Original Article

Short- and Long-Term Outcomes at 2, 5 and 8 Years Old for Neonates at Borderline Viability—An 11-Year Experience

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Abstract

Introduction: Neurodevelopmental outcome of borderline viability neonates have lagged behind improvement in survival figures. Accurate figures based on local outcome allow us to better counsel parents and to prognosticate with greater accuracy on both short- and long-term outcomes. Materials and Methods: A retrospective cohort study of 101 consecutively born neonates, born from 21 to 26 weeks gestation over an 11-year period from 1 January 1994 to 31 December 2005 was conducted. Long-term outcomes were assessed at 2, 5 and 8 years of age in terms of mental developmental index (MDI) or intelligence quotient (IQ) scores, hearing and visual impairments, handicaps and impairments, school placement and interventions required. Results: Survival rates were 20.0%, 60.9%, 70.4% and 73.2% for neonates born at 21 to 23, 24, 25 and 26 weeks gestation respectively. Factors that predicted increased mortality included higher alveolar-arterial oxygen difference ($AaDO_2$) with odds ratio (OR) 1.005 and lower birth weight OR 0.993. Rates of severe retinopathy of prematurity (ROP) (stage 3 or worse) were 100%, 57.1%, 42.1% and 26.7% for 21 to 23, 24, 25 and 26 weeks gestation respectively. Rates of bronchopulmonary dysplasia (BPD) were 100.0%, 57.1%, 63.2% and 60.0% respectively. Rates of severe intraventricular haemorrhage (IVH) were 0%, 7.1%, 5.3% and 10.0% respectively. Moderate to severe disability rates at 2 years old were 100%, 44.4%, 33.3% and 30.4% respectively. At 5 years old, moderate to severe disability rates were 16.7%, 22.2% and 14.3% respectively for those born at 24, 25 and 26 weeks gestation. Interpretation at 8 years was limited by small numbers. Conclusion: Our results indicated that local figures for mortality and morbidity remained high at the limits of viability, although they were comparable to outcomes for large scale studies in advanced countries.

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Key words: Borderline viability, Extremely low birth weight (ELBW), Extremely low gestational age, Neurodevelopmental outcomes, Very low birth weight (VLBW)

Introduction

Singapore was listed consistently among the top 3 countries in the world with the lowest infant mortality rate.[1] In particular, Asia had seen its infant mortality rate improve dramatically with time. Advances in perinatal care had however, failed to improve the survival of extremely low birth weight infants of gestation age ≤26 weeks in recent years.[2] Decision-making about the treatment for neonates at the threshold of viability is a complex process that involves the physicians, other health care professionals and the family.

The definition of borderline viability is generally accepted as being gestation of 23 to 25 weeks.[3] Globally, the neurodevelopmental outcome of borderline viability neonates had lagged behind improvement in survival figures.[4] Although each neonatal unit has its own resuscitation guidelines at the limits of viability, accurate figures based on experience and outcome data are necessary before these guidelines can be formed. Such figures also allow us to better counsel parents and to prognosticate with greater accuracy on both short- and long-term outcomes.

Aim of Study

The aim of our study was to conduct a review on the outcome of borderline viability neonates in our centre, in

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terms of both short- and long-term mortality and morbidity. This would include neurodevelopmental outcomes at 2, 5 and 8 years of age. Our hypothesis was that borderline viability gestation neonates, defined as 25 weeks and below had worse outcomes compared to a 26 weeks gestation comparison group. Primary outcome was survival and secondary outcomes included hyaline membrane disease (HMD), patent ductus arteriosus (PDA), PDA requiring ligation, sepsis, rate of intubation, significant metabolic acidosis, bronchopulmonary dysplasia (BPD), severe intraventricular haemorrhage (IVH), severe retinopathy of prematurity (ROP), 2-year disability (moderate-severe), 5-year disability (moderate-severe) and 8-year disability (moderate-severe).

Materials and Methods

The outcome for our neonates at borderline viability from our centre in Singapore over an 11-year period starting from 1 January 1994 to 31 December 2005 was reviewed. Our centre is one of 3 public Level 3 neonatal intensive care unit (NICU) in Singapore, which together, managed the vast majority of borderline viability neonates in the nation. These children were followed up till 8 years of age, with scheduled assessments at 2, 5 and 8 years old by child psychologists.

Our inclusion criteria included all liveborn neonates born 26 weeks gestation post-menstrual age (PMA) and below from 1 January 1994 to 31 December 2005. Although the definition of borderline viability was generally accepted as being gestation of 23 to 25 weeks, we also collected 26 weeks gestation neonates as a comparison group for the borderline viability neonates. This retrospective cohort study was carried out on 101 consecutively born neonates. All short- and long-term outcome data was collected prospectively in our departmental very low birth weight (VLBW) database as part of our departmental statistics collection.

Gestation age by weeks by last menstrual period or early ultrasound dating was counterchecked with Dubowitz or new Ballard scoring for all babies post-delivery. Where Dubowitz or Ballard scoring differed by more than 2 weeks from the last menstrual period and in the absence of early dating scans, the Dubowitz or Ballard scored gestation age was taken. This was consistently and rigorously applied throughout the entire period of study.

