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Original Article

Outcomes and resource usage of infants born at ≤ 25 weeks gestation in Canada

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ABSTRACT

Objectives: To determine the outcomes and resource usage of infants born at ≤ 25 weeks gestational age (GA).

Methods: Retrospective study of infants born between April 2009 and September 2011 at ≤ 25 weeks' GA in all neonatal intensive care units in Canada with follow-up in the neonatal follow-up clinics. Short-term morbidities, neurodevelopmental impairment, significant neurodevelopmental impairment, and resource utilization of infants born at ≤ 24 weeks were compared with neonates born at 25 weeks.

Results: Of 803 neonates discharged alive, 636 (80.4%) infants born at ≤ 25 weeks' GA were assessed at 18 to 24 months. Caesarean delivery, lower birth weight, and less antenatal steroid exposure were more common in infants born ≤ 24 weeks as compared with 25 weeks. They had significantly higher incidences of ductus arteriosus ligation, severe intracranial hemorrhage, retinopathy of prematurity as well as longer length of stay, central line days, days on respiratory support, days on total parenteral nutrition, days on antibiotics, and need for postnatal steroids. Neurodevelopmental impairment rates were 68.9, 64.5, and 55.6% ($P=0.01$) and significant neurodevelopmental impairment rates were 39.3, 29.6, and 20.9% ($P<0.01$) for infants ≤ 23, 24, and 25 weeks GA, respectively. Postdischarge service referrals were higher for those ≤ 23 weeks. Nonsurviving infants born at 25 weeks GA had higher resource utilization during admission than infants born less than 25 weeks.

Conclusions: Adverse outcomes and resource usage were significantly higher among infants born ≤ 24 weeks GA as compared with 25 weeks GA.

Keywords: *Neurodevelopment; Periviable; Prematurity*

Preterm infants, born less than 37 weeks' gestational age (GA), are among the highest cost users in any health care system (1). In Canada, the preterm birth rate is approximately 8%, which poses a significant burden on the health care system (2,3). Advances in obstetrical and neonatal care have improved survival rates of extremely preterm (≤25 weeks GA) infants and in Canada, the survival rates among admissions, excluding delivery room deaths, of ≤ 22, 23, 24, and 25 weeks GA have improved to 31, 57, 73, and 81% respectively in 2016 (4–6). These infants have the highest morbidity rates among preterm infants, including bronchopulmonary dysplasia (BPD), late-onset sepsis, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and retinopathy of prematurity (ROP) (5,7–12). These extremely preterm neonates are also at risk of

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disability (13–16). Rysavy et al. reported the rate of severe disability among survivors in a cohort of 4,987 infants to be 33, 24.2, 18.5, and 14% in those born at 22, 23, 24, and 25 weeks GA, respectively (17). The higher incidence of both short-term and long-term morbidities requires extensive resources and resource planning.

There are relatively few studies that have reported resource utilization among extremely preterm neonates (≤25 weeks GA). An economic analysis of cost-of-illness studies reported that costs correlated inversely with GA at birth over various periods of follow-up from discharge to 18 years of age, with over $100,000 in United States Dollars (USD) spent for primarily hospitalization per extreme preterm birth < 28 weeks' GA (18). Many of these infants go on to have a disability, which requires ongoing management and resource utilization, the extent of which has not been well elucidated (19). Therefore, the objective of this study is to determine the rates of neonatal morbidities, neurodevelopmental impairment (NDI), significant neurodevelopmental disability, and resource utilization among preterm infants born at ≤ 23, 24, and 25 weeks GA in a national cohort of preterm infants.

METHODS

The Canadian Neonatal Network (CNN) maintains a standardized nationwide neonatal database and includes data from tertiary-level neonatal intensive care units (NICUs) in Canada. Data were abstracted from infant medical records according to standardized definitions (20) and were electronically transmitted to the CNN coordinating centre as previously described (21). Individual data from 28 of the total 30 NICUs in Canada collected from the CNN database were linked to the Canadian Neonatal Follow-Up Network (CNFUN) database using a unique identifier, which contains prospectively collected neurodevelopmental outcomes at 18 to 24 months corrected age (CA) of infants born < 29 weeks GA from 26 CNFUN clinics according to a standardized protocol as previously described (22,23).

