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ORIGINAL ARTICLE

Changes in Outcome and Complication Rates of Very-low-birth-weight Infants in One Tertiary Center in Southern Taiwan Between 2003 and 2010

Shen-Dar Chen [a], Yung-Chieh Lin [b], Chin-Li Lu [c,d], Solomon Chih-Cheng Chen [a,e,*]

[a] *Department of Pediatrics, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi City, Taiwan*
[b] *Department of Pediatrics, National Cheng Kung University Hospital, Tainan, Taiwan*
[c] *Department of Medical Research, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi City, Taiwan*
[d] *Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[e] *School of Medicine, Taipei Medical University, Taipei City, Taiwan*

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Key Words
length of stay;
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Background: Neonatal intensive care has changed dramatically over the past few decades and the survival of infants has generally improved in many countries. The purpose of this study was to explore the recent evolution of mortality and morbidities among very-low-birth-weight (VLBW) infants in southern Taiwan.
Methods: We retrospectively reviewed the medical records of VLBW (birth weight <1500 g) infants who were admitted to a neonatal intensive care unit at a tertiary medical center in southern Taiwan from 2003 to 2010. The study period was divided into two cohorts: the first cohort of 2003–2006 and the second cohort of 2007–2010. Demographic profiles and complications were recorded, including the following information: sex, birth body weight (BBW), gestational age (GA), Apgar score, patent ductus arteriosus (PDA), necrotizing enterocolitis, retinopathy, chronic lung disease (CLD), inguinal hernia, and sepsis. The length of stay (LOS) in hospital was compared between the two cohorts.
Results: A total of 420 (212 male) VLBW infants were enrolled with 52 (12.4%) deaths. Compared to surviving infants, deceased infants had significantly lower GA, Apgar scores,

* Corresponding author. Department of Pediatrics, Ditmanson Medical Foundation Chiayi Christian Hospital, Taiwan, Number 539, Zhongxiao Road, East District, Chiayi City 60002, Taiwan.
E-mail address: solomon.ccc@gmail.com (S.C.-C. Chen).

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and BBW. The mortality of VLBW infants remained static between the two birth cohorts, but the incidence of major morbidities generally decreased. The LOS for overall surviving infants and the proportion of LOS > 60 days were both reduced in the period of 2007–2010. With further stratification by BBW, the major reduction of long LOS was only found in the group of BBW ≥ 1000 g. The multivariate logistic regression model found PDA, CLD, and BBW < 1000 g were major complications to be associated with long LOS among surviving infants.

Conclusion: Periodic evaluation of the mortality and morbidity of preterm infants can help to understand the changes and trends of our neonatal care. Further study using the national dataset to provide more representative information is warranted.

1. Introduction

Neonatal intensive care has changed dramatically over the past decades, with advances in technology such as high-frequency oscillation,[1,2] inhaled nitric oxide,[3] antenatal corticosteroids, and surfactant therapy.[4,5] The survival rate of preterm infants has improved,[6–8] but morbidity of survivor infants remained static or even increased,[9,10] especially for those infants with lower gestational age (GA) or low birth weight.

Taiwan, an island country in southeastern Asia with a population of 23 million, has established a high-quality medical care system during the past decades, and the general infant mortality in Taiwan has improved.[11] There have been several previous reports regarding the incidences and survival rates of very-low-birth-weight (VLBW) infants in Taiwan.[12–18] The most recent paper was published in 2008 regarding the outcomes of VLBW between 1999 and 2006 at one tertiary medical center in central Taiwan.[18] However, there was no report on VLBW for southern Taiwan in recent years. We wondered how medical advances had affected the outcomes for VLBW infants in the neonatal intensive care unit (NICU) recently and if there were any geographic differences. Thus, the purpose of this study was to explore the evolution of mortality and morbidities among VLBW infants in southern Taiwan between 2003 and 2010.