Definitions

Severe IVH was defined as Papile's grade 3 and 4 IVH.[5] Cranial ultrasound was done twice a week for the first 2 weeks of life and weekly subsequently, unless abnormalities discovered required more frequent scans. Periventricular leukomalacia (PVL) was defined as cranial ultrasound findings of periventricular white matter injury denoted by presence of cysts with or without the presence of echodensities. Severe ROP was defined as stage 3, 4 or 5 ROP. This was screened by an opthalmologist at 6 weeks of life or 34 weeks PMA, whichever was earlier. Subsequent reviews were at 1 to 2 weekly intervals. Culture proven sepsis was defined as blood culture proven sepsis during the course of initial hospitalisation. Bronchopulmonary dysplasia (BPD) was defined as oxygen requirement at 36 weeks PMA. Significant metabolic acidosis was defined by base excess worse than –10 within the first 96 hours of life. Prolonged rupture of membranes (PROM) was defined as rupture of membranes for less than 24 hours before delivery. Necrotising enterocolitis (NEC) was diagnosed based on Bell's criteria.

Cerebral palsy was a heterogeneous group of non-progressive clinical syndromes that was characterised by motor and postural dysfunction. These conditions, which range in severity, were due to abnormalities of the developing brain resulting from a variety of causes. Diagnosis was based on clinical assessment by developmental paediatricians following up the patients.

Visual impairment was defined as any child with visual refractive errors with or without amblyopia, while blindness was defined as visual acuity <6/60 or central visual field <20°. Hearing impairment was defined as any child screened with hearing loss requiring the use of hearing aids. All neonates were screened with otoacoustic emission (OAE) and automated auditory brainstem response (AABR) before discharge.

During the study period, our departmental resuscitation guidelines were as follows: all newborns of gestation more than or equal to 24 weeks gestation and/or 500 g would be resuscitated unless parental objections were present. For neonates less than 24 weeks gestation, a joint decision after discussion with the parents would decide on the resuscitation status, subject to the assessment at birth of clinical features of viability, e.g. eyes are not fused, skin is not jelly-like, degree of maceration.

All patients were followed routinely by developmental paediatricians till 8 years old at 4 monthly intervals in the first year, 6 monthly intervals in the second year and subsequently at yearly intervals. Psychological assessments were performed at 2, 5 and 8 years old by trained child psychologists. Multi-disciplinary intervention was instituted when deemed necessary by doctors or child psychologists. Psychological assessment for mental development index (MDI) or intelligence quotient (IQ) scores was carried out at 2 years (corrected age) using Bayley Scales of Infant Development (BSID), at 5 years (chronological age) using Stanford Binet Intelligence Scale (SBIS) 4th edition, and at 8 years using Wechsler Intelligence Scale for Children

(WISC-IV). Special schools were defined as Movement for the Intellectually Disabled Special Education Schools (MINDS) and Educational Subnormal Special Schools (ESN).

All information was analysed using SPSS version 11. Continuous variables were expressed as median and range. Statistical significance was determined by using χ^2 for categorical data and Mann Whitney test for continuous data. Statistical analysis was performed by comparing across each individual gestation group categories (≤23 weeks, 24 weeks, 25 weeks and 26 weeks) and also by pooling borderline viability (25 weeks and below) and comparing against the 26 weeks comparison groups. Comparisons of binary outcomes were also analysed using logistic regression as appropriate. This study was approved by the Institution Review Board.

Results

One hundred and one consecutive live neonates less than or equal to 26 weeks gestational age admitted to the NICU were included (Fig. 1). No neonate had any major malformations or signs of intrauterine infection. Follow-up data from outpatient records were collected till 31 December 2005. At the time of the study conclusion, only 53 had reached 2 years old, only 36 had reached 5 years old and only 25 had reached 8 years. There were 3 patients at 21 weeks, 2 at 22 weeks and 5 at 23 weeks gestation, making a total of 10 at 23 weeks and below. The median birth weight for borderline viability neonates (≤25 weeks) was 665 g (range, 415 g to 870 g) versus 835 g (range, 415 g to 1075 g) in 26 weeks gestation. In our borderline viability cohort, there were no livebirths of neonates which were small for gestational age, reflecting the importance of birth weight on survival. There was a disproportionate ratio of multiple pregnancies at these gestations, ranging from 30.4% to 70%. All baseline risk factors as summarised in Table 1 were not statistically significant across the gestations except for birth weight and mode of delivery. There were more caesarean sections for lower gestational ages.

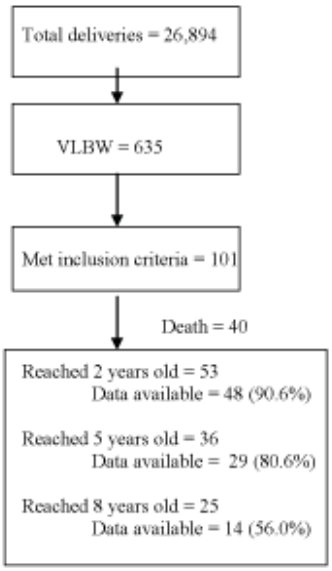

Fig. 1. A patient flow diagram.

Neonatal mortality and hospitalisation duration for survivors were summarised in Table 2. Statistical significance was found between gestation and the primary outcome of survival rate ($P = 0.031$). No statistical significance was found for median day of death, median corrected age by gestational week at discharge among survivors or duration of hospital stay or duration of NICU stay. All deaths occurred within the first 40 days of life. The majority of mortality occurred within the first 7 days of life, as could be seen from the median day of death. Mortality was particularly concentrated within the first 3 days of life.

