Original Article

Borderline Viability—Neonatal Outcomes of Infants in Singapore over a Period of 18 Years (1990 – 2007)

Pratibha Agarwal, [1]*MD (Paeds), DNB (Paeds), M MED (Paeds)*, Bhavani Sriram, [1]*MBBS, MRCP (Paeds)*, Sok Bee Lim, [2]*MBBS, M MED (Paeds) FAMS*, Aung Soe Tin, [3]*MBBS, MMed Public Health (Singapore)*, Victor S Rajadurai, [1]*MBBS, MD (Paeds), MRCP*

Abstract

Introduction: This study assesses the trends and predictors of mortality and morbidity in infants of gestational age (GA) <27 weeks from 1990 to 2007. Materials and Methods: This is a retrospective cross-sectional cohort study of infant deliveries between 1990 and 2007 in the largest perinatal centre in Singapore. This is a study of infants born at <27 weeks in 2 Epochs (Epoch 1 (E1):1990 to 1998, Epoch 2 (E2):1999 to 2007) using logistic regression models to identify factors associated with mortality and composite morbidity. The main outcomes that were measured were the trends and predictors of mortality and morbidity. Results: Four hundred and eight out of 615 (66.3%) live born infants at 22 to 26 weeks survived to discharge. Survival improved with increasing GA from 22% (13/59) at 23 weeks to 87% (192/221) at 26 weeks (*P* <0.01). Survival rates were not different between E1 and E2, (61.5% vs 68.8%). In logistic regression analysis, higher survival was independently associated with increasing GA and birthweight, while airleaks, severe intraventricular haemorrhage (IVH) and necrotizing enterocolitis (NEC) contributed to increased mortality. Rates of major neonatal morbidities were bronchopulmonary dysplasia (BPD) (45%), sepsis (35%), severe retinopathy of prematurity (ROP) (31%), severe IVH/periventricular leucomalacie (PVL) (19%) and NEC (10%). Although composite morbidity comprising any of the above was not significantly different between the 2 Epochs (75% vs 73%) a decreasing trend was seen with increasing GA (*P* <0.001). Composite morbidity/mortality was significantly lower at 26 weeks (58%) compared to earlier gestations (*P* <0.001, OR 0.37, 95% CI, 0.28 to 0.48) and independently associated with decreasing GA and birth weight, male sex, hypotension, presence of patent ductus arteriosus (PDA) and airleaks. Conclusion: Increasing survival and decreasing composite morbidity was seen with each increasing week in gestation with marked improvement seen at 26 weeks. Current data enables perinatal care decisions and parental counselling.

Ann Acad Med Singapore 2013;42:328-37

Key words: Composite Morbidity, Neonatal Mortality

Introduction

Advances in perinatal and neonatal care have resulted in the increased survival of extremely preterm infants in the nineties.[1-4] As limits of viability continue to be lowered, it is important to evaluate any further improvement in the new millennium.[5-9] Accurate data on the probability of survival and the outcome of surviving infants are critical in developing appropriate perinatal guidelines and in counselling parents regarding treatment options available. Most recent survival data, and early morbidity and childhood outcomes based on accurate gestational age (GA) are required to make sound decisions regarding care of the high-risk mother and newborn.[2-14] There is however limited information reported from perinatal centres in Asia.[14]

Materials and Methods

The primary endpoint of the study was to determine survival trends and the risk factors for mortality in extremely preterm infants at borderlines of viability between 22+0 weeks and 26+6 weeks gestation over an 18-year period (1990 to 2007). Among the survivors, composite morbidity including severe intraventricular haemorrhage (Grade III to IV IVH)/periventricular leucomalacie (PVL), severe retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and nosocomial culture proven sepsis were also assessed.

This is a cross-sectional study of a cohort of infants born <27 weeks carried out in a tertiary perinatal hospital in Singapore. From January 1990 to December 2007, perinatal

[1]Department of Neonatology, KK Women's and Children's Hospital
[2]Department of Child's Development, KK Women's and Children's Hospital
[3]SingHealth Centre for Health Services Research, Singapore Health Services
Address for Correspondence: Dr Pratibha Agarwal, Department of Neonatology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: Pratibha.Agarwal@kkh.com.sg

and neonatal data of all live born infants who were born less than 27 weeks gestation were collected. The data were obtained from KK Women's and Children's Hospital (KKH), the largest tertiary perinatal centre in Singapore with approximately 12,000 deliveries annually. KKH provides care for more than two thirds of infants born at the threshold of viability in Singapore (unpublished Singapore NICU network data).

Prior to mid 1998, the decision for resuscitation and intensive care at borderline viability was made in the delivery room depending on the infant's condition at birth.

In 1999, a structured policy was established wherein the limit of viability was set at 24 weeks gestation and no resuscitation was instituted at 23 weeks except upon specific parental request and appropriate counselling. Palliative comfort care was provided to infants born alive but not resuscitated. At 24 weeks gestation, resuscitation was commenced unless parents refused. From 25 weeks onwards, all babies were resuscitated unless parents refused active care despite counselling. All babies were to be resuscitated at 26 weeks. The neonatologist counselled parents regarding the estimated survival rates, short-term neonatal morbidities and long-term possible outcomes based on local hospital data.

Based on this change in resuscitation policy at borderlines of viability, the cohort was divided into 2 periods with Epoch 1 (E1) comprising infants born from 1990 to 1998 and Epoch 2 (E2) from 1999 to 2007 to calculate trends and compare mortality and changes in morbidity. The study was approved by the hospital's institutional review board.

Demographic perinatal data were obtained from a prospectively maintained database. Assessment of gestational age was done by the neonatologist based on the best obstetric estimate and relied on the last menstrual period and early dating scan. If no antenatal data were available, gestational age estimation was done by postnatal neonatal assessment. Lubchenco's growth charts were used to classify gestational age status through 2004 and Fenton's growth charts were used from 2005 onwards.[15,16]

Definitions and Practices

Neonatal data on treatment modalities and complications were collected prospectively. Surfactant was instituted from June 1991 onwards as early rescue therapy for infants with respiratory distress syndrome (RDS). Moderate to severe lung disease was clinically defined based on radiological findings and clinical assessments.

