Neonatal outcomes of very preterm infants from a neonatal intensive care center

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***Background*: Information about clinical outcomes of very preterm (VPT) infants in tertiary neonatal intensive care unit (NICU) setting is scant in China. This study aimed to investigate the mortality and morbidity of VPT infants admitted to BaYi Children's Hospital, which serves as a NICU referral center for the city of Beijing, China.**

***Methods*: Retrospectively collected perinatal/neonatal data on all admissions of infants born at <32 weeks of gestational age and subsequently admitted to the VPT-NICU from clinical records between October 2010 and September 2011.**

***Results*: Totally 729 infants were identified. 90% of VPT infants were outborn. The overall survival of the infants to discharge was 92%, which increased with increasing gestational age (range from 69% at <28 weeks to 99% at 31 weeks). The incidence of bronchopulmonary dysplasia was 4%, retinopathy of prematurity requiring treatment 2%, intraventricular hemorrhage III-IV 6%, and periventricular leukomalacia 2%. 10% of the VPT infants had a major morbidity at discharge.**

***Conclusions*: The outcomes of the VTP infants at this referral NICU were comparable to those in tertiary centers in developed countries. The most common complications were lower than those in other cohorts. Accordingly, high-volume NICU may minimize the adverse effects of VPT infants' transport.**

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***Key words:* morbidity;
mortality;
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Introduction

In the past two decades, tertiary care centers with neonatal intensive care units (NICUs) have increased with the rising number of preterm births in China.[1] This change in the pattern of provided services has improved the morbidity and mortality of low gestational age (GA) high-risk infants, who are born at level I and II nurseries in community hospitals and transferred to a level III medical center NICU for additional care.[2-4] We have established a tertiary pediatric hospital (BaYi Children's Hospital, affiliated to the General Hospital of Beijing Military Region) with a specialized neonatal care center that serves as a referral center for the city of Beijing in 2007. The neonatal care center has developed with 450 infant incubators, more than 8000 admissions in 2011 and four subspecialty NICUs (includes full term-, late preterm-, very preterm- and surgical-NICU). As a high-volume care center, it serves a largely outborn population and cares for all regional infants requiring complex medical and surgical subspecialty care in Beijing.

Active treatment of very preterm (VPT) infants (born at <32 weeks of GA) has been a major topic of discussion in China,[5-7] but information about clinical outcomes of VPT infants is scant. We hypothesized that, with the high-volume NICU and the well-developed hospital referral/infant transport systems, the outcomes and mortality of VPT infants treated in this NICU are now similar to those in tertiary centers in western countries. The aim of this study was to evaluate clinical management, morbidity, mortality, and disease burden as well as to analyze the impact of perinatal-neonatal risk factors for death of VPT infants during hospitalization in the NICU.

Methods

We analyzed clinical data collected by a standardized

data collection sheet through medical record review. The cohort consisted of infants born at <32 weeks of GA and admitted to the VPT-NICU of BaYi Children's Hospital between October 2010 and September 2011. The study was approved by the Research Ethics Committee of the General Hospital of Beijing Military Region. The informed parental consent was waived due to retrospective nature of this study.

Information collected included demographic data, maternal and prenatal history, postnatal clinical characteristics, primary and secondary diagnoses, respiratory therapy, major complications, survival rate, length of stay (LOS) and cost of NICU care.