Logistic regression was performed among the entire cohort comparing causes of mortality and taking into account birth weight, gestation, race, sex, mode of delivery, multiple births, maternal pre-eclampsia/PROM/diabetes mellitus (DM)/antenatal steroids, significant metabolic acidosis, hypothermia, HMD, need for surfactant, need for intubation, alveolar-arterial oxygen difference ($AaDO_2$), airleaks, PDA requiring treatment, septicaemia, NEC, severe IVH. Statistically significant factors that affected mortality include

- $AaDO_2$ OR 1.005 (95% CI, 1.002 to 1.009) $P = 0.007$
- Birth weight OR 0.993 (95% CI, 0.988 to 0.998) $P = 0.006$

Tables 3 and 4 compared outcomes during hospitalisation. Comparing 25 weeks and below together and against the 26 weeks gestation neonates (i.e. <25 weeks vs 26 weeks), significance was found in terms of metabolic acidosis ($P = 0.002$) and PDA requiring ligation ($P = 0.048$). PDA ligation rates generally reduced with increasing gestational age. No statistical significance was found in the secondary outcomes of HMD, PDA requiring treatment and sepsis.

Intubation rate was high among our cohort, ranging from 88% to 100%. All neonates 24 weeks or less were intubated. If we group 25 weeks and below together and compare against the 26 weeks gestation for the rate of intubation, this was statistically significant ($P = 0.044$). Comparing across gestational groups in Table 4, the duration of intubation had a tendency towards significance ($P = 0.066$). There

Table 1. Baseline Characteristics

Gestation (Number, N)	<23 weeks (10)	24 weeks (23)	25 weeks (27)	26 weeks (41)
Birth weight, median (range)*	518 (415 to 650)	665 (530 to 745)	710 (460 to 870)	835 (415 to 1075)
Race ratio (Chinese : Malay : Indians : Others)	5 : 3 : 2 : 0	18 : 3 : 1 : 1	18 : 6 : 0 : 3	27 : 6 : 2 : 6
Male gender, N (%)	5 (50.0)	12 (52.2)	12 (44.4)	22 (53.7)
SGA, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	6 (14.6)
LGA, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)
Mode of delivery ratio (NVD : LSCS : Others)	4 : 0 : 1	8 : 9 : 6	8 : 16 : 3	8 : 8 : 25
Multiple pregnancy, N (%)	7 (70.0)	7 (30.4)	13 (48.1)	13 (31.7)
Antenatal steroids, N (%)	8 (80.0)	16 (69.6)	20 (74.1)	29 (70.7)
Maternal diabetes/gestational diabetes, N (%)	1 (10.0)	4 (17.4)	2 (7.4)	4 (9.8)
Maternal APH, N (%)	0 (0.0)	4 (17.4)	6 (22.2)	10 (24.3)
IVF, N (%)	0 (0.0)	4 (17.4)	4 (14.8)	6 (14.6)
PROM, N (%)	7 (70.0)	9 (39.1)	15 (55.6)	17 (41.5)
Maternal clinical chorioamnionitis, N (%)	3 (30.0)	8 (34.8)	8 (29.6)	9 (22.0)
Maternal PIH, N (%)	0 (0.0)	0 (0.0)	2 (7.4)	8 (19.5)

*P <0.05

APH: Antepartum haemorrhage; IVF: In vitro fertilisation; LGA: Large for gestation age; LSCS: Lower segment caesarean section; NVD: Normal vaginal delivery; PIH: Pregnancy induced hypertension; PROM: Prolonged rupture of membranes; SGA: Small for gestational age

Table 2. Neonatal Mortality and Hospitalisation Duration for Survivors

Gestation (Number, N)	<23 weeks (10)	24 weeks (23)	25 weeks (27)	26 weeks (41)
Survival rate, N, (% [95 % CI]) *(primary hospital)	2 (20 [4.6 to 52.1])	14 (60.9 [40.7 to 77.9])	19 (70.4 [51.4 to 84.3])	30 (73.2 [57.9 to 84.4])
Median day of death (range)	1 (1, 23)	3 (1, 40)	6.5 (1, 18)	2 (1, 17)
Median corrected age by gestational week at discharge among survivors (range)	41.5 (40, 43)	43 (40, 78)	40 (36, 50)	40 (34, 59)
Days of hospitalisation among survivors (range)	134 (125, 143)	137.5 (112, 376)	110 (74, 180)	102 (58, 234)
Days of NICU stay among survivors (range)	103 (99, 107)	93 (74, 209)	80 (58, 164)	64 (31, 127)

*Small for gestational age (SGA) confidence interval calculated by modified Wald method

CI: Confidence interval; NICU: Neonatal intensive care unit

Table 3. Neonatal Outcome During Primary Hospitalisation

Gestation (Number, N)	<23 weeks (10)	24 weeks (23)	25 weeks (27)	26 weeks (41)
1st pH within 1st hour of life	7.35 (6.99 to 7.52)	7.31 (6.77 to 7.55)	7.31 (6.95 to 7.53)	7.37 (6.77 to 7.62)
Significant metabolic acidosis, N (%)*	9 (90.0)	17 (73.9)	15 (55.6)	14 (34.1)
HMD (%)	6 (60.0)	19 (82.6)	19 (70.4)	26 (63.4)
Surfactant rate, N (% among HMD)†	5 (83.3)	13 (68.4)	13 (68.4)	24 (92.3)
Hypotension requiring inotrope, N (%)	10 (100.0)	20 (87.0)	21 (77.8)	31 (75.6)
PDA requiring treatment, N (%)	5 (50.0)	16 (69.6)	18 (66.7)	27 (65.9)
PDA ligation rate, N (% among PDA)‡	2 (40.0)	6 (37.5)	4 (22.2)	1 (4.9)
Hypoglycaemia, N (%)	4 (40.0)	10 (43.5)	18 (66.7)	16 (39.0)
Sepsis, N (%)§	3 (30.0)	6 (26.1)	5 (18.5)	8 (19.5)