A haemodynamically significant patent ductus arteriosus (PDA) on 2D echocardiography was treated with intravenous indomethacin or surgical ligation if medical treatment was unsuccessful or contraindicated. BPD was defined as oxygen dependency at 36 weeks postmenstrual age.[17]

Serial cranial ultrasounds were done according to unit protocol at days 1, 3, 7, 14, 30, 60 and at term. The Papile grading system was used to grade IVH while a standard definition of cystic PVL was used.[18] Presence of grade III/IV IVH or PVL was considered to be a major ultrasonographic abnormality. A paediatric ophthalmologist examined surviving infants at 4 to 6 weeks postnatal age and established presence and staging of ROP according to international classification.[19] Stage III ROP or presence of plus disease was considered to be severe and treated with cryotherapy / laser photocoagulation when indicated. NEC was defined according to modified Bell's criteria and ≥Stage II was considered to be significant. Presence of focal intestinal perforation (FIP) was also grouped together with NEC ≥Stage II as a significant gastrointestinal morbidity.[20] Nosocomial sepsis was defined as blood culture positive sepsis occurring beyond 72 hours of life.

Among the survivors, the major morbidities with potential long-term sequelae were severe IVH, PVL, BPD, severe ROP, NEC ≥2A/FIP and nosocomial sepsis. The presence of any one or more of the above morbidities was considered as a composite morbidity.[21-24]

The presence of death or composite morbidity was considered as an adverse outcome and the rates of adverse outcome were also calculated for the different gestational ages.

Statistics Analysis

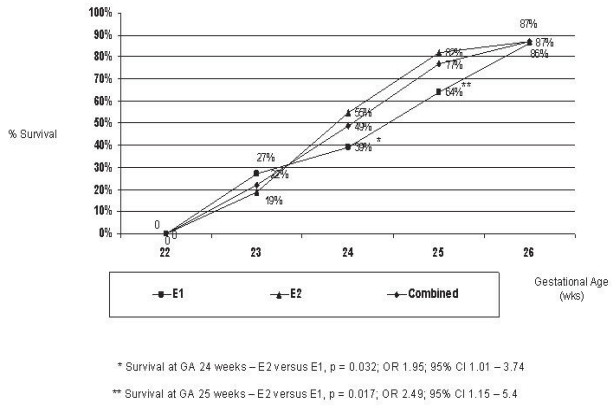
Data were analysed using statistical package for social science (SPSS) Window version 14. Study infants were categorised into E1 (1990 to 1998) and E2 (1999 to 2007). Obstetric and neonatal data were summarised and compared by epochs. Categorical variables were compared using chi-square tests or Fisher's exact tests while continuous variables were compared using independent sample t-test. Linear trends in survival with increasing gestational age were analysed using a linear regression model. Odds ratio (OR) with 95% confidence interval (CI) was calculated using multiple logistic regression analysis.

Logistic regression models were run to determine risk factors for mortality and mortality/composite morbidity (adverse outcome) with adjustment for confounding factors. Factors which were found to be significantly associated with adverse outcome on univariate analysis were included in the regression model. The level of statistical significance was set at $P < 0.05$ in all analyses.

Results

Six hundred and fifteen live born infants <27 weeks of gestation were born alive or admitted to the KKH neonatal

FIGURE 1: COMPARISON OF GESTATIONAL AGE SPECIFIC SURVIVAL BETWEEN EPOCH 1 AND 2



* Survival at GA 24 weeks – E2 versus E1, p = 0.032; OR 1.95; 95% CI 1.01 – 3.74

** Survival at GA 25 weeks – E2 versus E1, p = 0.017; OR 2.49; 95% CI 1.15 – 5.4

Fig. 1. Comparison of gestational age specific survival between Epoch 1 and 2.

intensive care unit (NICU) from 1990 to 2007 with 208 in E1 and 407 in E2.

Overall, 408 (66.3%) of the 615 infants survived to discharge in our entire cohort with survival improving significantly with increasing GA from 0% (0/12) at 22 weeks, 22% (13/59) at 23 weeks, 49% (79/160) at 24 weeks, 77% (124/161) at 25 weeks and 87% (192/221) at 26 weeks (Fig 1, P <0.001). Forty-five (7.3%) infants were born alive but provided comfort care only. The mean GA and birth weight of infants who received comfort care only were significantly lower than those who received NICU care, 23.1 ± 1.1 weeks vs 24.9 ± 0.9 weeks and 584 ± 119g vs 750 ± 155 g respectively (P <0.001). Comfort care was provided to 12/14 (86%) of infants at 22 weeks, 19/59 (32%) at 23 weeks, 9/160 (6%) at 24 weeks, 3 (2%) at 25 weeks and 2 (0.9%) at 26 weeks. The 2 babies born at 26 weeks had severe intrauterine growth restriction (IUGR) with birthweight <400 g and thus were not provided with NICU care. At 25 weeks, 3 babies were provided palliative care, after parental counselling and accepting parental decision of non-initiation of NICU care. In the other cases between 22 and 24 weeks, decision for comfort care was made after parental counselling and in keeping with our hospital resuscitation policy.

Six babies in the cohort had lethal malformation and these included bilateral polycystic kidney (n = 2), thanatophoric dwarfism, hypoplastic left heart, hydranencephaly and hydrops with cleft palate

Of the 162 deaths in NICU admission, 33 were postneonatal deaths beyond 28 days of life. The 3 main causes of death in this group were sepsis (n = 13); NEC (n = 10) and BPD (n = 10). Of the 129 neonatal deaths, the main causes of death were related to severe IVH, severe lung disease, airleaks, sepsis, asphyxia, congenital malformations. The distribution was sepsis (n = 36), severe lung disease ± persistent pulmonary hypertension of the newborn (PPHN) (30), airleaks (24), IVH (n = 21), asphyxia (n = 7), NEC (n = 5) and pulmonary haemorrhage (n = 3).