Definitions

GA was based on best obstetrical estimate in the medical records. The birth weight (BW) below the appropriate 10th percentile (customised Chinese centiles) was classified as small for GA. Antenatal steroids treatment was regarded as a partial or complete course of antenatal corticosteroids given to the mother at any time before delivery for accelerating fetal maturation. Maternal complications were defined as the occurrence of premature rupture of membranes (PROM) and pregnancy-induced hypertension, preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP syndrome) summarized as maternal hypertension. Respiratory distress syndrome (RDS) was diagnosed in cases with onset of respiratory signs shortly after birth and a compatible radiograph appearance. Mechanical ventilation (MV) was defined as either nasal continuous positive airway pressure (nCPAP) or endotracheal intubation and mechanical ventilation. Patent ductus arteriosus (PDA) was diagnosed in the presence of clinical findings and documented on cardiac echocardiography. Bronchopulmonary dysplasia (BPD) was defined as oxygen dependence at 36 weeks' postmenstrual age (PMA). Sepsis was defined as the presence of characteristic clinical signs and typical laboratory data (positive blood culture, abnormal differential blood count or increased C-reactive protein). Retinopathy of prematurity (ROP) was graded in accordance to the International Classification of Retinopathy of Prematurity.[8] Infants were given laser coagulation in case of ROP stage III with plus disease. Necrotizing enterocolitis (NEC) was diagnosed according to the criteria of Bell ≥II a.[9] Intraventricular hemorrhage (IVH) was diagnosed on ultrasound. Hemorrhages were graded from 1 to 4 according to the criteria of Papile et al[10] and periventricular leukomalacia (PVL) according to de Vries et al.[11] Severe brain injuries included PVL and IVH of grades 3 or 4. Severe morbidity was defined as BPD and/or ROP stage ≥3 and/or severe brain injury.

Statistical analysis

SPSS 20.0 (Chicago, IL, USA) was used for statistical analysis. Continuous variables were presented as means and standard deviation (SD) or medians and range or interquartile range (IQR, 25th to 75th percentile), depending on whether their distributions were highly skewed or not. Categorical variables were taken as counts or rates and odds ratios (ORs) with 95% confidence intervals (CI). Comparison between continuous variables was made using the Mann-Whitney *U* test. Univariate analyses on categorical data were performed using a 2-tailed Chi-square test or Fisher's exact test when appropriate. Logistic-regression models were used to analyze the risk factors for death in VPT infants. For incidence and ORs from multivariate logistic-regression analysis of risk of death, 95% CI was computed around the point estimation value. A *P* value <0.05 was considered statistically significant.

Results

A total of 729 infants met the inclusion criteria for the study.

Perinatal characteristics and delivery room interventions

Maternal characteristics, obstetric interventions and perinatal characteristics of infants, subdivided by GA (72 infants born at 23-27 weeks of GA were included into <28 weeks group, which included 1, 1, 3, 23 and 44 infants born at 23-27 weeks of GA, respectively) are shown in Table 1. Seventy-two (10%) infants were extremely preterm (EPT) infants (GA <28 weeks). 66% of the infants were classified to be very low birth weight (VLBW, <1500 g; *n*=478), and 9% classified to be extremely low birth weight (ELBW, <1000 g; *n*=68). There were 362 (50%) cesarean deliveries and the cesarean delivery rate increased with GA (OR=1.6; 95% CI=1.4-1.8; *P*<0.001).

Morbidities and clinical practices

Infants at the lowest GA were at the greatest risk for morbidities of prematurity (Table 2). Overall, 68% of infants experienced RDS, 90% of whom were given surfactant treatment, 13% were administered surfactant more than once, 16% were treated with nCPAP alone, and 59% were ventilated by endotracheal intubation.

All infants underwent ≥1 transthoracic echocardiogram test after admission. As a result, 3% of the infants were diagnosed with congenital heart diseases, 63% with PDA. Of the infants 52% were treated with indomethacin and/or ligation of PDA. All infants underwent ≥1 cranial ultrasound evaluation after admission, but 22% of them showed abnormal results and 97% were detected IVH.

In 18% (*n*=131) of VPT infants, support was

withdrawn from the treatment, including 28% (*n*=20) in EPT infants. The withdrawal rate of support was 21% (*n*=98) among VLBW infants and 25% (*n*=12) among ELBW infants. Of all infants withdrawn from the treatment, 51% (*n*=67) were withdrawn due to the parents' inability to afford the high cost of continued medical treatment. Thirty-seven percent (*n*=48) of infants died after withdrawal of support in the care unit.