2. Materials and Methods

2.1. Ethical approval

The Ethics Review Board of Ditmanson Medical Foundation Chiayi Christian Hospital (Chiayi City, Taiwan) approved the study protocol. The data was collected without identification. Because this was a retrospective data analysis, no informed consent was necessary.

2.2. Cases and enrollment criteria

This study retrospectively reviewed the medical records of VLBW (birth body weight <1500 g) infants who were consecutively admitted to the NICU of a tertiary medical center from 2003 to 2010. In order to assess the evolution of the mortality and morbidity of VLBW infants across the study period, we divided the cases into two birth cohorts: the first cohort encompassing the years 2003–2006 and the second cohort consisting of the years 2007–2010.

2.3. Demographic data and outcomes

Demographic information including sex, birth body weight (BBW), GA, and 1st minute and 5th minute Apgar scores were recorded. The main outcomes were death and any morbidity, including patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), chronic lung disease (CLD), inguinal hernia (IH), and sepsis. PDA was diagnosed by a pediatric cardiologist through heart echo examination. Grades 3 and 4 IVH were defined as severe IVH. NEC was diagnosed by the presence of intestinal intramural gas on X-ray film, perforation, or the finding of necrosis during an operation. Sepsis was confirmed by positive blood culture. CLD was defined as dependence on supplemental oxygen at 36 weeks' postmenstrual age.[19] Treated ROP was defined as treatment with pan-retinal photocoagulation performed by ophthalmologists.

The secondary measured outcome was the length of stay (LOS) in hospital. Because there was no definition for long LOS in previous literature, we subjectively chose the cutoff of LOS over 60 days, in order to compare the proportion change of LOS between two time periods. One reason for choosing 60 days as the cutoff was that the median LOS of all live births in this study was 53 days. Deceased infants were excluded from the analysis of LOS, because these infants usually had a shorter LOS, reducing the possibility of developing some specific complications due to their premature death.

2.4. Statistical analyses

Data were analyzed using Microsoft Excel and IBM SPSS Statistics for Windows (Version 21.0. Armonk, NY: IBM Corp.). Continuous variables were expressed as mean ± standard deviation (SD), but the LOS of each complication was expressed as median and interquartile range (IQR). Student *t* test was used for continuous variables and the non-parametric median test was used to test the median (IQR) of LOS for infants with/without each complication because of the skewness of the data. Chi-square test was used for categorical data. A p value <0.05 was considered significant. Multivariate logistic regression analysis adjusting for confounders was performed by using LOS over 60 days as the

Table 1 Characteristics of alive or dead very-low-birth-weight infants.

	Alive (n = 368)	Dead (n = 52)	p value
Gestational age, wk	28.9 ± 3.0	26.4 ± 2.9	<0.001
Apgar 1	5.0 ± 2.3	3.2 ± 2.0	<0.001
Apgar 5	7.2 ± 2.4	5.6 ± 2.7	<0.001
Birth body weight, g	1074 ± 260	797 ± 305	<0.001
Length of hospital stay, d	67.0 ± 42.8	18.7 ± 28.4	<0.001
Sex, male (%)	182 (49.5%)	30 (57.7%)	0.266
PDA, n (%)	125 (34.0%)	22 (42.3%)	0.238
Sepsis, n (%)	126 (34.2%)	7 (13.5%)	0.003
ROP, n (%)	102 (27.7%)	3 (5.8%)	0.001
CLD, n (%)	113 (30.7%)	7 (13.5%)	0.010
Severe IVH, n (%)	20 (5.4%)	4 (7.7%)	0.512
NEC, n (%)	23 (6.3%)	1 (1.9%)	0.208
Hernia, n (%)	34 (9.2%)	2 (3.8%)	0.193

PDA = patent ductus arteriosus; ROP = retinopathy of prematurity; CLD = chronic lung disease; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis.

dependent variable. In the regression model, we used BBW but not GA, because these two factors have a high correlation, and GA has a higher possibility of error due to memory bias or poor estimates by the obstetrician.