In univariate analysis of all live born infants, survival rate in E2 was not significantly higher than E1, 280/407 (68.8%) vs 128/208 (61.5%) (P = 0.07, OR 1.38, 95% CI, 0.97 to 1.95). For babies who were born between 23 and 25 weeks of gestation, combined survival rate for the entire study period was 57% (216/380). For babies born at 23 weeks, there was a non-significant reduction in survival in E2 (19%) as compared to E1 (27%) (P = 0.52, OR 0.62, 95% CI, 0.18 to 2.16). Significantly higher survival was seen in E2 for GA 24 and 25 weeks (Fig. 1). For this GA group, survival in E2 was 151/217 (64%) and was higher than the survival of 52/104 (50%) in E1 (P = 0.001, OR 2.29, 95% CI, 1.41 to 3.70). Survival at 26 weeks was comparable in both epochs. As Figure 1 shows, there was a positive relationship between GA and survival in both periods.

Maternal, perinatal and neonatal data revealed that in E2, there was a higher incidence of maternal preterm premature rupture of membranes (PPROM) and higher caesarean section rates (Table 1). The use of antenatal steroids increased significantly in E2 and there was a decrease in the number of babies with 5 minute Apgar score ≤6. There was a higher use of surfactant in E2 despite decrease in the incidence of RDS. The incidence of airleaks also decreased significantly from 26% in E1 to 14% in E2 (P = 0.001). Gestational age and birth weight in the 2 epochs were comparable. There were no differences in the incidence of severe IVH, NEC ≥2A/FIP, sepsis, PDA and chronic lung disease (CLD) between the 2 epochs. However E2 showed a significantly higher incidence of severe ROP compared to E1 (37% vs 18%).

Forty-four out of 45 babies provided with palliative comfort care were born in E2. After excluding these 45 babies provided with comfort care alone, univariate analysis revealed that factors associated with survival included later period of birth (E2), antenatal steroids, increasing gestational age, birth weight and caesarean section delivery. Presence of 5 minute Apgar scores ≤6, hypotension in the first 72 hours needing inotropes, airleaks, severe IVH, NEC and moderate to severe respiratory distress syndrome were associated with increased mortality (Table 2). Factors which showed significant association in univariate analysis were then put into logistic regression model to calculate adjusted odds ratio for survival.

In logistic regression analysis, we used survival status as the dependent variable (survive/die). Increasing survival

Table 1. Perinatal Demographic Data & Neonatal Morbidity (E1 Vs E2)

Maternal n (%)	n	Epoch 1 (n = 208) (%)	Epoch 2 (n = 407) (%)	OR (95% CI)
Antenatal steroids	582	92 (52%)	268 (66.3%)	1.84 (1.29 – 2.64)‡
Preterm premature rupture of membrane	531	47 (28%)	134 (37%)	1.54 (1.08 – 2.30)*
Pregnancy induced hypertensions	531	20 (12%)	30 (8%)	0.68 (0.37 – 1.24)
Multiple pregnancy	615	33 (16%)	59 (14%)	0.91 (0.57 – 1.45)
Caesarean section delivery	569	59 (28%)	142 (39%)	1.17 (1.03 – 1.32)†
Race				
Chinese		127 (61%)	239 (59%)	
Malay	615	55 (26%)	108 (26%)	NS
Indian		22 (11%)	38 (9%)	
Others		4 (2%)	22 (6%)	
Perinatal				
Male sex	615	122 (59%)	231 (57%)	1.08 (0.77 – 1.52)
Mean birthweight (g ± SD)	615	735 ± 165	739 ± 155	NS
Mean GA (weeks ± SD)	615	24.9 ± 1.05	24.8 ± 1.12	NS
SGA	614	19 (9%)	32 (8%)	1.14 (0.59 – 2.1)
5 minute Apgar ≤6	558	92 (46%)	105 (29%)	2.05 (1.43 – 2.94)‡
Neonatal n (%)				
Survival	615	128 (61.5%)	280 (68.8%)	1.38 (0.97 – 1.95)
Surfactant therapy	555	124 (65%)	281 (77%)	1.82 (1.20 – 2.7)†
Moderate severe lung disease	561	147 (72%)	226 (63%)	0.67 (0.46 – 0.97)*
Presence of air leak	556	52 (26%)	51 (14%)	0.49 (0.32 – 0.76)‡
Major IVH / PVL	557	43 (22%)	68 (19%)	0.86 (0.56 – 1.32)
Culture proven sepsis	558	69 (34%)	145 (41%)	1.31 (0.91 – 1.88)
NEC ≥ST 2A / FIP	492	12 (7.4%)	38 (12%)	1.64 (0.83 – 3.24)
Severe ROP	427	24 (18%)	107 (37%)	2.75 (1.67 – 4.54)‡
BPD	430	69 (49%)	126 (43%)	0.79 (0.53 – 1.18)
Composite morbidity	516	130/173 (75%)	249/343 (73%)	0.87 (0.58 – 1.33)
Mortality / Composite morbidity	615	165 (79%)	312 (77%)	0.86 (0.57 – 1.28)

*$P \leq 0.05$; †$P \leq 0.01$; ‡$P \leq 0.001$

SD: Standard deviation; GA; Gestational age; SGA: Small for gestational age; IVH: Intraventricular haemorrhage; PVL: Periventricular leukomalacia; NEC: Necrotizing Enterocolitis; ST: Stage; ROP: Retinopathy of prematurity; BPD: Bronchopulmonary dysplasia; NS: Not significant

was independently associated with increasing gestational age and birth weight, while presence of airleaks, severe IVH and NEC ≥St2A/FIP contributed to the mortality (Table 2). Epochs, caesarean section delivery and antenatal steroids were no longer independent predictors of survival in logistic regression analysis.