Among 668 survivors, 94% underwent at least an ophthalmologic examination before hospital discharge. Of 122 EPT infants with VLBW, 9% were subjected to laser coagulation while infants born at higher GA or BW >1500 g were not detected for the development of ROP stage ≥3 and/or with plus disease. Because of severe pulmonary morbidities, 22 (4%) of 606 survived infants needed oxygen therapy at 36 weeks and developed BPD (Table 3).

Mortality according to GA or BW

The overall mortality of VPT infants until discharge from the hospital was 8%, which consisted of hospital deaths either in the process of intensive care (2%) or after the withdrawal/withholding of support (7%). The mortality of VLBW and ELBW infants was 11% and 27%, respectively, which was higher than that in 4% of infants with a BW ≥1500 g. Most of deaths occurred within the neonatal period: 44% occurred in the early neonatal period (0-6 days postpartum), 49% in the late neonatal period (7-28 days postpartum), and 7% after the neonatal period (Fig. 1).

Table 1. Perinatal-neonatal information for very preterm infants

Characteristics	GA (wk)					Total
	<28	28	29	30	31	
n	72	92	118	226	221	729
Birth weight, mean (SD), g	1010 (163)	1212 (181)	1313 (209)	1487 (232)	1561 (259)	1399 (285)
Age at entry, median (IQR), h	2 (1-3)	2 (1.5-3)	2 (1.4-3)	2 (1-2.5)	2 (1-2)	2 (1-2.5)
Male, %	58	66	63	59	54	59
Outborn, %	88	91	87	94	87	90
Prenatal steroids treatment, %	14	21	26	32	30	27
Premature rupture of membranes, %	32	36	34	31	35	34
Prenatal antibiotic, %	11	7	11	9	8	9
Gestational hypertension, %	18	19	17	19	31	22
Maternal diabetes mellitus, %	19	11	7	10	8	10
Placental abruption, %	7	11	11	11	9	10
Prenatal care, %	99	99	100	99	100	100
Multiple births, %	28	16	20	20	24	22
Cesarean section, %	21	30	47	48	70	50
Small for GA, %	10	10	9	8	15	10
5 min Apgar score <7, %	35	20	16	9	10	14
Resuscitation in delivery room, %	63	30	30	25	25	31
Endotracheal intubation in delivery room, %	22	22	17	12	12	15

GA: gestational age; SD: standard deviation; IQR: interquartile range.

Table 2. Clinical characteristics and morbidities of very preterm infants

Characteristics	GA (wk)					Total
	<28	28	29	30	31	
n	72	92	118	226	221	729
RDS, %	97	87	76	65	51	68
Surfactant use, %	97	80	70	58	45	63
Pneumonia/sepsis, %	83	64	60	46	35	51
Pulmonary hemorrhage, %	31	13	4	7	3	8
Air leak, %	6	3	3	1	1	2
nCPAP only, %	13	11	13	14	14	13
EI & MV, %	86	79	66	56	41	59
PDA, %	82	75	64	60	56	63
Treated PDA, %*	71	66	56	48	43	52
IVH, any grade, %	49	37	23	19	8	22
IVH, grade 3 or 4, %	25	22	9	6	1	9
Congenital anomalies, %	4	5	2	2	2	3
Mortality, %	31	14	14	3	1	8
Withdrawal of care to discharge alive, %	10	14	12	14	8	11

GA: gestational age; RDS: respiratory distress syndrome; nCPAP: nasal continuous positive airway pressure; EI & MV: endotracheal intubation and mechanical ventilation; PDA: patent ductus arteriosus; IVH: intraventricular hemorrhages. *: PDA treated with indomethacin and/or ligation regardless of symptomatic persistent arterial duct or not.