Study population

This retrospective cohort study of a prospective cohort included data from preterm infants born at ≤ 25 weeks GA and born at a CNN-affiliated NICU between April 1, 2009 and September 30, 2011 with follow-up information at 18 to 24 months CA. Infants with a major congenital anomaly (20), those who were moribund on admission (comfort care planned at birth), or had missing data on GA were excluded. Infants who died prior to discharge from the NICU were included in a separate analysis. Follow-up data excluded infants that were lost to follow up, or died before discharge or the 18 to 24 follow-up assessment. Infants who received follow up were compared with the infants who were lost to follow up in a separate analysis.

Outcomes

Short-term morbidities measured included patent ductus arteriosus (PDA) ligation, late-onset sepsis as defined by positive blood and/or cerebral spinal fluid culture after the first 2 days of birth (6), severe IVH grade 3 or higher according to the criteria of Papile et al. (24), NEC as defined by Bell's criteria stage 2 or higher (25), BPD defined as need for oxygen at 36 weeks postmenstrual age or at the time of discharge or transfer to level 2 NICUs (26), and severe ROP defined as ≥ stage 3 retinopathy (27) in either eye or receipt of treatment.

Resource utilization was measured as length of stay until discharge from a Level III NICU, duration of central line use, duration of mechanical ventilation, duration of noninvasive ventilation, duration of total parenteral nutrition, and frequency of steroid usage for BPD. Postdischarge from the Level III NICU included the frequency of gavage feeding at follow-up, ileostomy, colostomy, tracheostomy or gastrostomy at follow-up visit. Need for regular medications, re-hospitalization rates, reasons for re-hospitalization, and length of stay in days as determined by patient report were documented. Frequency of referral to services outside of neonatal follow-up including an early intervention program, rehabilitation program, dietitian, occupational therapy, physiotherapy, speech and language services, neurology, and social work were identified.

At 18 to 24 months, CA participants were assessed using a standardized history, physical examination, neurological examination, and the Bayley Scales of Infant and Toddler Development-Third Edition testing (Bayley-III) administered by trained examiners (28). The definition for cerebral palsy (CP) by Bax et al. was used and the Gross Motor Function Classification System (GMFCS) was used to classify the degree of functional impairment in children with CP as defined by Palisano et al. (29,30). Hearing testing results and the need for hearing aids or cochlear implants was obtained from patient history. Vision impairment was determined by ophthalmology follow-up for ROP and if unknown, a vision assessment was performed. A small, scarred eye, sustained sensory nystagmus, or lack of response to a 1cm object on a white background from a distance of 30 cm was deemed as a visual impairment (22). Significant neurodevelopmental impairment (sNDI) was defined as cerebral palsy (CP) with gross motor functional classification scale (GMFCS) ≥ 3 or Bayley composites scores (language, motor, or cognitive) of < 70 or need for cochlear implant or bilateral visual impairment. NDI was defined as CP with GMFCS ≥ 1 or Bayley composite scores (language, motor, or cognitive) of < 85 or sensorineural hearing loss or unilateral or bilateral visual loss.

Statistical analyses

Infants were divided into three groups according to GA: ≤ 23, 24, and 25 weeks GA. Rates of baseline characteristics and outcomes were calculated for each GA group and compared using the Pearson Chi-square for categorical variables. For continuous data, mean (standard deviation) or median (interquartile range) was reported and differences were assessed by analysis of variance or Wilcoxon rank test, respectively. Multivariable logistic regression was used to analyze the association between outcomes and GA. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. In multivariate regression, the model was adjusted for small for GA (birth weight < 10th percentile for GA) (31), sex, receipt of antenatal corticosteroids, outborn status, mode of delivery, site of delivery, and multiple gestation. All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC) and significance was evaluated using two-sided P-values at the 5% testing level.

Ethics

CNN and linked CNFUN data were collected after approval from the local research ethics board or quality improvement committee as appropriate. The study protocol was approved by the CNN and CNFUN steering committees and approved by the research ethics board at Mount Sinai Hospital, Toronto, Canada. Measures were taken to avoid the possibility of patient identification by marking variables as 'not reported (NR)' when there were fewer than five patients in any cell.