The neonatal morbidities and characteristics of the babies provided with NICU care are described in Table 3 according to GA and provides *P* value and odds ratio after adjustment for epoch of birth. There was a significantly higher use of antenatal steroids from 24 weeks GA and above, as well as higher rates of caesarean section delivery with increasing gestational age. As expected, birth weight significantly improved with increasing gestational age. The incidence of airleaks was significantly higher at 23 and 24 weeks and then decreased ≥25 weeks. There was a marginal reduction in PDA while other major morbidities such as nosocomial sepsis, IVH, CLD, and severe ROP, decreased more significantly with increasing gestation. The largest reduction was seen between 25 and 26 weeks.

Among the infants who received NICU care, the percentage of babies who had an adverse outcome (death or composite morbidity) trended downwards from 100% at 22 weeks to 95% at 23 weeks, 91% at 24 weeks, 82% at 25 weeks and 58% at 26 weeks (Table 3). Factors associated with presence of an adverse outcome are shown in Table 4 and primarily included lack of antenatal steroids, male sex, lower gestational age and birth weight, 5 minute Apgar

Table 2. Factors Associated with Survival in NICU Admissions

Characteristics	Mortality (n = 162)	Survival (n = 408)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Epochs				
Epoch 1	79 (38%)	128 (62%)	2.08(1.43 – 3.02)‡	1.11(0.56 – 2.09)
Epoch 2	83 (23%)	280 (77%)		
Maternal factors n (%)				
Antenatal steroids	64 (39%)	286 (70%)	2.65 (1.77 – 3.95)‡	1.41(0.71 – 2.79)
Multiple pregnancy	26 (16%)	58 (14%)	0.87 (0.52 – 1.43)	
Caesarean section delivery	42 (26%)	154 (38%)	1.74 (1.14 – 2.56)†	1.20(0.59 – 2.45)
Perinatal factors				
Male sex	99 (61%)	228 (56%)	1.24 (0.86 – 1.79)	
Mean GA (weeks ± 2SD)	24.3 ± 0.99	25.2 ± 0.86	2.59 (2.09 – 3.22)‡	1.61(1.12 – 2.33)†
Mean birthweight (g ± 2SD)	662 ± 145	784 ± 145	1.006 (1.005 – 1.008)‡	1.006(1.003 – 1.009)‡
SGA	17 (11%)	32 (8%)	0.7 (0.36 – 1.36)	
5 minutes Apgar ≤6	82 (51%)	115 (28%)	0.34 (0.23 - 0.51)‡	0.98(0.50 – 1.89)
Neonatal factors n (%)				
Hypotension needing inotropes in 1st 72 hours	73 (46%)	127 (31%)	0.53 (0.36 – 0.77)‡	0.71 (0.38 – 1.34)
Moderate to severe lung disease	122 (79%)	251 (62%)	0.41 (0.26 – 0.63)‡	1.35 (0.69 – 2.66)
Airleaks	57 (38%)	46 (11%)	0.20 (0.13 – 0.32)‡	0.32(0.16 – 0.63)‡
Surfactant	120 (77%)	295 (72%)	0.78 (0.51 – 1.21)	
PDA	79 (76%)	305 (75%)	0.95 (0.57 – 1.56)	
Major IVH /PVL	59 (40%)	52 (13%)	0.22 (0.14 – 0.35)‡	0.38(0.19 – 0.80)†
NEC ≥ST 2A / FIP	22 (26%)	28 (7%)	0.21 (0.11 – 0.39)‡	0.29 (0.13 – 0.65)‡
Culture proven sepsis	58 (39%)	156 (38%)	0.98 (0.66 – 1.44)	

Adjusted odds ratios were calculated using the logistic regression analysis. Survival status was used as the dependent variables. Variables entered for regression analysis as independent variables: caesarean section delivery, epoch of birth, antenatal steroids, birth weight, gestational age, 5 minutes Apgar ≤6, early hypotension needing inotropes, moderate to severe respiratory distress, airleaks, severe IVH, severe NEC, sepsis.

*$P \leq 0.05$, †$P \leq 0.01$, ‡$P \leq 0.001$

SD: Standard deviation; GA; Gestational age; SGA: Small for gestational age; PDA: Patent ductus arterious; IVH: Intraventricular haemorrhage; PVL: Periventricular leukomalacia; NEC: Necrotizing Enterocolitis; ST: Stage; FIP: focal intestinal perforation

score ≤6, hypotension needing inotropes in the first 72 hours, more severe respiratory distress syndrome, presence of airleaks and significant PDA. When these factors were put into a regression model, decreasing gestational age and birth weight, male sex, presence of hypotension, PDA and airleaks were the independent risk factors for an adverse outcome.

Discussion

Borderline viability is an extremely difficult and controversial term, open to many interpretations and varying definitions depending on countries and individual perinatal centres.[25] The definitions will be affected by both medical and non-medical factors such as culture, religion, financial constraints, parental preferences, physician's perspective and societal values.[25-27] Definitions can range from the ability to sustain life with a ventilator to ability to live and grow and develop normally.[28,29] As there is still no uniform consensus on the definition, the term "periviable" was used by the National Institute of Child Health and Human Development (NICHD) workshop on borderline viability, to refer to the foetus between 20 and 26 weeks of gestation.[30] In our study, we adopted the definition by Rennie as being the gestation less than 26+6 weeks.[28] Overall survival to discharge in our entire cohort was 66% with survival improving significantly with increased gestational age from 22% at 23 weeks to 87% at 26 weeks. Our findings are similar to those published by single centre and multicentre studies in the United States and Europe.[2,4,5,7,28,31-37] There was no survivor at 22 weeks and this dismal outcome has been widely reported.[5,32-34] The non-significant reduction in survival at 23 weeks GA in E2 probably reflected the new hospital policy of non-resuscitation at 23 weeks. The survival of more than two thirds of our neonates at 26 weeks with a corresponding reduction in composite morbidity implies that 26 weeks is no longer at the threshold of viability in our population.