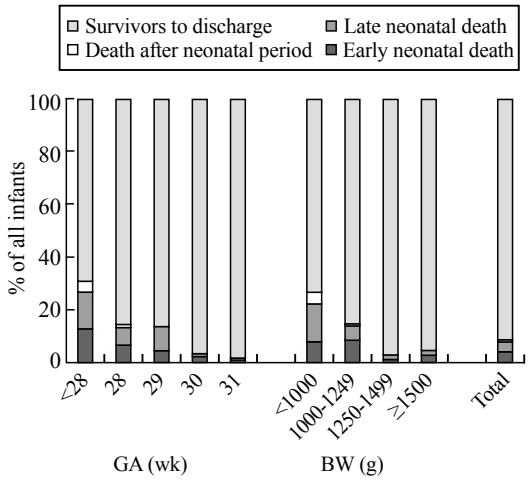

Fig. 1. Mortality of all infants born at <32 weeks of gestational age and subsequently admitted (*n*=729) to BaYi Children's Hospital between October, 2010, and September, 2011, according to gestational age (GA) and birth weight (BW).

Table 3. Survivals with selected neonatal morbidities, length of stay and cost of neonatal intensive care units

Characteristics	GA (wk)					Total
	<28	28	29	30	31	
n	50	79	102	219	218	668
PDA treated surgically (%)	18	8	3	1	1	3.3
NEC (%)	4	4	3	1	1	2.1
NEC treated surgically (%)	2	0	3	0	0	0.6
IVH, grade 3 or 4 (%)	16	18	4	6	1	5.8
PVL (%)	12	1	3	0	1	1.6
Hydrocephalus (%)	10	5	1	1	1	2.1
Infants who survived to PMA of 36 wk	*n*=50	*n*=68	*n*=89	*n*=194	*n*=205	*n*=606
BPD, *n* (%)*	9 (18)	4 (6)	2 (2)	3 (2)	4 (2)	22 (4)
ROP examination performed in hospitalization	*n*=50	*n*=72	*n*=94	*n*=203	*n*=211	*n*=630
ROP any stage, *n* (%)†	31 (62)	27 (38)	16 (17)	13 (6)	17 (9)	104 (17)
ROP laser coagulation, *n* (%)†	6 (12)	4 (6)	0 (0)	0 (0)	0 (0)	10 (2)
Severe brain injury (%)‡	24	18	7	6	1	7
Two or more morbidities (%)§	14	5	0	0	1	2
Severe morbidities (%)‖	38	23	9	7	2	10
Days on MV (d); median (IQR)	18 (11-29)	10 (3-20)	4 (1-9)	3 (0-7)	1 (0-5)	3 (0-10)
Days on oxygen use (d); median (IQR)	40 (25-59)	21 (10-38)	10 (4-21)	7 (2-15)	4 (0-9)	8 (2-20)
LOS (d); median (IQR)	77 (65-93)	61 (49-68)	49 (40-59)	39 (29-49)	37 (26-45)	43 (31-56)
Costs of NICU, CNY; median (IQR), 10^3	94 (69-133)	68 (51-88)	52 (37-73)	42 (30-59)	38 (26-50)	46 (31-68)

*: proportions among infants who survived to postmenstrual age (PMA) of 36 wk and had non-missing outcome data (*n*=606). Bronchopulmonary dysplasia (BPD) diagnosed by oxygen dependence at PMA of 36 wk. BPD could not be determined for 62 infants at discharge; †: Proportions among survivals with retinopathy of prematurity (ROP) examination performed in hospitalization (*n*=630); ‡: severe brain injuries including intraventricular hemorrhages (IVH) grade 3 or more and/or periventricular leukomalacia (PVL); §: morbidities including BPD, IVH grade 3 or 4, PVL, necrotizing enterocolitis (NEC) treated surgically and ROP laser coagulation; ‖: severe morbidities including: BPD, IVH grade 3 or 4, PVL and ROP laser coagulation. PDA: patent ductus arteriosus; MV: mechanical ventilation; LOS: length of stay; CNY: Chinese Yuan, 6.5 CNY=1 USD; IQR: interquartile range; GA: gestational age.