RESULTS

A flow diagram of the infants included in the study is shown in Figure 1. Among the 803 survivors, there were 12, 49, and 106 infants born at ≤ 23, 24, and 25 weeks GA respectively that were lost to follow up. Therefore, 636 infants had a CNFUN assessment at 18 to 24 months CA. Primary caregiver, maternal, and infant baseline characteristics are reported in Table 1. There was

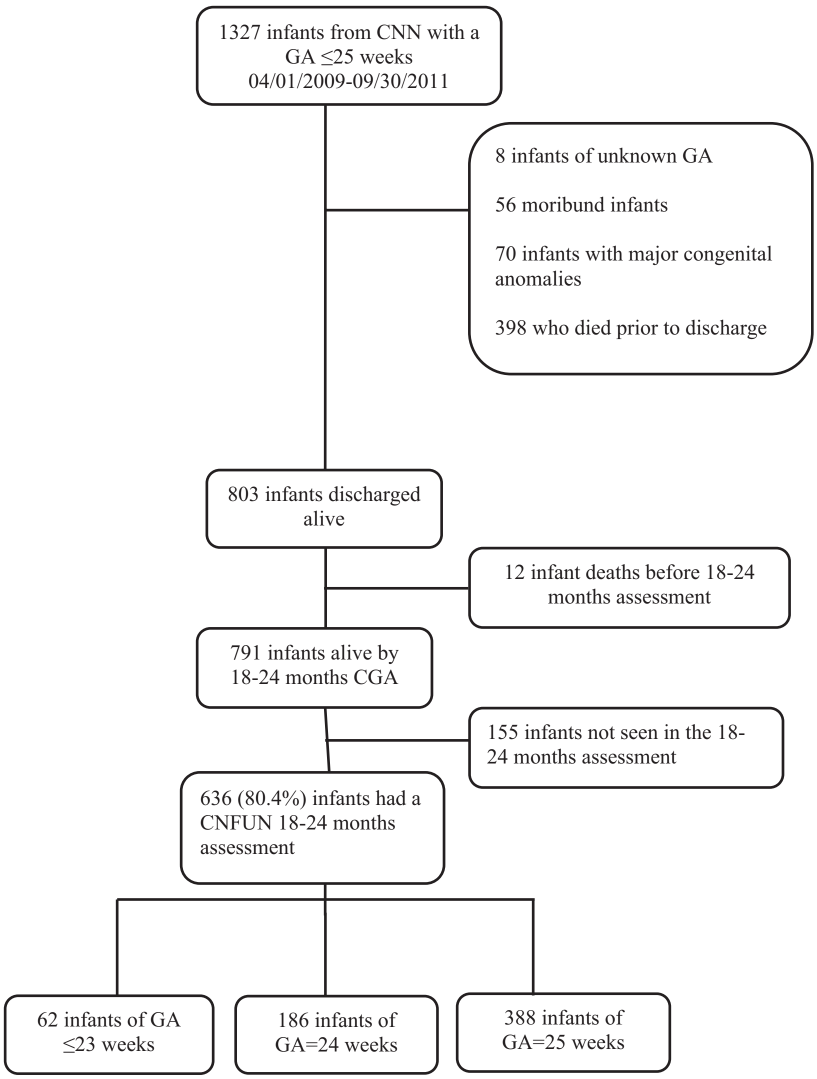

Figure 1. Study participant flow diagram.

Table 1. Maternal and surviving infant characteristics

	≤23 weeks (n=62)	24 weeks (n=186)	25 weeks (n=388)	P-value
Primary caregiver characteristics				
Ethnicity				0.31
Caucasian, n (%)	29 (54)	104 (62)	224 (66)	
Black, n (%)	6 (11)	22 (13)	39 (12)	
Asian/Hispanic/First Nation, n (%)	19 (35)	41 (25)	75 (22)	
Completion of high school, n (%)	45 (85)	153 (89)	330 (93)	0.11
Financial Support				0.79
Paid employment, n (%)	40 (70)	134 (74)	276 (73)	
Social welfare, n (%)	8 (14)	22 (12)	37 (10)	
Maternal baseline characteristics				
Maternal hypertension, n (%)	NR	17 (9.4)	51 (13.4)	0.02
Multiple gestation, n (%)	13 (21)	52 (28)	89 (23)	0.35
Rupture of membranes >24 h, n (%)	14 (24)	37 (20)	88 (23)	0.72
Chorioamnionitis, n (%)	20 (36)	43 (28)	105 (33)	0.43
Caesarean section, n (%)	20 (32)	89 (48)	206 (53)	0.01
Antenatal steroids, n (%)	47 (78)	165 (91)	346 (91)	0.01
Infant characteristics and neonatal outcomes				
Outborn, n (%)	9 (15)	25 (14)	44 (11)	0.66
Birth weight, g mean (SD)	637 (104)	694 (98)	778 (113)	<0.01
Male, n (%)	26 (42)	95 (51)	208 (54)	0.23
Small for gestational age[a], n (%)	0 (0)	8 (4)	14 (4)	0.3
Apgar <7 at 5 min, n (%)	38 (61)	97 (53)	163 (42)	<0.01
Neonatal outcomes				
Late-onset sepsis, n (%)	32 (52)	89 (48)	148 (38)	0.03
Ductus arteriosus ligation, n (%)	32 (52)	66 (35)	88 (23)	<0.01
Intraventricular hemorrhage, grade 3 or higher, n (%)	14 (23)	42 (23)	47 (12)	<0.01
Periventricular echodensity or echolucencies, n (%)	7 (12)	20 (11)	26 (7)	0.18
Retinopathy of prematurity ≥stage 3, n (%)	29 (50)	59 (37)	96 (27)	<0.01
Necrotizing enterocolitis ≥ stage 2, n (%)	9 (15)	21 (11)	37 (10)	0.45
Bronchopulmonary dysplasia, n (%)	44 (71)	126 (68)	232 (60)	0.07