Table 3. Neonatal, Demographics and Morbidity in NICU Admissions According to Gestational Age

Maternal n (%)	n	22 weeks n = 2	23 wks n = 40	24 wks n = 151	25 wks n = 158	26 wks n = 219	Overall n = 570	OR (95% CI)
Antenatal steroids	538	1 (50%)	18 (49%)	83 (61%)	103 (69%)	145 (68%)	350(61%)	1.24 (1.03 – 1.49)*
Caesarean section	569	-	2 (5%)	42 (28%)	48 (30%)	104 (48%)	196(34%)	1.76 (1.44 – 2.14)‡
Multiple pregnancy	570	-	6 (15%)	17 (11%)	23 (15%)	38 (17%)	84 (15%)	1.19 (0.94 – 1.53)
Perinatal								
Male sex	570	-	26 (65%)	89 (59%)	96 (61%)	116 (53%)	327 (57%)	0.90 (0.76 – 1.06)
5 minutes Apgar ≤6	558	-	20 (54%)	59 (40%)	60 (39%)	58 (27%)	361(35%)	0.73 (0.62 – 0.88)‡
Mean birthweight (g ± SD)	570	497 ± 109	565 ± 90	663 ± 103	752 ± 117	844 ± 152	750 ± 155	
Neonatal n (%)								
Hypotension needing inotropes	565	2 (100%)	14 (35%)	62 (41%)	61 (39%)	61 (28%)	200 (35%)	0.77 (0.64 – 0.92)†
Moderate to severe lung disease	560	2 (100%)	29 (76%)	111 (75%)	106 (68%)	125 (58%)	373(65%)	0.71 (0.58 – 0.85)‡
Airleaks	556	-	11 (29%)	38 (26%)	24 (16%)	30 (14%)	103(18%)	0.74 (0.59 – 0.91)†
Surfactant	564	2 (100%)	28 (70%)	119 (79%)	128 (81%)	138 (63%)	415 (74%)	0.71 (0.57 – 0.87)‡
PDA	511	1 (100%)	22 (67%)	114 (86%)	102 (73%)	145 (71%)	384 (75%)	0.81 (0.65 – 0.99)*
Severe IVH / PVL	557	1 (50%)	11 (28%)	41 (28%)	30 (20%)	28 (13%)	111 (19.5%)	0.67 (0.55 – 0.83)‡
≥Stage II NEC / FIP	492	1 (50%)	2 (7%)	16 (14%)	17 (12%)	14 (7%)	50 (10%)	0.75 (0.56 – 1.01)
Nosocomial sepsis	558	1 (50%)	17 (44%)	67 (46%)	57 (56.5%)	53(24.5%)	195(35%)	0.70 (0.59 – 0.84)‡
Survivors till 36 weeks PMA	430	n = 0	n = 17	n = 89	n = 129	n = 196	n = 430	
BPD 36 weeks	430	-	12 (71%)	58 (65%)	67 (52%)	58 (30%)	195 (45%)	0.47 (0.37 – 0.60)‡
Survivors till eye review	426	n = 0	n = 17	n = 93	n = 127	n = 196	n = 426	
Severe ROP	426	-	8 (47%)	47 (50%)	50 (39%)	26 (13.3%)	131(31%)	0.41 (0.32 – 0.54)‡
Composite morbidity	516	2 (100%)	27(90%)	114 (88%)	118 (81%)	118 (56%)	379 (73%)	0.41 (0.32 – 0.54)†
Mortality / Composite morbidity	570	2 (100%)	38 (95%)	137 (91%)	129 (82%)	126 (58%)	432(76%)	0.37 (0.28 – 0.48)‡

*$P \leq 0.05$; †$P \leq 0.01$; ‡$P \leq 0.001$

P values and OR were determined by wald chi-square tests for differences according to GA, with adjustment for epoch of birth using multiple logistic regression.

SD: Standard deviation; IVH: Intraventricular haemorrhage; PVL: Periventricular leukomalacia; NEC: Necrotizing Enterocolitis; FIP: Focal intestinal perforation; PMA: Postmenstrual age; BPD: Bronchopulmonary dysplasia; ROP: Retinopathy of prematurity

Table 4. Factors Associated with Mortality / Composite Morbidity (Adverse Outcome) in NICU Admissions

Characteristics	No Mortality / Morbidity (n = 138)	Mortality / Morbidity Present (n = 432)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Epochs of birth				
E1	43 (21%)	164 (79%)		
E2	95 (26%)	268 (74%)	0.74 (0.49 – 1.11)	0.95 (0.57 – 1.59)
Maternal, n (%)				
Antenatal steroids	100 (73.5%)	250 (62%)	0.59 (0.34 – 0.91)*	0.81 (0.48 – 1.35)
Caesarean section	56(41%)	140 (33%)	0.92 (0.8. – 1.02)	
Multiple pregnancy	16 (12%)	68 (16%)	1.42 (0.79 – 2.55)	
PPROM	47 (34%)	134 (34%)	0.99 (0.66 – 1.49)	
PIH	11 (8%)	39 (10%)	1.25 (0.63 – 2.53)	
Perinatal				
Male sex	66 (48%)	261 (60%)	1.66 (1.13 – 2.45)*	1.89 (1.25 – 2.43)†
Mean GA (weeks ± SD)	25.5 ± 0.74	24.7 ± 0.98	0.36 (0.28 – 0.48)‡	0.57 (0.41 – 0.80)‡
Mean Birthweight (g ± SD)	845 ± 139	720 ± 148	0.994 (0.993 – 0.996)‡	0.997 (0.995 – 0.99)†
SGA	8 (6%)	41 (10%)	1.72 (0.79 – 3.76)	
5 minutes Apgar ≤6	30 (22%)	167 (40%)	2.34 (1.49 – 3.67)‡	1.37 (0.79 – 2.37)
Neonatal n (%)				
Hypotension needing inotropes in 1st 72 hours	28 (20%)	172 (40%)	2.65 (1.68-4.19)‡	1.78 (1.05 – 3.03)*
Moderate severe lung disease	65 (47%)	308 (73%)	3.01 (2.02 – 4.47)‡	1.47 (0.9 – 2.41)
Airleaks	6 (4.3%)	97 (23%)	6.65 (2.84 – 15.54)‡	3.39 (1.35 – 8.52)†
PDA	83 (60%)	301 (81%)	2.77 (1.81 – 4.25)‡	2.05 (1.23 – 3.44)†

*$P \leq 0.05$; †$P \leq 0.01$; ‡$P \leq 0.001$

Variables entered for regression analysis: antenatal steroids, male sex, birth weight, gestational age, 5 minutes Apgar ≤6, early hypotension needing inotropes, moderate to severe respiratory distress, airleaks, PDA.