Table 4. Risk factors for death of very preterm infants by multivariate logistic-regression analysis

Variables	Odds ratio	95% CI	*P*
GA (wk)			
<28	8.5	2.2-32.1	0.002
28	7.8	2.1-29.2	0.002
29	4.0	1.0-15.9	0.045
30	1.4	0.3-5.9	0.643
31	1.0		
Endotracheal intubation in delivery room	2.6	1.3-5.1	0.007
Mechanical ventilation	6.3	3.1-12.8	0.000
Pulmonary hemorrhage	4.4	2.1-9.2	0.000
Air leak	5.3	1.5-18.2	0.009

GA: gestational age; CI: confidence interval.

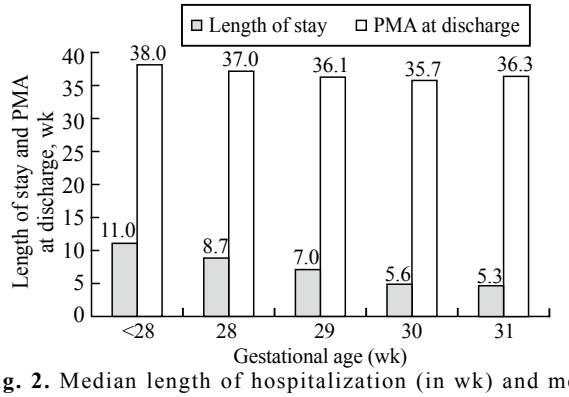

Fig. 2. Median length of hospitalization (in wk) and median postmenstrual age (PMA) at discharge (in wk) according to gestational age at birth among 668 very preterm infants who survived to discharge.

Risk factors for death

On the basis of univariate analyses, including outborn and age at entry, all variables that were significantly associated with death were used for forward stepwise logistic-regression analysis. Table 4 presents the results of the multivariate logistic-regression analysis as the adjusted odds ratios for death. The data revealed that low GA by stepwise weekly analysis, endotracheal intubation in delivery room, mechanical ventilation, pulmonary hemorrhage, and air leak were statistically significant.

Length and costs of hospitalization

Survival data, with selected neonatal morbidities according to GA, are shown in Table 3. Rates of survival with severe morbidities decreased from 38% at <28 weeks to 2% at 31 weeks of GA. IVH was the most frequent morbidity. The median LOS of survivors was 43 days, and decreased with increasing GA, from 77 days at <28 weeks to 37 days at 31 weeks (P<0.001). PMA at discharge decreased from 38.0 weeks for surviving infants born at <28 weeks to 35.7 weeks or 36.3 weeks for those born at 30 or 31 weeks, respectively (Fig. 2). The median cost of surviving infants was 1.4 fold the entire annual income of a Beijing urban resident in 2011 (32 903 CNY).

Discussion

In this study, we summarized the management, mortality and morbidity of VPT infants at a tertiary NICU. Overall, 92% of the infants survived to discharge, and 90% of them were free from a diagnosis of severe morbidity during the hospital stay. The short-term outcomes suggested that VPT infants were at high risk of mortality and morbidity.

It is often difficult to make a direct comparison of survival to discharge between this center with that reported recently from other countries considering that rates are usually given for all births, rather than just admissions, and most importantly, the sample size of EPT infants was limited in this study. The reason is that premature infants are defined as having a GA between 28 and 36 weeks in China. In the current study, we assessed outcomes of VPT infants according to GA, which included 66% (n=478) of VLBW infants. Ninety precent (n=428) VLBW infants survived to discharge, which achieved the Healthy People 2010 objective to deliver 90% of infants born with VLBW in subspecialty perinatal centers in the United States.[12]