[a]Birth weight <10th percentile for GA. All data are reported as n (%), except for birth weight (g, SD); Percentages calculated from available data; NR = Not reported because category included fewer than five patients.

a statistically significant lower use of antenatal corticosteroids and caesarean section births for infants born at ≤ 23 weeks GA as compared with those born at 25 weeks GA. Infants born at ≤ 23 weeks GA had a longer length of stay, and higher rates of PDA ligation, severe IVH, and severe ROP (Tables 1 and 2). The incidence of BPD was not significantly different but was very high (>60%) in all groups. The length of stay was statistically longer in infants born less than 25 weeks GA as compared with 25 weeks GA. Surviving infants less than 25 weeks GA had a statistically higher number of days of central line use, invasive ventilation, noninvasive ventilation, oxygen use, TPN use, postnatal steroid usage, and antibiotic usage compared with 25 weeks GA.

After NICU discharge, almost 50% of all infants had one or more re-hospitalizations but there were no statistical differences in the rates of re-hospitalizations and reasons for re-hospitalizations by GA (Table 2). The frequencies of definitive CP, hearing impairment, bilateral visual impairment, NDI and sNDI, and composite scores on the Bayley-III are shown in Table 3. There was a statistically significant increase in abnormal neurological examinations, NDI and sNDI in infants born at ≤ 23 and 24 weeks GA, as compared to those born at 25 weeks GA. There was no statistically significant difference in the frequency of CP, the type of CP (spastic, or nonspastic), or the degree of hearing impairment. The cognitive, language, and motor composite scores were significantly lower in infants born at ≤ 23 and 24 weeks GA, as compared with 25 weeks. Referral to allied health services occurred significantly more in ≤ 23 weeks GA as compared with 25 weeks GA. The unadjusted rates and the

Table 2. NICU resource utilization of surviving infants born ≤ 25 weeks GA

NICU resource requirements	≤23 weeks (n=62)	24 weeks (n=186)	25 weeks (n=388)	P-value
Length of stay in Level III NICU, median (IQR)	127 (106, 149)	115 (89, 138)	101 (76, 123)	<0.01
Days of central line use, median (IQR)	57 (37, 74)	33 (21, 45)	26 (18, 42)	<0.01
Days of invasive ventilation, median (IQR)	49 (34, 64)	39 (25, 54)	29 (12, 43)	<0.01
Days of noninvasive respiratory support, median (IQR)	108 (91, 131)	97 (71, 125)	78 (59, 106)	<0.01
Days on oxygen, median (IQR)	84 (51, 122)	71 (33, 111)	56 (26, 94)	<0.01
Days on TPN, median (IQR)	39 (28, 66)	37 (28, 54)	30 (19, 46)	<0.01
Steroids for BPD, n (%)	47 (75.8)	108 (58.1)	195 (50.3)	0.1
Days of antibiotic usage, median (IQR)	36 (22, 67)	31 (20, 47)	24 (13, 38)	<0.01
Infants discharge and postdischarge characteristics				
Discharge destination from NICU				0.09
Level III, n (%)	23 (38)	60 (32)	93 (24)	
Level II, n (%)	16 (26)	52 (28)	120 (31)	
Home, n (%)	18 (30)	63 (34)	160 (41)	
Other, n (%)	4 (7)	10 (5)	14 (4)	
Support at discharge from NICU				
Ileostomy/Colostomy/Tracheostomy/Gastrostomy, n (%)	NR	8 (4)	11 (3)	0.55
Need for regular medications, n (%)	28 (45)	110 (59)	205 (53)	0.13
Hospitalization				
Number who required re-hospitalization through 18–24 months, n (%)	29 (49)	85 (47)	169 (45)	0.73
Reasons for hospitalization				0.64
Respiratory issues, n (%)	20 (69)	49 (58)	90 (53)	
Non-respiratory issues, n (%)	9 (31)	36 (42)	79 (47)	
Length of stay at re-hospitalization, mean days (SD)	6 (8)	4 (3)	5 (6)	0.24