*Defined as base excess worse than –10 within the first 96 hours of life

†Proportion of babies with surfactant administered among all with HMD

‡Proportion of babies with PDA ligation among all with PDA

§Blood culture positive sepsis during the course of primary hospitalisation, including both congenital and nosocomial sepsis

HMD: Hyaline membrane disease; PDA: Patent ductus arteriosus

Table 4. Neonatal Ventilatory Requirements Among Those Intubated During Primary Hospitalisation

Gestation (Number, N)	<23 weeks (10)	24 weeks (23)	25 weeks (27)	26 weeks (41)
Intubation rate, N (%)	10 (100.0)	23 (100.0)	26 (96.3)	36 (87.8)
Median MAP (range)*	11.0 (6, 17)	8.3 (4, 17)	6.4 (4, 16)	7.0 (4, 16)
Median PiP(range)*	24.9 (13, 41)	17.5 (12, 32)	16.5 (12, 35)	17.0 (11, 35)
Median FiO_2 (range)*	71.0 (22, 100)	40.0 (22, 100)	25.5 (21, 94)	30.0 (22, 100)
Median $AaDO_2$ (range)*	315 (33, 522)	174 (52, 578)	155.5 (9, 561)	207 (1, 591)
Median number of days intubated among survivors (range)†	53.5 (39, 68)	37 (2, 81)	22 (0, 67)	5.5 (0, 97)
Median number of days on CPAP among survivors (range)	46 (28, 64)	49 (24, 101)	47 (20, 75)	48.5 (1, 79)
Median number of days on oxygen among survivors (range)	95.5 (86, 105)	70.5 (24, 101)	47 (10, 149)	40 (0, 177)

*All respiratory data calculated as average within 1st week of life; $AaDO_2$ ratio as defined as (713 x FiO_2) – (pCO_2/0.8) – (paO_2) within 1st day of life

†$P = 0.066$

$AaDO_2$: Alveolar-arterial oxygen difference; CPAP: Continuous positive airway pressure; FiO_2: Oxygen concentration (in %); MAP: mean airway pressure (in cm H_20); PiP: Peak inspiratory pressure, positive inspiratory pressure (in cm H_20)

Table 5. Inpatient Morbidity Among Survivors

Gestation (Number, N)	<23 weeks (2)	24 weeks (14)	25 weeks (19)	26 weeks (30)
ROP, N (%)	2 (100)	13 (92.9)	18 (94.5)	19 (63.3)
Severe ROP, N (%)*	2 (100)	8 (57.1)	8 (42.1)	8 (26.7)
ROP requiring treatment, N (%)	2 (100)	9 (64.2)	2 (10.5)	5 (16.7)
BPD, N (%)	2 (100)	8 (57.1)	12 (63.2)	18 (60.0)
BPD requiring dexamethasone, N (%)	0	5 (35.7)	7 (36.8)	7 (23.3)
IVH, N (%)	1 (50)	5 (35.7)	5 (21.1)	8 (26.7)
Severe IVH, N (%)	0	1 (7.1)	1 (5.3)	3 (10.0)
White matter changes, N (%)†	1 (50)	2 (14.3)	2 (10.5)	3 (10.0)

*Defined as stage 3 or worse ROP

†Defined as cysts, ventriculomegaly or echogenicity

BPD: Bronchopulmonary dysplasia; IVH: Intraventricular haemorrhage; ROP: Retinopathy of prematurity

Table 6. Outcome at 2 Years Old

Gestation	<23 weeks	24 weeks	25 weeks	23 to 25 weeks	26 weeks
Number reached 2 years old	1	10	17	28	25
Follow-up, N (rate %)	1 (100)	9 (90)	15 (88.2)	25 (89.3)	23 (92)
Epilepsy, N (%)	0	1 (11.1)	1 (6.7)	2 (8.0)	1 (4.3)
CP, N (%)	1 (100)	1 (11.1)	1 (6.7)	3 (12.0)	3 (13.0)
Visual impairment, N (%)	0	5 (55.6)	5 (33.3)	10 (40.0)	7 (30.4)
Hearing impairment, N (%)	0	0	2 (13.3)	2 (8.0)	0
Disability (moderate-severe), N (%)	1 (100)	4 (44.4)	5 (33.3)	10 (40.0)	7 (30.4)
Disability (severe), N (%)	1 (100)	4 (44.4)	4 (26.7)	9 (36.0)	6 (26.1)
EIP, N (%)	1 (100)	3 (33.3)	2 (13.3)	6 (24.0)	4 (17.3)
Median corrected age at MDI	27	28 (27, 29)	27 (24, 29)	27 (24, 29)	27 (24, 29)
MDI <70, N (%)	1 (100)	3 (33.3)	2 (13.3)	6 (24.0)	5 (21.7)
Median MDI	50	88 (50, 108)	88 (50, 117)	88 (50, 117)	83 (50, 114)