3. Results

3.1. Basic information of surviving and deceased infants

This study analyzed the basic data and clinical information of VLBW infants admitted to the NICU at a tertiary medical center in southern Taiwan during the years 2003–2010. A total of 420 (212 male, 50.5%) VLBW infants were enrolled. There were 52 deaths, giving a mortality rate of 12.4%. The characteristics of surviving and deceased VLBW infants are compared in Table 1. Compared to surviving infants, deceased infants had significantly lower GA, lower Apgar scores, lower BBW, shorter LOS, and lower incidence rates of all complications except for severe IVH and PDA (Table 1).

3.2. Comparison of complications in two birth cohorts

The GA, BBW, sex, and clinical outcomes of VLBW infants stratified by BBW < 1000 g and BBW ≥ 1000 g in two birth cohorts (2003–2006 and 2007–2010), were compared in Table 2. All complications occurred less frequently in the latter period except for death, severe IVH, and IH among the group of BBW < 1000 g, although no significant statistical difference was observed in the frequency of these three complications.

3.3. Comparison of LOS in two birth cohorts

The LOS of 368 surviving infants with/without each complication, stratified by two birth cohorts, is compared in Table 3. Infants with any complication or BBW < 1000 g usually had a longer LOS than infants without any complication.

The overall median (IQR) of LOS for surviving infants was reduced from 62.0 days (38.5– 83.0 days) in 2003–2006 to 48.0 days (37.0–72.3 days) in 2007–2010, with a significant p = 0.036. The proportion of long LOS, i.e., >60 days, was significantly higher among the 2003–2006 birth cohort than the 2007–2010 birth cohort (57.4% vs. 38.4%, p = 0.001). We further performed a stratified analysis by BBW ≥ 1000 g and BBW < 1000 g: a higher proportion of long LOS was only found among the groups with BBW ≥ 1000 g (32.3% for the 2003–2006 birth cohort vs. 19.5% for the 2007–2010 birth cohort, p = 0.035), but it was not found among the group with BBW < 1000 g (85.6% for the 2003–2006 birth cohort vs. 84.8%

Table 2 Mortality and morbidity of low-birth-weight infants stratified by birth body weight less than or 1000 g or more.

	BBW < 1000 g (n = 183)							BBW ≥ 1000 g (n = 237)						
	Subtotal		2003–2006		2007–2010		p value	Subtotal		2003–2006		2007–2010		p value
	N	%	N	%	N	%		N	%	N	%	N	%	
Sex, male (%)	88	48.1	46	43.4	42	54.5	0.136	124	52.3	44	41.9	80	60.6	0.004
Death	39	21.3	20	18.9	19	24.7	0.344	13	5.5	6	5.7	7	5.3	0.890
PDA	87	47.5	58	54.7	29	37.7	0.023	60	25.3	37	35.2	23	17.4	0.002
Sepsis	78	42.6	52	49.1	26	33.8	0.039	55	23.2	28	26.7	27	20.5	0.260
ROP	74	40.4	57	53.8	17	22.1	0.000	31	13.1	20	19.0	11	8.3	0.015
CLD	85	46.4	53	50.0	32	41.6	0.258	35	14.8	20	19.0	15	11.4	0.098
Severe IVH	13	7.1	6	5.7	7	9.1	0.372	11	4.6	9	8.6	2	1.5	0.010
NEC	15	8.2	14	13.2	1	1.3	0.004	9	3.8	8	7.6	1	0.8	0.006
Hernia	24	13.1	12	11.3	12	15.6	0.399	12	5.1	6	5.7	6	4.5	0.684
Gestational age, week (mean, SD)	26.4	2.5	26.5	2.5	26.3	2.7	0.556	30.2	2.4	30.2	2.5	30.1	2.3	0.771
BBW, g (mean, SD)	772	155	773	154	770	156	0.895	1246	152	1253	158	1240	149	0.516

BBW = birth body weight; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity; CLD = chronic lung disease; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; SD = standard deviation.