[a]Percentages calculated from available data; NR = Not reported because category included fewer than five patients.

GA Gestational age; IQR Interquartile range; NICU Neonatal intensive care unit.

adjusted odds ratios of NDI and sNDI were significantly higher in infants born at ≤ 23 weeks GA and infants born at 24 weeks GA, as compared with the infants born at 25 weeks GA.

Among nonsurvivors of the NICU, infants born less than 25 weeks GA were smaller and had higher rates of NEC (Supplementary Appendix, Table 1). However, babies born at 25 weeks GA survived longer and had more days with central lines, ventilation, antibiotic use, and use of steroids compared with those born at less than 25 weeks GA (Supplementary Appendix, Table 2).

The infants who were not followed up were significantly more likely to be outborn, to not have received antenatal steroids, and to have had a shorter length of stay in the NICU, with less days on noninvasive respiratory support, less days on oxygen, and less days on TPN (Supplementary Appendix, Table 3).

DISCUSSION

Current Canadian recommendations include active resuscitation of all appropriate infants ≥ 26 weeks GA with a discussion with the family around management of infants born ≤ 25 completed weeks (32); however, these periviable infants have high rates of morbidities and long-term adverse neurodevelopmental outcomes, and the health resources required to support them are less well known.

In this large multicentre, national cohort study, surviving infants who were born before 25 weeks GA required more resources compared to those born at ≥ 25 weeks GA. In contrast, nonsurviving infants born at 25 weeks had more resource usage, which was likely due to their longer length of stay prior to death and thus had more days of resource usage than those infants born ≤ 24 weeks GA. Petrou et al. reported a literature review of 52 studies, which showed that extremely preterm infants < 28 weeks GA had higher costs, longer length of stays, increased need for assisted ventilation, and were more likely to have a surgical intervention (33). In a sample of 425 very low birth weight infants (<1,500 g), when GA, birth weight, and socioeconomic status were controlled for, the presence of IVH, NEC, BPD, and late-onset sepsis, were all associated with higher costs (34). Postdischarge, in the USA, the mean cost per surviving infant for early intervention services for infants born between 24 and

Table 3. Neurodevelopmental outcomes at 18–24 months corrected age follow-up assessment

	≤23 weeks (n=62)	24 weeks (n=186)	25 weeks (n=388)	P-value
Abnormal Neurological exam (n, %)	17 (28)	41 (22)	57 (15)	0.01
Cerebral Palsy (n, %)	8 (13)	22 (12)	32 (8)	0.24
Bayley-III (median, IQR)				
Cognitive composite score	90 (80–95); n=51	90 (80–100); n=172	95 (85–105); n=364	<0.01
Language composite score	83 (68–94); n=49	83 (74–97); n= 169	89 (77–100); n=356	<0.01
Motor composite score	85 (73–94); n=49	88 (79–97); n=168	91 (82–100); n=351	0.01
Hearing impairment (n, %)	9 (15)	19 (11)	43 (12)	0.67
Bilateral visual impairment (n, %)	7 (13)	6 (4)	10 (3)	<0.01
Developmental resources (n, %)				
Referred to services outside of neonatal follow-up	59 (96.7)	169 (91.9)	323 (84.6)	<0.01
Dietitian	20 (34.5)	53 (33.3)	103 (32.8)	0.97
Early intervention program	29 (50.9)	64 (40.0)	135 (43.1)	0.36
Neurologist	12 (21.4)	22 (13.9)	38 (12.3)	0.19
Occupational therapist	34 (57.6)	86 (52.8)	170 (54.0)	0.81
Physical therapist	41 (69.5)	93 (56.4)	176 (56.4)	0.16
Rehabilitation program	12 (23.3)	32 (20.1)	50 (16.1)	0.33
Speech and language pathologist	26 (45.6)	88 (54.3)	151 (48.7)	0.40
Social worker	15 (25.4)	25 (15.7)	31 (10.0)	<0.01
Neurodevelopmental outcomes				
Significant neurodevelopmental impairment Rates (n, %)	24 (39.3)	55 (29.6)	81 (20.9)	<0.01
Unadjusted OR	2.45 (1.39, 4.33)	1.59 (1.06, 2.36)	Ref	NA
Adjusted OR[a]	4.31 (2.18, 8.51)	1.82 (1.15, 2.87)	Ref	NA
Neurodevelopmental impairment Rates (n, %)	42 (68.9)	120 (64.5)	215 (55.6)	0.01
Unadjusted OR	1.77 (0.99, 3.15)	1.46 (1.01, 2.09)	Ref	NA
Adjusted OR[a]	2.31 (1.21, 4.42)	1.62 (1.09, 2.39)	Ref	NA