*Percentage in brackets indicate percentage with denominator as followed-up patients

CP: Cerebral palsy; EIP: Early intervention programme; MDI: Mental development index

Table 7. Outcome at 5 Years Old

Gestation	24 weeks	25 weeks	24 to 25 weeks	26 weeks
Number reached 5 years old	8	11	19	17
Follow-up rate, N (%)	6 (75)	9 (81.8)	15 (78.9)	14 (82.4)
Epilepsy, N (%)	1 (16.7)	1 (11.1)	2 (13.3)	1 (7.1)
CP, N (%)	1 (16.7)	1 (11.1)	2 (13.3)	2 (14.3)
Visual impairment, N (%)	5 (83.3)	6 (66.7)	11 (73.3)	4 (28.6)
Hearing impairment, N (%)	0	1 (11.1)	1 (6.7)	0
Disability (moderate-severe), N (%)	1 (16.7)	2 (22.2)	3 (20.0)	4 (28.6)
Disability (severe), N (%)	1 (16.7)	2 (22.2)	3 (20.0)	2 (14.3)
Special schools (ESN/MINDS), N (%)	0	1 (11.1)	1 (6.7)	2 (14.3)
Median corrected age at SBIS test in months	60 (59, 61)	60 (58, 69)	60 (58, 69)	60 (51, 63)
IQ <70, N (%)	0	1 (11.1)	1 (6.7)	2 (14.3)
Median IQ	94 (78, 119)	92 (59, 107)	93 (59, 119)	94 (50, 119)

No survivors at this age for gestation <23 weeks

*Percentage in brackets indicate percentage with denominator as followed-up patients

CP: Cerebral palsy; ESN: Educational Subnormal Special Schools; MINDS: Movement for the Intellectually Disabled Special Education Schools; SBIS: Stanford Binet Intelligence Scale

Table 8. Outcome at 8 Years Old

Gestation	24 weeks	25 weeks	24 to 25 weeks	26 weeks
Number reached 8 years old	6	8	14	11
Follow-up rate, N (%)	3 (50)	7 (87.5)	10 (71.4)	4 (36.4)
Epilepsy, N (%)	0	1 (14.3)	1 (10.0)	0
CP, N (%)	0	0	0	2 (50.0)
Visual impairment, N (%)	2 (66.7)	5 (71.4)	7 (70.0)	2 (50.0)
Hearing impairment, N (%)	0	0	0	1 (25.0)
Disability (moderate-severe), N (%)	0	1 (14.3)	1 (10.0)	2 (50.0)
Disability (severe), N (%)	0	0	0	0
Median corrected age at WISC test in months	96 (95, 97)	98 (96, 102)	96.5 (95, 102)	96 (96, 97)
IQ <70	0	0	0	0
Median IQ	97 (95, 102)	100 (87, 109)	98.5 (87, 109)	105.5 (90, 121)

No survivors at this age for gestation <23 weeks

*Percentage in brackets indicate percentage with denominator as followed-up patients

CP: Cerebral palsy; IQ: Intelligence quotient; WISC: Wechsler Intelligence Scale for Children

Table 9. Survival

Survival %	Study cohort (n = 60)*	UK EPICure (n = 811)[9] (EPICure 2) (n = 1351)[10]	French Epipage* (n = 558)[11]	USA NICHD (n = 4160)*[12]	Belgium Epibel (n = 175)*[13]	World review* (n = 5578)[14]
≤23 weeks	20.0 %	9.1% to 19.9 % (0 to 18%)	16% to 22 %	6% to 26 %	0 to 5.5 %	0 to 41 %
24 weeks	60.9 %	33.6 % (41 %)	37 %	55 %	29.2 %	16% to 70 %
25 weeks	70.4 %	52.1 % (63%)	58 %	72 %	55.5 %	44% to 85 %

% refers to % of total livebirths

*Number of livebirths ≤25 weeks gestation

NICHD: National Institute of Child Health & Human Development; UK: The United Kingdom; USA: The United States of America

were no statistical significance in terms of the secondary outcomes of ROP, severe ROP, ROP requiring treatment, BPD, BPD requiring steroids, IVH, severe IVH or white matter changes.

Tables 6, 7 and 8 showed the outcomes at ages 2, 5 and 8 years old respectively. A disability was defined as 'severe' if it was considered likely to make the child highly dependent on caregivers and if it included non-ambulant cerebral palsy, an IQ score more than 3 SD below the mean (IQ <70), profound sensorineural hearing loss, or blindness. A disability was defined as 'moderate' if reasonable independence was likely to be reached and if it included ambulant cerebral palsy, an IQ score 2 to 3 SD below the mean (IQ range, 70 to 84), sensorineural hearing loss that was corrected with a hearing aid, and impaired vision without blindness. 'Mild' disability included neurologic signs with minimal functional consequences or other impairments such as squints or refractive errors.[6,7]

Follow-up rates were good at 2 years old, ranging from 88% to 100%, with an overall of 90.6% and at 5 years old ranging from 75% to 82%, with an overall of 80.6%. No statistical significance was found at 2 years and 5 years old in the rates of epilepsy, cerebral palsy, visual impairment, hearing impairment, moderate to severe disability, severe disability, need for early intervention or requirement for special schools and median mental development index (MDI)/IQ.