The prevalence of morbidity in hospital in our unit was similar or even lower than those from western countries' reports.[13-15] For example, the rate of mortality and BPD in VPT infants was 8.4% and 3.6%, respectively, whereas it was 16.0% and 16.2% in the MOSAIC Cohort, respectively.[14] This difference may be due to a small sample size of selected EPT infants in this cohort.[5,7]

Prenatal steroid treatment has been applied in clinical practice for decades[16] and recent reports have affirmed that antenatal exposure to corticosteroids is associated with a lower rate of severe morbidity, death or neurodevelopmental impairment among EPT infants.[17,18] In our cohort, unadjusted rates of active obstetric intervention in VPT infants with VLBW, as indicated in prenatal steroids administration and cesarean delivery, were much lower than those from the United States (25.7% *vs.* 88.0% and 50.4% *vs.* 67.1%, respectively).[13] The lower rates of active obstetric intervention suggested a less aggressive obstetrical approach for VPT infants at lower GA and the majority of pregnancies terminated with abrupt deliveries. This seems to be a favorable explanation for the limited admissions and poor outcome of EPT infants in the NICU.

It should be noted that death after withdrawal or withholding from intensive care contributed to the high mortality which accounted for 79% of the total deaths in this study; the problem was also reported in other western countries.[19,20] The high cost of continued medical treatment and the high risk of poor outcomes often withdraw or withhold the parents' decisions to provide active intensive care for EPT infants.

Recent studies[21,22] highlighted the value of high-volume level III NICU care to minimize neonatal mortality among VLBW infants and effective maternal transfer strategies enhance this value.[13] Nonetheless, antenatal maternal transport of the high-risk fetus to a tertiary perinatal center is optimal but cannot always be achieved in China. An extremely high percentage of neonatal transfer, rather than maternal transfer, has reached a parallel survival rate to discharge among developed countries. The capacity of the NICU may be associated more strongly with mortality than that of the delivery hospital; the interpretation of this paradox seems the best.[22]

Regionalization of perinatal care has been shown to improve utilization of resources and outcomes.[2] To promote national health promotion, the National Recommended Guidelines and Standards of Newborn ICU Design, have been published in Chinese.[23] As these recommendations are still at their primary stage, emphasizing the need of perinatal regionalization systems in states with high percentages of VPT infants born outside of level III centers could substantially improve survival rates and outcome of newborns.

This study had several limitations. This was a retrospective survey of newborns admitted to one NICU. Stillborns and those who died before transport to the NICU were not included. Moreover, a proportion of patients who gave up care to discharge alive due to financial restraint or fear of poor prognosismay not complete the treatment and affect the outcome measurement. The last but not the least, a small sample size of EPT infants may influence neonatal mortality. This is likely to explain the differences in the present results in comparison with other reports. Despite all its limitations, this investigation extends our knowledge and can serve as a benchmark of future outcome measurement using similar methodologies.

In clonclusion, the mortality and morbidity rates of the VPT infants admitted to the referral NICU are comparable to those in tertiary centers in developed countries. 90% admissions to the NICU are not born at the affiliated hospital and were transferred to this institution by the regional active neonatal transport network. Our study suggested that short-distance neonatal ground transport by well-developed hospital referral/infant transport systems and high-volume NICU may minimize the adverse effects of transport. Future studies should focus on the need for centralization of perinatal care and long-term developmental follow-up of these discharged VPT infants in China.

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Competing interest: The authors have no conflicts of interest to disclose.

Contributors: Zhou WQ contributed to data analysis, study design, drafting the initial manuscript, and approving the final manuscript as submitted. Mei YB undertook the initial analysis, supervised data collection, reviewed and revised the manuscript, and approved the final manuscript as submitted. Zhang XY supervised data collection, reviewed and revised the manuscript, and approved the final manuscript as submitted. Li QP designed the data collection records, and coordinated and supervised data collection, reviewed the manuscript, and approved the final manuscript as submitted. Kong XY reviewed the manuscript, and approved the final manuscript as submitted. Feng ZC supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

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