Table 3 Univariate analysis for the mean and standard deviation of length of stay in hospital of 335 survivors with/without each complication, stratified by two birth cohorts.

	Year 2003–2006							Year 2007–2010						
	Without			With			*p* value	Without			With			*p* value
Complication	*N*	Mean	SD	*N*	Mean	SD		*N*	Mean	SD	*N*	Mean	SD	
Sex (male vs. female)	71	71.9	34.9	105	68.9	38.3	0.610	94	64.7	43.8	65	61.9	54.7	0.726
PDA	97	62.7	35.1	79	79.3	37.2	0.003	114	60.2	54.7	45	72.1	25.1	0.161
Sepsis	100	57.3	25.8	76	87.0	42.1	0.000	110	54.9	29.6	49	83.1	72.0	0.011
ROP	105	57.8	37.3	71	88.4	27.6	0.000	133	61.9	51.3	26	71.9	28.7	0.341
CLD	108	54.3	22.5	68	95.2	41.3	0.000	116	54.2	36.9	43	88.8	64.8	0.000
Severe IVH	162	68.8	31.8	14	85.7	73.9	0.409	154	62.8	48.5	5	87.6	44.2	0.261
NEC	155	67.6	37.4	21	88.4	26.3	0.015	158	63.4	48.6	1	88	–	0.614
Hernia	159	66.9	34.1	17	100.4	48.2	0.000	142	58.3	41.4	17	107.7	75.7	0.017
BBW (≥1000 g vs. <1000 g)	93	54.0	32.4	83	88.1	33.2	0.000	113	48.1	19.0	46	101.5	72.6	0.000

SD = standard deviation; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity; CLD = chronic lung disease; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; BBW = birth body weight.

for the 2007–2010 birth cohort, $p = 0.907$) as shown in Figure 1. Nevertheless, as the LOS was treated as a continuous variable, the differences of median were not statistically significant irrespective of BBW ≥ 1000 g or BBW < 1000 g. Among the group of BBW ≥ 1000 g, the median LOS was 47.0 days (IQR: 36.5–66.5) for the 2003–2006 birth cohort and 46.0 days (IQR: 36.0–55.0) for the 2007–2010 birth cohort ($p = 0.229$); among the group of BBW < 1000 g, LOS was also similar between these two birth cohorts [median (IQR) of LOS for the 2003–2006 birth cohort was 84.0 days (72.0– 104.0 days) and for the 2007–2010 birth cohort it was 86.0 days (70.8–100.5 days), $p = 0.937$].

3.4. Risk factors associated with long LOS in survivors

Table 4 shows the odds ratio (OR) and 95% confidence interval (95% CI) of each complication to be associated with long LOS > 60 days in the multivariate logistic regression modeling of the two birth cohorts. PDA, CLD, and BBW < 1000 g were the major complications to be associated with long LOS > 60 days. Sepsis and hernia were factors which were only significant in the second cohort, but the relatively wide 95% CI suggested an unstable statistic probably due to a small case number.

4. Discussion

This study summarized the mortality and morbidity of VLBW infants at a tertiary medical center in southern Taiwan from 2003 until 2010. The mortality remained static, but the incidences of morbidities and the median of LOS of surviving infants decreased significantly from the first cohort (2003–2006) to the second cohort (2007–2010). The reasons for such improvement, although not clear, may be due to a combination of several factors including the advancement of medical intervention, improved prenatal care, and more skilled medical professionals in Taiwan.

