100)	72 (50–90)	84 (61–100)	88 (76–100)	92 (88–100)	72 (55–95)
Network	<25 wk		25–26 wk		27–28 wk		Total
CNN ⁸	47.7		82.1		92.7		82
NRNJ ⁸	72.9		90.4		95.9		89

The values are presented as % (range) or %, ranges are across all participating centers. No range is available for the data of the CNN and NRNJ.⁸ Taiwan: 1718 infants in five centers from the PBFT, 2007–2012; NICHD NRN: 9575 infants in 20 centers from the NICHD NRN,⁷ 2003–2007; CNN: 2872 infants in 28 tertiary NICUs,⁸ 2006–2008; NRNJ: 5069 infants in 70 tertiary NICUs from NRNJ,⁸ 2006–2008. Taiwan was significantly higher than the NICHD NRN (* $p < 0.0001$), but was lower than the CNN and NRNJ (* $p < 0.0001$).

CNN = Canadian Neonatal Network; NICHD NRN = National Institute of Child Health and Human Development Neonatal Research Network; NICU = neonatal intensive care unit; NRNJ = Neonatal Research Network of Japan; PBFT = Premature Baby Foundation of Taiwan.

of BPD ($p < 0.0001$). The rates of severe ROP did not differ among Taiwan, the NICHD NRN (USA), and NRNJ (Japan), but the CNN (Canada) had a significantly lower rate than the others ($p = 0.0001$). Taiwan and the NRNJ (Japan) had similar rates of NEC and were lower than the NICHD NRN (USA) and CNN (Canada) ($p < 0.0001$). For management of PDA, Taiwan and the CNN (Canada) had similar rates of indomethacin (or ibuprofen) treatment, and were lower than the NICHD NRN (USA) and NRNJ (Japan) ($p < 0.0001$). Taiwan had a higher rate of PDA ligation than the CNN (Canada) and NRNJ (Japan), but had a lower rate than the NICHD NRN (USA) ($p < 0.0001$). As for the length of hospital stay for all VLBW infants, infants in Taiwan had longer hospital stays than the CNN (Canada) and NRNJ (Japan) [no available data for the NICHD NRN (USA)]. The NRNJ (Japan) had the lowest rates of severe neurological injury, NEC,

late-onset sepsis, and PDA ligation among these four countries.

4. Discussion

Our study revealed that the survival rates of VLBW infants from Taiwan of GA ≤28 weeks was higher than VLBW infants assessed in the NICHD NRN (USA), but was lower than in VLBW infants in the CNN (Canada) and NRNJ (Japan). Although previous reports have used BW as the reference for morbidity and survival rates, our current study assessed outcomes according to GA. GA-based outcomes may be valuable in offering additional information for prenatal counseling and for physicians and parents to make an informed decision. To improve the outcomes of VLBW

Table 2 Comparison of outcomes in very low birth weight infants of gestational age ≤28 weeks in networks from Taiwan, the USA, Canada, and Japan.

Network	Severe neurological injury	BPD	Severe ROP	NEC	Late-onset sepsis	Indomethacin for PDA	PDA ligation	Length of stay, median (IQR)
PBFT	14* (5–20)	56 [†] (21–76)	21 [‡] (2–45)	3 [§] (1–12)	19 [¶] (7–32)	28 (10–82)	20 [†] (3–44)	88 (78–97)
NICHD NRN ⁷	19 (1–23)	42 (20–89)	16 (6–28)	11 (4–19)	36 (18–51)	71 (33–91)	27 (10–41)	NA
CNN ⁸	18	20	11 [‡]	8	25	27	14	43 (20–69)
NRNJ ⁸	10	25	18	3 [§]	8	41	9	81 (58–115)

Values are presented as a % (range) or % except where noted, ranges are across all participating centers. No range is available for the data of the CNN and NRNJ. Severe neurologic injury: IVH Grade 3 or Grade 4 or periventricular leukomalacia; BPD: oxygen use at postmenstrual age 36 weeks; severe ROP: Stage III or above according to international classification; NEC: according to Bell's criteria Stage 2 or higher; late-onset sepsis: sepsis at ≥3 days of life; PDA: clinical or echocardiographic diagnosis of PDA.

BPD = bronchopulmonary dysplasia; CNN = Canadian Neonatal Network; IQR = interquartile range; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; NICHD NRN = National Institute of Child Health and Human Development Neonatal Research Network; NRNJ = Neonatal Research Network of Japan; PBFT = Premature Baby Foundation of Taiwan; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity.