E: Epoch; PPROM: Preterm premature rupture of membranes; PIH: Pregnancy-induced hypertension; GA: Gestational age; SD: Standard deviation; SGA: Small for gestational age; PDA: patent ductus arteriosus

The survival rates between 23 and 25 weeks in our study were 57%. We had lower survival rates than the 50% survival at 23 weeks and 85% at 24 and 25 weeks between 1992 and 1998 reported by Serenius et al.[3] This difference in survival may be due to the active resuscitation policy and universal initiation of neonatal intensive care by the 2 Swedish tertiary care centres.[3] The trend for increasing survival for infants 23 to 26 weeks as well as improved gestational age specific survival over time has been reported by studies from the UK, Europe, Australia and North America.[1-6,8,10,23,36-39] However, in the new millennium, especially in the second half of the decade, there has been no further improvement in survival at 23 weeks in our cohort as well in the reported literature, reflecting the limit to which the boundaries can be pushed by technological and medical advances.[2,5,6,36,37,40] This could also be a reflection of the restrictive resuscitation policy in our institute at 23 weeks which is also a common practice internationally in units in North America, UK and Europe.[25] In stark contrast, Japan shows continuing improvement in survival from 2000 to 2005 for all gestational age categories between 22 and 27 weeks.[41] Improved survival in Japan could probably be attributed to the policy of resuscitation of babies at 22 and 23 weeks or with birthweight <500 g. There is however one study from Japan which demonstrated that rate of CLD had increased in 2000 compared to 1995. Additionally, in another unpublished study, the rate of cerebral palsy (CP) increased from 12% in 1990 to 16% in 2000 in Japan.[41] Thus, improved survival in Japan does not necessarily reflect an improved outcome and the authors have specifically said that data was not available to elucidate factors contributing to mortality reduction.[41]

The improvement in survival over time has been postulated in the literature to be due to a variety of reasons including increased use of antenatal steroids, improved obstetric care, enhanced NICU management and regionalization of perinatal care.[1,9,11,23,28,35,38,40-43] Another possible contributing factor could be the high-risk perinatal consultation service, which was established in 1997 in our centre. This is reflected in our cohort with higher use of antenatal steroids in Epoch 2 and better condition of the babies at birth reflected by improved Apgar scores at 5 minutes, which was also reported by Hintz et al.[44]

After a systematic review of 67 studies, Evans[45] concluded that there was evidence of selection bias in preterm survival studies with overestimation of survival in studies which did not take into account stillbirths or live births not resuscitated. In our institution, taking into account this bias, we are now capturing data on liveborn infants not resuscitated in labour wards since 1999. The drop in survival rates at 23 weeks from 27% in Epoch 1 to 19% in Epoch 2 reflected our new guidelines of providing comfort care at 23 weeks but including the live births not resuscitated in the delivery room in the denominators for survival estimation. The improved survival at 24 and 25 weeks in the later part of the study, with no corresponding improved at 23 weeks, is very closely mirrored in the data from a geographic population by Field et al.[5] Despite being a single centre study, our survival data are consistent with findings reported from geographically defined populations in England[5] and probably reflects centralisation of perinatal care at the threshold of viability in Singapore. Even within geographic areas, centralisation of perinatal care for extremely preterm deliveries to centers of excellence has been recommended in Sweden and Finland.[43] Thus, our study has the advantage of reflecting centralised perinatal care in Singapore as KKH is the regional referral unit with highest volume of extreme preterm births. It has now been increasingly reported that high level NICUs and high volume centres like our institution have better neonatal survival for extremely preterm infants.[43,46,47]

Surfactant therapy has been reported to be beneficial in improving survival in the extremely preterm infants of 23 to 26 weeks.[6,32] In our study, the use of surfactant was significantly higher after 1998, reflecting the changing trend in neonatal practice of earlier surfactant use. However, infants in both cohorts were born in the post surfactant era and there was no significant difference in the usage of surfactant in the survivors.

The prevalence of SGA of 10% in our cohort is comparable to the NICHD data from Stoll et al[36] which reported prevalence of 4% to 10%. In our study, SGA was not an independent risk factor for increased mortality in the NICU admissions unlike reported literature and may possibly be due to the fact that the severely growth restricted foetuses at threshold of viability may have suffered from in utero fetal demise or may not have been offered NICU care in view of severe growth restriction and birth weight below 400 to 500 g.[48]

Antenatally known factors like gestational age and postnatal variables like birth weight, airleaks, severity of lung disease, severe IVH and NEC/FIP independently predicted mortality. In our cohort, caesarean section was not independently associated with improving survival similar to reports by other authors.[3,32]

The higher use of antenatal steroids and higher caesarean section rates beyond 24 weeks probably reflect the willingness of the obstetric and neonatal teams to provide active perinatal care.