Previous studies showed that mortality of preterm infants may decline due to improvement of neonatal care,[6–8] but morbidity may, by contrast, increase because infants with morbidities that might previously have died now survive.[9,10] Fortunately, our results did not show an increase of incidences of morbidity despite the stationary mortality between two birth cohorts. Some previous studies found that morbidities were mostly shifted to respiratory problems.[6,7] However, this study found that the impact of CLD on long LOS has decreased, as its OR of being associated with long LOS > 60 days has decreased from 4.57 to 2.92 (Table 4). The median LOS of infants with CLD also decreased from 95 days in the first cohort to 88 days in the second cohort (Table 3). The evidence above suggests a remarkable improvement in the quality of respiratory care. As described in other papers but not investigated in this study, the increased use of nasal continuous positive airway pressure, early surfactant treatment, and rapid extubation[20] may have contributed to reducing the CLD-related LOS and minimizing the clinical burden of respiratory complications of VLBW infants in Taiwan.

Septicemia is a major antecedent of morbidity and mortality in VLBW infants and can prolong hospital stay among VLBW survivors.[21,22] The present study found that

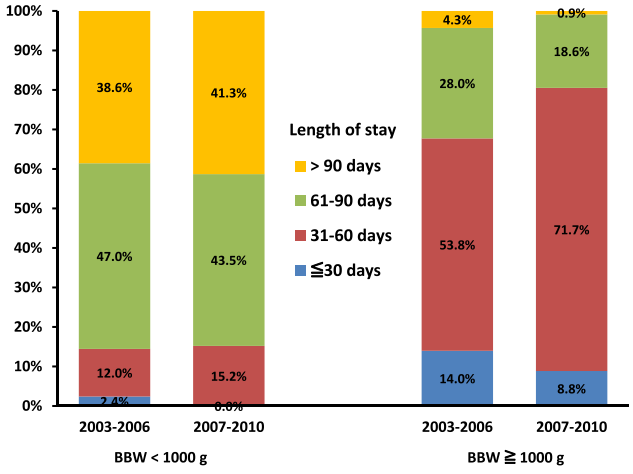

Figure 1 Stacked bar charts representing proportions of <30 days, 31–60 days, 61–90 days, and >90 days for hospital length of stay during two study periods (2003–2006, 2007–2010) are depicted for live births with birth body weight (BBW) ≥ 1000 g and BBW < 1000 g, respectively.

Table 4 The odds ratio and 95% confidence interval of each complication associated with long length of stay >60 days in multivariate logistic regression modeling, stratified by two birth cohorts of years 2003–2006 and 2007–2010.

		Year 2003–2006 (N = 185)			Year 2007–2010 (N = 183)		
		OR	95% CI	p value	OR	95% CI	p value
Sex	Male vs. female	1.182	0.49–2.87	0.712	0.789	0.32–1.97	0.611
PDA	With vs. without	2.912	1.28–6.62	0.011	4.413	1.63–11.96	0.004
Sepsis	With vs. without	1.977	0.85–4.60	0.114	3.763	1.50–9.41	0.005
ROP	With vs. without	2.014	0.82–4.96	0.128	2.740	0.78–9.66	0.117
CLD	With vs. without	4.565	1.76–11.83	0.002	2.920	1.07–7.96	0.036
Severe IVH	With vs. without	1.082	0.24–4.84	0.918	5.176	0.23–116.72	0.301
NEC	With vs. without	4.378	0.97–19.77	0.055	1.189	0.25–5.69	0.828
Hernia	With vs. without	5.020	0.76–33.05	0.093	6.048	1.42–25.72	0.015
BBW	<1000 g vs. ≥1000 g	5.120	2.19–12.00	<0.001	5.661	2.26–14.21	<0.001

OR = odds ratio; CI = confidence interval; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity; CLD = chronic lung disease; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; BBW = birth body weight.

infants with sepsis were more likely to have a significantly longer LOS (Table 3). Sepsis was a significant factor to be associated with long LOS > 60 days in the second cohort, but not the first cohort. The reason for its resurgence in the second cohort was not clear. We guess it might be due to the redistribution of other competing causes. Whether the advancement of medical intervention, such as the administration of central lines, contributed to its occurrence requires further studies for clarification.