* $p < 0.002$

[†] $p < 0.0001$ when Taiwan compared with the NICHD NRN, CNN or NRNJ.

[‡] $p = 0.0001$ when Taiwan compared with the CNN.

[§] $p < 0.0001$ when Taiwan and the NRNJ compared with the NICHD NRN or CNN.

^{||} $p < 0.0001$ when Taiwan compared with the NICHD NRN or NRNJ.

[¶] $p < 0.0005$ when Taiwan compared with the CNN.

infants, it is important to evaluate the differences in outcomes among countries and to investigate the reasons for those differences.

Previous studies in various countries or networks have compared mortality and morbidity and reported a wide variation in outcomes.^{7,8,12,13} It is difficult to conduct a study to compare outcomes among networks using data from the same period of time unless collaborative international studies are set up such as that seen between Canada and Japan.⁸ In a recent study from Sweden,¹² the neonatal outcomes of extremely preterm infants during 2004–2007 were compared with those from the UK¹³ during 2000–2005. Our study included the period between 2007 and 2012, which was several years later than the first NIHCD NRN (USA) study that reported outcomes on the basis of GA-specific information (2003–2007),⁷ and the comparison study between Canada and Japan (2006–2008).⁸ Although the study periods of these four networks were not the same, all were recent analyses of the individual networks. The outcomes from the PBFT (Taiwan) were not the most favorable among these four networks. Therefore, the results of our current study provide a valuable reference for neonatologists to help them in developing strategies for improving the survival of VLBW infants of GA <28 weeks.

Although many large multicenter neonatal networks report that survival rate has probably reached a plateau,^{7,8} the survival rate of VLBW infants has continued to improve over the past 6 years (rising from 72% to 78%) in Taiwan. This evidence suggests that further follow up may lead to additional improvement in survival rate for VLBW infants in Taiwan.

The NRNJ (Japan) had the highest survival rates, especially at lower GAs, among the networks from the four countries. The major difference in survival rates between Taiwan and Japan was attributed to the lower survival rates in infants with lower GAs (≤ 26 weeks) in Taiwan. The possible explanations for these differences include the lower rates of severe neurological injury, NEC, late-onset sepsis in the NRNJ (Japan),^{14,15} and differences in philosophy of medical care for lower-GA infants.¹⁶ The policy for treatment of extremely preterm infants with borderline viability in Japan seemed to be more aggressive than in other countries.^{16–18}

Severe neurological injury with severe IVH and/or PVL was an important morbidity because of its association with long-term neurodevelopmental outcomes.^{14,19} Our results showed the NRNJ (Japan) had the lowest incidence of severe neurological injury among these four countries, suggesting that the differences in routine practices in extremely preterm infants in the 1st week of life, such as fluid management, and differences in strategies of PDA treatment and respiratory care in Japan, may have a significant impact on severe neurological injury. Many neonatologists in Japan performed functional echocardiography during the early period after birth, two or three times a day, to assess the hemodynamic status and the emergence of PDA. This enabled stabilization of the circulation and early diagnosis and treatment of hemodynamically significant PDA, resulting in a reduction in the incidence of severe IVH.^{11,20,21}

Considering the substantially increased use of continuous positive airway pressure therapy in recent years in

Taiwan,^{22–25} it was surprising that Taiwan had the highest rate of BPD among these four countries. Unfortunately, data on ventilator management were not available to explain this finding. However, there was a diverse range of rates of BPD (21–76%) among the five centers in Taiwan. We propose that this difference was mainly due to either the different strategies of respiratory care, or the different target ranges of oxygen saturation among the centers. It is imperative that further investigations are conducted to establish optimal methods to improve this outcome. A prospective study using similar saturation targets for VLBW infants among the centers may help to identify the best clinical practice.

The rates of severe ROP were not significantly different among Taiwan, the NIHCD NRN (USA), and NRNJ (Japan), but the CNN (Canada) had a significantly lower rate of severe ROP than the other countries. This finding highlights the importance of identifying and adopting the clinical methods used in Canada to reduce the incidence of this severe complication by other countries.

Taiwan and the NRNJ (Japan) had similar rates of NEC, which were lower than the NIHCD NRN (USA) and CNN (Canada). The rate of late-onset sepsis in Taiwan was higher than the NRNJ (Japan), but also lower than the NIHCD NRN (USA) and CNN (Canada). Although we do not have the information about clinical practices in these countries, it is possible that the increased use of maternal or donor breast milk, and probiotics in the NRNJ (Japan) and Taiwan populations may have resulted in decreased rates of NEC and late-onset sepsis.^{26–31} However, this hypothesis should be verified by further investigation.