Major neonatal morbidities which have potential long-term implications for growth and development include severe BPD, grade III-IV IVH/PVL, severe ROP, NEC> Stage II and culture proven sepsis and the presence of one or more of these morbidities was defined as an composite morbidity.[21-24,36,44] Rates of composite morbidity in our cohort were similar to findings reported by Hussain and others and decreased with increasing GA.[7,21-23,36,44]

We also looked at presence of mortality and composite morbidity as a combined adverse outcome in the babies provided with NICU care and it was seen that an adverse outcome was significantly associated with male sex, lower birth weight and gestational age and postnatally with the presence of hypotension, airleaks and PDA. The increased adverse neonatal outcome in boys seen in our study has been well documented historically and from recent data but the exact pathogenesis remains unclear.[49] In our study the composite morbidity / mortality were comparable between the 2 epochs. There was however an increase in severe ROP seen in E2 compared to E1 and this is in keeping with the reported association of ROP with increased survival at threshold viability.[44,45] However, Hameed et al, who defined severe ROP, similar to our study, documented an increasing trend in very low birth weight (VLBWs) <1250 g and concluded that the significantly increased risk of severe ROP was independent of the increase in survival.[50] One of the possible reasons for the increase in the incidence of ROP in E2 could be related to higher survival in E2 for GA 24 weeks and 25 weeks documented in our study. Another possible reason may be due to proinflammatory events such as intrauterine infection associated with a higher incidence of PPROM and chorioamnionitis in E2. It has been now well documented that exposure to perinatal infection/ inflammation is associated with an increased risk of ROP.[51]

There is thus a need to further analyse the reasons for the increasing incidence of severe ROP and subsequently look at possible interventions to reverse this trend. Reduction in airleaks would also be critical in decreasing the incidence of major morbidity in this vulnerable group. This would be of benefit not only in the neonatal period but also importantly may decrease long-term morbidity. These data will serve as a useful quality improvement (QI) tool to audit and improve our NICU practices.

Conclusion

Major neonatal morbidities decreased with increasing gestational age with significant major reductions noted at 26 weeks. Thus, the upper end of the limits of viability has shifted from 26 to 25 weeks in our practice. In the new

millennium, there was no further improvement in survival at 23 weeks, reflecting the boundaries of advances in perinatal care. There was a significant increase in the incidence of severe ROP in Epoch 2, which needs further monitoring.

Neonatal mortality and morbidity data are invaluable tools in the decision-making process along with data on neurodevelopmental outcome in childhood. Thus all extremely high-risk preterm infants need to be followed up for long-term neurodevelopmental morbidities and outcome, which is currently being done in our cohort up to 8 years of age. The final determinant regarding the extent of care for infants born at the margins of viability should be an informed parental decision made after detailed communications with the perinatal team. The limits of viability should be based on individual centre related outcomes rather than relying on international or national figures.

REFERENCES

1. Emsley HCA, Wardle SP, Sims DG, Chiswick ML, D'souza SW. Increased survival and deteriorating developmental outcome in 23 to 25 week old gestation infants. Arch Dis Child Fetal Neonatal Ed 1998;78:F99 - F104.
2. Hack M, Fanaroff AA. Outcomes of Children of extremely low birth weight and gestational age in the 1990s. Semin Neonatol 2000;5:89-106.
3. Serenius F, Ewald U, Farooqi A, Holmgren PA, Håkansson S, Sedin G. Short-term outcome after active perinatal management at 23 – 25 weeks of gestation. A study from two Swedish tertiary care centers. Part 2: infant survival. Acta Pediatr 2004;93:1081-9.
4. Lorenz JM. Survival of the extremely preterm infant in North America in the 1990s. Clin Perinatol 2000;27:255-62.
5. Field DJ, Dorling JS, Manktelow BN, Draper ES. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994-9 compared with 2000-5. BMJ 2008;336:1221-3.
6. Costeloe K, Hennessy E, Myles J, Draper E for the EPICure group. Epicure 2: Survival and Early Morbidity of Extremely Preterm Babies in England: Changes since 1995. Arch Dis Child 2008;93:A33-4.
7. EXPRESS Group, Fellman V, Hellström-Westas L, Norman M, Westgren M, Källén K, Lagercrantz H, et al. One-Year survival of extremely preterm infants after active perinatal care in Sweden. JAMA 2009.;301:2225-33.
8. Lundqvist P, Kallen K, Hallstrom I, Westas LH. Trends in outcomes for very preterm infants in the southern region of Sweden over a 10-year period. Acta Pediatr 2009;98:648-53.
9. Zayek MM, Trimm RF, Hamm CR, Peevy KJ, Benjamin JT, Eyal FJ. The limit of viability – A single regional unit's experience. Arch Pediatr Adolesc Med 2011;165:126-33.
10. Serenius F, Ewald U, Farooqi A, Holmgren PA, Håkansson S, Sedin G. Short Term outcome after active perinatal management at 23 – 25 weeks of gestation. A study from two Swedish tertiary care centers. Part 3: neonatal morbidity. Acta Pediatr 2004;93:1090-7.
11. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR, for the EPICure Study Group. The EPICure Study: Outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 2000;106:659-71.
12. Wood N, Marlow N, Costeloe K, Gibson AT, Wilkinson AR for the EPICure Study Group 2000. Neurological and developmental disability following extremely preterm birth. N Engl J Med 2000;343:378-84.
13. Lorenz JM. Management decisions in extremely premature infants. Semin Neonatol 2003;8:475-82.
14. Partridge JC, Martinez AM, Nishida H, Boo NY, Tan KW, Yeung CY, et al. International comparison of care for very low birthweight infants: Parents' perceptions of counselling and decision making. Pediatrics 2005:116;e263-71.
15. Lubchenco LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birth-weight data at 24 to 42 weeks of gestation. Pediatrics 1963;32:793-800.
16. Fenton TR. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC Pediatr 2003;3:13.
17. Jobe AH, Bancalari E. Bronchopulmonary Dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.
18. Papile LA, Munsick-Bruno G, Schaefer A. Relationship of cerebral intraventricular haemorrhage in early childhood neurological handicaps. J Pediatr 1983;103:273-7.
19. An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity Revisited. Arch Ophthalmol 2005;123:991-9.
20. Pumberger W, Mayr M, Kohlhauser C, Weninger M. Spontaneous localized intestinal perforation in very low birth weight infants: A distinct clinical entity different from necrotizing enterocolitis. J Am Coll Surg 2002; 195:796-803.
21. Husain N, Galou M, Ehrerikranz RA, Henson VC, Rowe JC. Pre-discharge outcome of 22-27 weeks gestational age infants born at tertiary care centers in Connecticut. Implications for perinatal management. Conn Med 1998;62:131-7.
22. Bassler D, Stoll BJ, Schmidt B, Asztalos EV, Roberts RS, Robertson CM, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: Added role of neonatal infection. Pediatrics 2009;123:313-8.
23. Hintz SR, Poole WK, Wright LL, Fanaroff AA, Kendrick DE, Laptook AR, et al. Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era. Arch Dis Child Fetal Neonatal Ed 2005;90:F128-F33.
24. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF. Impact of bronchopulmonary dysplasia, brain injury and severe retinopathy on the outcome of extremely low birth weight infants at 18 months results from the trial of indomethacin prophylaxis in preterm. JAMA 2003;289:1124-9.
25. Pignotti MS, Donzelli G. Perinatal care at the threshold of viability: an international comparison of practical guidelines for the treatment of extremely preterm births. Pediatrics 2008;121;e193-8.
26. Tyson JE, Stoll BJ. Evidence-based ethics and the care and outcome of extremely premature infants. Clin Perinatol 2003;30:363-87.
27. Watts JL, Saigal S. Outcome of extreme prematurity: as information increases so do the dilemmas. Arch Dis Child Fetal Neonatal Ed 2006;91:F221-5.
28. Rennie JM. Perinatal management at the lower margin of viability. Arch Dis Child Fetal Neonatal Ed 1996;74:F214-8.
29. Dunn PM, Stirrat GM. Capable of being born alive? Lancet 1984;1:553-555.
30. Higgins RD, Delivoria-Papadopoulos M, Raju TN. Executive summary of the workshop on the border of viability. Pediatrics 2005;115:1392-6.
31. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, et al. Very low birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. Pediatrics 2001;107:1-8.
32. El-Metwally D, Vohr B, Tucker R. Survival and neonatal morbidity at the viability in the mid 1990s:22 to 25 weeks. J Pediatr 2000;137:616-22.
33. Draper ES, Zeitlin J, Fenton AC, Weber T, Gerrits J, Martens G, et al. Investigating the variations in survival rates for very preterm infants in 10 European regions: the MOSAIC birth cohort. Arch Dis Child Fetal Neonatal Ed 2009;94:F158-63.