There was a non-statistically significant positive trend towards better outcome with increasing gestation in terms of disability rates. This pattern was seen at both 2 years and 5 years. Follow-up rates had dropped by 8 years old to 36% to 88%. Overall follow-up rate was 56%. No statistical significance was found in terms of the rates of epilepsy, cerebral palsy, visual impairment, hearing impairment, moderate to severe disability, severe disability and median IQ.

Discussion

Many reports on borderline viability outcomes previously reported outcomes based on birthweight, but gestational age outcomes were more valuable for prenatal counselling and physician or family decision-making. This was because prenatal estimation of estimated fetal weight was often inaccurate, and obstetricians, neonatologists and families often need to fall back on gestation to make decisions prenatally. The decision whether to provide active obstetric care and initiate neonatal intensive care for these borderline viability newborns remained controversial, especially at the lower limits at 23 weeks gestation and lower.

There was a decline in VLBW, (as defined by birth weight <1500 g) infant mortality rates in the United States in the 1980s and early 1990s. However, subsequent studies in the National Institute of Child Health & Human Development (NICHD) studies had failed to demonstrate further reduction in neonatal morbidity and mortality. In the EPICure 2 studies from the United Kingdom (UK), improvement in survival in the early to mid 2000s as compared to the 1990s were in babies with gestation of 24 weeks and above. As the proportion of delivery room deaths remained the same in the EPICure compared to EPICure 2 series, this indicated that the improvements in survival was likely due to improvement in NICU care standards.

Current literature confirmed that mortality and morbidity improved significantly with each additional gestational week in the borderline viability period. Each additional week of gestation at birth had substantial survival advantage with the most marked changes between 22 and 25 weeks. Survival rates increased from 6% to 72% in the NICHD study series.

Although the rate of survival at such borderline viable gestations could be affected by the aggressiveness of obstetric and neonatal care, the Swedish experience was important as they showed that, even with a policy of resuscitating every baby and almost never withdrawing life support, and majority of the babies at 23 weeks still died. Thirty percent of the babies born at 23 weeks died before 7 days, 20% died between 7 and 28 days of age and 10% died after 28 days. All infants with any signs of life were actively resuscitated and brought to the NICU. Decisions to withdraw respiratory care were avoided during the first days of life and subsequent withdrawal of intensive care was rare.[8]

Table 9 summarised the survival figures across different landmark studies.[9-14] Our figures for survival were comparable with world literature and with large cohorts with livebirths as denominator, such as the NICHD studies, of the same era between the 1990s till mid 2000s. However, our numbers were too small to provide any meaningful segregation between the 1990s, as compared to the early 2000s. Consistent with common trends, our study demonstrated substantial survival advantage at these borderline viability gestations with each additional gestation age. In our cohort, this increase in survival was as remarkable as our comparison cohorts, increasing from 20% to 70.4%.

In order to interpret the outcome measures in our local setting as compared to international studies, it is necessary to take into account the following factors: (i) difference in baseline incidence of prematurity; (ii) single or multicentre versus national outcomes; (iii) resuscitation guidelines, neonatal and obstetric care; (iv) stillbirths, resuscitation room deaths and other pitfalls; (v) pitfalls in measuring short- and long-term outcomes; and (vi) the number of study subjects.

1. Difference in Baseline Incidence of Prematurity

Starting from the overall incidence of prematurity between nations, of which borderline viability formed only a small proportion, the United States had an incidence of prematurity of 12.7% of all livebirths, of which 2% of all livebirths were less than 32 weeks gestation.[15] The local incidence of prematurity for Singapore was comparable at 10% to 12% in the 2000s.[16]

In addition, ethnicity may have an impact on survival in preterms. It was found that in the United States, Asian/Pacific Islanders subgroup had the lowest 2006 preterm-related infant mortality rates at 1.49 per 1000 live births compared to the national average of 2.42 per 1000 livebirths. This was compared to non-Hispanic blacks who had 6.01 per 1000 livebirths.[17]

To date, there had been no local published national statistics showing the number of preterm liveborns at borderline viability for Singapore. For purposes of comparison of incidence with other countries, we compared the figures for extremely low gestation age, defined as <27 weeks. The rate of extremely low gestation birth in our cohort was 3.8 births per 1000 infants. This was higher than Sweden's at 2.3 births per 1000 infants but lower than the United States NICHD study's approximately 10 per 1000.[9] The authors in the NICHD study postulated that the 5-fold difference in incidence may be explained by Sweden's universal health insurance, with free prenatal care and associated social services, as well as an ethnically more homogeneous and somewhat older pregnant maternal population.

However, this was bearing in mind that ours was a single centre study with possible selection bias and not a national study, and we were a high-risk tertiary centre accepting high risk deliveries from other centres, both antenatal and postnatally, and from both public as well as private healthcare facilities. The referrals to our institution included mothers with complex medical conditions such as those requiring dialysis, which require tertiary multi-disciplinary adult medical or surgical specialty input.

2. Single or Multicentre Versus National Outcomes

Single institution or multicentre studies may include inborn or outborn infants and were subject to changes in referral pattern. It had been shown that single centre studies generally have better morbidity and mortality outcomes, perhaps reflecting a bias towards academic institutions.[14] Centralising of care towards a few academic centres generally confer better outcomes. Publication bias from academic institutions may also play a role. Some centres use within-institution data of inborn infants or NICU admissions for counselling parents about the prognosis of infants who were likely to deliver in their institution and for purposes of annual audit.