Intravenous indomethacin has been unavailable for clinical use since 2008–2009 in Taiwan. This may explain the lower rate of indomethacin for PDA and higher rate of PDA ligation in Taiwan than in other networks. However, among the five centers in Taiwan, there was a diverse range in the incidence of use of indomethacin for PDA (10–82%) and PDA ligation (3–44%). These results suggest that different strategies of PDA management are being used, with some centers adopting a more conservative approach, whereas others are relatively aggressive in the treatment of PDA. It is important that population-based studies are conducted to determine the most effective clinical course for the management of PDA in Taiwan where treatment with intravenous indomethacin is not possible. This will enable alternative treatment regimens to be established for PDA in Taiwan.

In the USA, the NICHD NRN was established in 1986 and the Vermont Oxford Network in 1988.^{32,33} They analyzed neonatal outcomes and using the results of these clinical studies proposed evidence-based guidelines for clinical practice. They presented reports to establish benchmarking and quality improvement in neonatal care as well as regionalization of perinatal medicine.^{34–36} Although the data from the NIHCD NRN (USA) used in our current study were not from a population-based study, the information included all extremely low gestation births at 20 academic centers across the USA that together represent >110,000 live births per year.⁷

In Canada, the CNN was established in 1995, and 28 (of total 31) tertiary NICUs in Canada participated in the CNN in 2008. This may be considered a population-based network

that encompasses 95% of neonates admitted to tertiary NICUs, and 75% of VLBW infants admitted to tertiary NICUs in the CNN.³⁷

In Japan, special care for premature infants has been supported by the government since 1958. National support for perinatal care and the regionalization of perinatal medicine was introduced in 1979. National support for maternal–fetal ICUs was started in 1984 and expanded to include a Tertiary Central Perinatal Care Center and several Secondary Regional Perinatal Care Centers, so that organized networks existed in each prefecture from 1996.³⁸ Until 2012, there were 92 Tertiary Central Perinatal Care Centers and 284 Regional Perinatal Care Centers in Japan.³⁹ The highest survival rates for VLBW infants were attributed to this nationwide perinatal care system. There are two nationwide networks in Japan; the Neonatal Research Network was established in 1999 and Perinatal Care Center Network in 2003.^{40,41} All NICUs were included in these two networks and the results of the data analysis were published and shared among all centers. However, the database of the NRNJ (Japan) used in our current study only covered ~45% of VLBW infants born in Japan because many tertiary NICUs were not endorsed by the Japanese government.⁴²

Adopting methods from both the USA and Japanese models in Taiwan might improve outcomes by analyzing network data periodically for benchmarking, and assessing quality improvement initiatives. Although improving regionalization is important, it is equally important to establish open dialog among units. Ensuring that VLBW infants are born at hospitals with adequate experience is only one step towards improving the quality of care. Monitoring and reporting outcomes will not lead to improvements if this is not accompanied by a determined approach to investigate the differences in outcomes and to implement changes that can improve them.

There were limitations to our study because of the nature of retrospective studies on published reports, instead of conducting prospective studies on raw data so that confounding factors for the comparison can be taken into account. However, our study revealed that in-hospital morbidity rates remained high and correlated with mortalities among extremely preterm infants in Taiwan. Differences between centers in the incidence of specific morbidities were also noted. Reducing the high morbidity rates among extremely low-GA infants who have been provided with ongoing intensive care remains a challenge for neonatologists. Another limitation was that the data from Taiwan were collected from only five Medical Training Centers for the PBFT (Taiwan), rather than from population-based data. The PBFT (Taiwan) has sponsored a follow-up program examining VLBW infants since 1995, with 22 hospitals contracted to the PBFT (Taiwan), covering ~82% of VLBW infants born in Taiwan up to 2014.⁶ The five Medical Training Centers in the PBFT (Taiwan) covered ~50% of VLBW infants enrolled in the PBFT follow-up program, therefore, the results of this study could provide a benchmark for other hospitals in Taiwan.

In conclusion, the survival rate of VLBW infants with extremely low GA has improved over the past 6 years in Taiwan. It is higher than that of the NICHD NRN (USA), but lower than that of the CNN (Canada) and NRNJ (Japan).

However, the data from Taiwan were aggregated from only five Medical Training Centers for the PBFT instead of a population-based study. It is crucial to establish a nationwide neonatal research network to develop optimized clinical practice to improve outcomes of VLBW infants in Taiwan.

Conflicts of interest

The authors have no conflicts of interest to declare.

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