34. Markestad T, Kaaresen PI, Ronnestad A, Reigstad H, Lossius K, Medbo S et al on behalf of the Norwegian extreme prematurity study group. Early Death, Morbidity and Need of Treatment Among Extremely Premature Infants. Pediatrics 2005;115:1289-98.
35. Tommiska K, Heinonen K, Lehtonen L, Renlund M, Saarela T, Tammela O et al. No improvement in outcome of nationwide extremely low birth weight infant populations between 1996-1997 and 1999-2000. Pediatrics 2007;119:29-36.
36. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC et al. Neonatal outcomes of extremely preterm infants from NICHD Neonatal Research Network. Pediatrics 2010;126;443-56.
37. Berger TM, Steurer MA, Woerner A, Meyer-Schiffer P, Adams M. Trends and centre to centre variability in survival rates of very preterm infants (<32 weeks) over a 10 year period in Switzerland. Arch Dis Child Fetal Neonatal Ed 2012;97:F323-F328.
38. Kyser KL, Morriss FH Jr, Bell EF, Klein JM, Dagle JM. Improving survival of extremely preterm infants born between 22 and 25 weeks of gestation. Obstet Gynecol 2012;119:795-800.
39. Gultom E, Doyle LW, Davis P, Dharmalingam A, Bowman E. Changes over time in attitudes to treatment and survival rates for extremely preterm infants (23-27 weeks gestational age). Aust NZ J Obstet Gynaecol 1997;37:56-8.
40. Meadow W, Lantos J. Moral reflections on neonatal intensive care. Pediatrics 2009;123:595-7.
41. Itabashi K, Horiuchi T, Kusuda S, Kabe K, Itani Y, Nakamura T, et al. Mortality rates for extremely low birthweight infants born in Japan in 2005. Pediatrics 2009;123:445-50.
42. Kawamoto Y, Fujimura M, Ogawa Y. Is the incident of chronic lung disease decreasing? The national CLD survey in Japan: changes over 10 years. J Jpn Soc Premature Newborn Med 2002;14:352.
43. Rautava L, Lehtonen L, Peltola M, Korvenranta E, Korvenranta H, Linna M et al for the PERFECT Preterm Infant Study Group. The effect of birth in secondary – or tertiary level hospitals in Finland on mortality in very preterm infants: A birth-register study. Pediatrics 2007;119:e257-e263.
44. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD for the National Institue of Child Health and Human Development Neonatal Research Network. Changes in Neurodevelopmental outcomes at 18 to 22 months corrected age among Infants of less than 25 weeks' gestational age born in 1993-1999. Pediatrics 2005;115:1645-51.
45. Evans DJ, Levene MI. Evidence of selection bias in preterm survival studies: a systematic review. Arch Dis Child Fetal Neonatal Ed 2001;84:F79-F84.
46. Lorch SA, Baiocchi M, Ahlberg CE, Small DS. The differential impact of delivery hospital on the outcomes of premature infants. Pediatrics 2012;130;270-8.
47. Wehby GL, Lopez-Camelo J, Castilla EE. Hospital volume and mortality of very low-birthweight infants in South America. Health Serv Res. 2012;47:1502-21.
48. Damodaram M, Story L, Kulinskaya E, Rutherford M, Kumar S. Early adverse perinatal complications in preterm growth-restricted fetuses. Aust N Z J Obstet Gynaecol 2011;51:204-9.
49. Stevenson DK, Verter J, Fanaroff AA, Oh W, Ehrenkranz RA, Shankaran S, et al. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. Arch Dis Child Fetal Neonatal Ed 2000;83:F182-5.
50. Hameed B, Shyamanur K, Kotecha S, Manktelow BN, Woodruff G, Draper ES et al. Trends in the incidence of severe retinopathy of prematurity in a geographically defined population over a 10 year period. Pediatrics 2004;113:1653-7.
51. Lee J, Dammann O. Perinatal infection, inflammation, and retinopathy of prematurity. Semin Fetal Neonatal Med 2012;17:26-9.