3. Resuscitation Guidelines, Neonatal and Obstetric Care

Aggressiveness of resuscitation guidelines may vary between centre to centre, and between countries as well. Subsequent pro-active versus selective neonatal care would also impact on mortality and morbidity. For instance, a population cohort of all preterm infants born at gestation of <27 weeks in Sweden from 2004 to 2007 demonstrated survival rates higher than rates reported for other countries or reported previously in Sweden due to pro-active neonatal care. On the other hand, some centres in the large national studies reported no survival below and at 23 weeks gestation, possibly reflecting obstetric and neonatal practices there.

Our institution's resuscitation guidelines followed the 'Ethical Guidelines for Treatment of High Risk Infants' by the National Ethics Committee.[18] Through a process of communication and value exploration between parents and physicians, the goal is to reach a consensual decision with the best interests of the infant placed in the centre of the analysis.[19] From an international point of view, there is the general agreement that at 22 weeks, there is no hope of survival for the foetus/neonate. Week 22 0/7 to 22 6/7 is considered to be the cut-off of human viability. No scientific society recommends performing any kind of active treatment on the mother that is aimed at protecting the foetus or on the newborn except for offering compassionate care. A general agreement is also evident for week 25. Antenatal steroids are recommended, prenatal transport and caesarean section are also indicated to protect the foetus, and resuscitation is offered to all infants without fatal anomalies.[20] Weeks 23 to 24 were the gray zone internationally. In our centre almost all infants of 24 weeks gestation were considered candidates for resuscitation and intensive care, while those at gestation of 23 weeks were counselled regarding outcome and risks, with resuscitation and intensive care depending on parental wishes.

4. Stillbirths, Resuscitation Room Deaths and Other Pitfalls

The comparison between different studies may also be affected by the difference in denominators used. The comparison cohorts between different studies were heterogeneous, with the denominators used for calculating survival varying from all births (livebirths and stillbirths) to livebirths alone or to NICU admissions (inborn or outborn births). Although it is important to account for all births, including delivery room deaths, sometimes they were not included in the denominator of the overall survival figures, even when they were reported. In some studies, delivery room deaths comprised as many as 42% of all births at

25 weeks and younger gestational age. Inclusion of only infants who were resuscitated at birth or who were admitted to the NICU resulted in higher survival rates than would be otherwise. Where both stillbirths and livebirths were included, this might present its own problems as some of the comparison studies did not separate the number of infants between stillbirths and livebirths.

Our study cohort, though including all delivery room deaths, were unable to account for stillbirths, which were not collected. Hence, our denominator was livebirths only. However, most international comparison studies also collected livebirths as the denominator. The EPICure and NICHD studies used livebirths as the denominator, although the EPIBEL and EPIPAGE studies included stillbirths.

In addition, in adherence with World Health Organisation (WHO) norms, gestation should be in terms of number of completed weeks and not rounded up. This was adhered to in our study and also in all comparison studies.

5. Pitfalls in Measuring Short- and Long-term Outcomes

The 3 most commonly internationally reported morbidities and the ones that appear to have the most significant impact on long-term outcomes were: chronic lung disease (CLD), IVH/PVL, and severe ROP. The vast majority of studies of the above neonatal morbidities used survivors as the denominator, as did our study.

However, there were varying international criteria for defining 'severe' and for the reporting of CLD/IVH. CLD was the most prevalent morbidity in the infants, ranging from 13% to 74%, among survivors born at 25 weeks or less gestation, and from 86% to 100% for infants born at 23 weeks or less gestation. As seen in Table 5, our study's incidence of BPD ranged from 60% to 100% depending on gestation, with the incidence at 100% for 23 weeks gestation or less. However, the number of survivors was also small for 23 weeks gestation or less.

Depending on the definition, the reported international rates for grade 3/4 IVH/PVL ranged from 17% to 21%, and up to 42% for those of 23 weeks or less gestation. Our study had separated severe IVH from white matter changes/PVL. Incidence of severe IVH in our cohort ranged from 0% to 10% depending on gestation, while PVL ranged from 10 to 50%. Assuming most centres were using the International Classification of ROP, the prevalence of stage 3/4 ROP was 14% to 32% internationally. In our study, this ranged from 63.3% to 100%, depending on gestation.

Even to date, long-term studies on outcomes of borderline viability neonates remained lacking. This was due to both the cost and time required for long-term follow-up, particularly for ages of 5 years and older. High attrition rates, particularly as time went by, represented a significant issue in such long-term studies. Compliance to follow-up of 80% and higher were generally accepted internationally.[14] Our study cohort had good compliance rate at both 2 and 5 years, but unfortunately this dropped to 56% at 8 years. However, even in large national studies for follow-up, for which the EPICure represented the most comprehensive, at ages of above 6 years, the patients from all borderline viability gestations were all pooled together, likely due to loss of follow-up and small numbers. Table 10 is a comparison of long term outcomes with the Epicure study.

In addition, there was no consensus internationally in the type of psychological tests to use, or in the age of assessment for neurodevelopmental outcome. The EPICure study used Kaufmann Assessment Battery for Children-Mental Processing Composite (K-ABC MPC) score, while we used the Stanford Binet Intelligence Scale (SBIS) at 5 years and Wechsler Intelligence Scale for Children (WISC) at 8 years.