Data for neurologically abnormal exam, cerebral palsy, hearing impairment, bilateral visual impairment, sNDI, and NDI are reported as n (%); Data for Bayley-III are reported as median (IQR); Percentages calculated from available data; [a]Adjusted OR adjusted for small for gestational age (birth weight <10th percentile for GA), sex, receipt of antenatal corticosteroids, outborn status, mode of delivery, site of delivery, and multiple gestation.

IQR Interquartile range; OR Odds ratio.

31 weeks was more than seven times that of a term infant (35). Reducing morbidities in this population will likely reduce the overall health care system cost of caring for periviable infants.

Differences in approach by obstetricians and neonatologists to threatened preterm labour may affect the health care resources used and the outcomes of this periviable population. In our study, antenatal corticosteroid use among infants born ≤ 23 weeks GA was less than those born at 25 weeks GA, which reflects similar findings by Park et al. (36). In a population-based cohort in Sweden, regions with a 'pro-active policy' whereby infants less than 25 weeks GA were actively resuscitated, achieved an increased incidence of live births and higher numbers of infants alive at 1 year without increased morbidity in the first year of life, as compared to 'selective and active' regions, in which limited interventions were applied for infants less than 25 weeks GA (7). Chawla et al. reported death or neurodevelopmental impairment in 68.1, 54.4, and 48.1%, P<0.05, of patients who received no, partial, and complete antenatal corticosteroids respectively (37). Ogata et al. reported a 24 to 47% reduction in hospital services costs, and length of stay in surviving preterm infants born 26 to 32 weeks GA who were exposed to antenatal corticosteroids (38). In a study of 3,769 infants in the Canadian Neonatal Network, outborn infants as compared with inborns, had significantly higher mortality rates and morbidities including PDA, severe IVH, respiratory distress syndrome, and infection even after adjusting for admission illness severity and perinatal risk factors (39). In our study, patients lost to follow up were also more likely to be outborn with less resource usage and thus presumably were living too far to follow up. As a result, deriving outcome data from inborn infants in a level III hospital causes a significant denominator issue. Knowledge of these specific factors and their effects on outcome can affect the expected course of each individual infant born at borderline GA.

The strengths of this study include the national cohort data, the use of standardized collection of outcomes and covariates in a large sample size of preterm neonates of 22 to 25 weeks GA at birth, and a high follow-up rate of 80% at 18 to 24 months GA. This study also includes data on a large number of important antenatal confounders, allowing for the adjustment of these variables in our analysis. Despite these strengths, the major limitation of this study is that only infants who received active care were included. Neonates who died in the delivery room or prior to transfer to a tertiary care centre, and those who died postdischarge were not included. Another limitation is that our follow-up only extends to the first 2 years of life and it will be important to follow these children into school age or adolescence.

A surveillance of outcomes and resource utilization of periviable infants is important for outcomes-based health resource planning. Awareness of the needs of this special population by the generalist involved in their care is of vital importance. Following these outcomes will help with both establishing and increasing the access to further supports and resources to families of children born at the limits of viability beyond the NICU and into the community.

Our study highlights the increased health care resource needs and the risks of adverse outcomes at more immature GA. These outcomes reflect advancements of perinatal and neonatal care and their availability will lead to improvements in medical practice and resource allocation both in the hospital setting and in the community.

SUPPLEMENTARY DATA

Supplementary data are available at *Paediatrics & Child Health* Online.

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