Screening for ROP was highly recommended for VLBW infants or GA ≤ 31 weeks.[23] Surviving infants with ROP were associated with a longer LOS, although this difference was only significant in the first cohort (Table 3). The incidence of ROP was reduced from 36.5% in the first cohort to 13.5% in the second cohort (Table 2). A previous study suggested septicemia and respiratory problems were two major risk factors for developing ROP.[24] There was a much lower incidence of sepsis and CLD in the second cohort of our study, which may explain the reduction of ROP incidence among VLBW infants.

As found in previous studies, symptomatic PDA may occur in up to 50% of VLBW infants.[25] The incidence rate of PDA was 35% among all cases in this study and was slightly higher in deceased infants than surviving infants (Table 1). The incidence of PDA seemed to reduce over time, as it occurred in 45% of the first cohort but only in 25% of the second cohort (Table 2). One possible reason could be that the heart echo examination was routinely performed for every VLBW infant in the first period, but it was only performed for those VLBW infants with symptoms/signs in the second period. Therefore, the incidence of PDA could be severely underscored in the second birth cohort. Nevertheless, PDA was a significant risk factor associated with long LOS > 60 days in both cohorts (Table 4). Surviving infants with PDA had longer LOS than those without (Table 3).

A diagnosis of NEC in a VLBW infant may impose a significant additional LOS and medical burden on the neonatal community as a whole.[26] Our study found that infants with NEC had much longer LOS compared to those infants without NEC (Table 3). The case number of NEC dramatically dropped from 21 in the first cohort to only one in the second cohort (Table 3). We considered that the great improvement was due to early detection of potential NEC cases. Attention to vulnerable cases and early detection could have reduced the chance of NEC, leading to a subsequent decrease of medical burden.[26]

IH is a common disease seen in pediatric practice and may cause complications such as abdominal distension, feeding intolerance, and incarceration. Prematurity is the single most important predisposing factor for the development of IH.[27] Compared to full-term newborns, its incidence is relatively high in VLBW infants.[28] We found that IH was more common in male infants (13.7%) than female infants (3.4%), which was in agreement with previous studies that male sex was an important factor significantly associated with IH.[29] Although IH was not a significant factor associated with mortality in this study (Table 2), infants with IH had much longer LOS than those infants without IH (Table 3), which was consistent with one previous study.[29] Finally, in the multivariate logistic regression, infants with IH had 5–6 times the OR of having long LOS > 60 days, although the OR had a wide range of 95% CI (Table 4).

Some limitations of this study should be mentioned. First, it was based on only one neonatal care center and the sample size was not large, although we followed for a long period spanning 8 years. A relatively small size may adversely affect the statistical power; thus, the 95% CI of some risk factors were relatively wide. However, we consider that this study still provides valuable information about the evolution of neonatal care in Taiwan. Second, this study was conducted at a tertiary medical center in southern Taiwan. Because the approaches to neonatal care and outcomes may vary among centers,[30,31] the representativeness of the outcomes of this study may be limited. Thus, if possible, we would like to analyze the national registry dataset of preterm babies in order to get a whole picture of neonatal care in Taiwan.

In conclusion, deceased infants have much lower GA, Apgar scores, and BBW than surviving infants. The mortality of VLBW infants remained static between two birth cohorts, but the incidence rates of major morbidities were generally reduced. The median LOS for overall surviving infants and the proportion of long LOS > 60 days were both reduced in the second birth cohort 2007–2010. However, if stratified by BBW ≥ 1000 g and BBW < 1000 g, the significant reduction of proportion of long LOS was only found among the groups with BBW ≥ 1000 g. PDA, CLD, and BBW < 1000 g were three major complications associated with long LOS

among surviving infants. Evaluation of the mortality and morbidity of preterm infants across a long period can help to understand the changes and trends of neonatal care. Further study using the national registry dataset to provide more representative information is warranted.

Conflicts of interest

All authors declare no conflicts of interest.

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