Table 10. Comparison of Long-Term Outcomes

	Study cohort*	**EPICure**
	Moderate-severe disability (at 2 years old)	**Moderate-severe disability (at 30 months old)**
≤23 weeks	100 %	27 %
24 weeks	44.4 %	30 %
25 weeks	33.3 %	30 %
	MDI <70 (at 2 years old)	**MDI<70 (at 30 months old by Bayley's)**
≤23 weeks	100 %	27 %
24 weeks	33.3 %	30 %
25 weeks	13.3 %	30 %
	Moderate-severe disability (at 5 years old)	**Moderate-severe disability (at 6 years old)**
≤23 weeks	-	63 %
24 weeks	16.7 %	51 %
25 weeks	22.2 %	40 %
	IQ <70 (at 5 years old by SBIS)	**IQ <70 (at 6 years old by K-ABC MPC score)**
≤23 weeks	-	25 %
24 weeks	0 %	27 %
25 weeks	11.1%	17 %
	IQ <70 (at 8 years old by WISC-III)	**IQ <70 (at 11 years old by K-ABC MPC score)**
25 weeks and below	0 %	39.7 %

*% of total livebirths

IQ: Intelligence quotient; MDI: Mental developmental index; K-ABC MPC: Kaufmann Assessment Battery for Children-Mental Processing Composite; MDI: Mental development index; SBIS: Stanford Binet Intelligence Scale; WISC: Wechsler Intelligence Scale for Children

We attempted a comparison of outcome at 2 years, 5 years and 8 years with the EPICure Study group, although the ages were not strictly similar. The definitions for disability were the same as our study.

Our comparison was hampered by the low survival rates and numbers, particularly for the ≤23 weeks gestation. In fact, there were no survivors with available test scores at 5 years. However, it was heartening to note that for 25 and 26 weeks, the rate of moderate to severe handicap reduced substantially with gestation. In addition, in our cohort, long-term outcomes improved as they grew older from 2 to 5 years and then finally at 8 years. These were important findings, which were also replicated in other studies.[21] This improvement over time was especially true in those neonates without severe IVH, as shown in the study by Ment et al.[21] Causes which had been postulated included environmental factors such as parental involvement in upbringing, the benefits of school education, early intervention programmes and good follow-up. A study by Farooqi et al[22] for the 23 to 25 weeks cohort born in 1990 to 1992, assessed at 11 years had 21% (18/86) of disability, as defined by moderate or severe cerebral palsy CP, severe visual impairment <6/60 in at least one eye, sensorineural deafness requiring hearing aids or special school.

6. The Number of Study Subjects

The number of study subjects were smaller as the gestation lowers, especially for ≤23 weeks gestation. The interpretation of results should thus be made with caution, taking into account the 95% CI in Table 2. For instance, the 95% CI for survival at ≤23 weeks gestation range from 4.6% to 52.1%.

Our study provided the first published local data on incidence, epidemiology and outcome centred on borderline viability neonates. Previous local studies were centred on birth weight as their inclusion criteria, such as ELBW at <1000 g. There were no small for gestational age (SGA) livebirths for our borderline viability cohort, reinforcing the existing literature that although gestation played the more important role in determining mortality, morbidity and long-term outcome, birth weight also had an important role. For instance, a 27 weeks gestation neonate with small for gestational age SGA may have as poor an outcome as a borderline viability neonate.

The birthweight of our mostly Asian neonates at these gestations were comparable to those of different ethnicity e.g. Caucasian and different nations in the comparison studies. For instance EPICure 23, 24 and 25 weeks gestations had median birth weights of 621 g, 680 g and 770 g. Our study cohort of 23 and below, 24 and 25 weeks gestation had median birth weights of 518 g, 665 g and 710 g.

The timing of the mortality provided useful information on the timing of greatest risk, namely within the first 7 days, and particularly within the first 3 days of life. Other findings in our study included the statistical significance of gestation for survival, which reinforced the importance of this study. In addition, in our logistic regression, $AaDO_2$ and birth weights were found to be significant predictors for survival. All these would provide useful information in the initial period after birth on counselling survival.

Among the statistically significant findings which our study added included the following associations with gestational age in the borderline viability versus the 26 weeks comparison group, included: (i) survival (our primary outcome) and the following secondary outcomes including: (ii) PDA ligation rate, (iii) rate of intubation and (iv) significant metabolic acidosis. These encompass the hemodynamics, respiratory and metabolic aspects of care respectively.

In addition, our study provided the first gestation specific long-term outcome at 2 and 5 years, useful for neurodevelopmental counselling. Our figures for 24 and 25 weeks were comparable to the EPICure cohort, although our numbers were small. Our study provided some markers on the healthcare costs involved in the care of these high risks neonates, in terms of morbidity, length of hospitalisation stay and length of NICU stay.

Finally, the poor survival figures at 23 weeks gestation and below, though comparable to international figures, provided justification for our current practice, which was to actively manage 24 weeks gestation and above, and counsel parents regarding the high risk at 23 weeks, and come to a joint decision on resuscitation and NICU care.

We acknowledge the limitation of our data, with small numbers in a single centre. Although follow-up rates were good at 2 and 5 years old, this had dropped off at 8 years due to the prolonged follow-up period. Data were also limited especially for the smallest gestational age of 23 weeks and below. In addition, the rates of stillbirths or intrauterine deaths were not collected.

Conclusion

The management of the borderline viability neonate remains a challenge. Review of the outcome provided justification for our current management, which was consistent with international recommendations. Prognosis for babies of 23 weeks gestation and below neonates were guarded, while 25 weeks and above justified active obstetric and neonatal management. Parents need to be counselled accordingly, in terms of both survival and morbidity.

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