Original article

Sex differences in the outcome of very low birth weight premature infants born in a regional Australian Neonatal Intensive Care Unit

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Abstract

Background: Advancements in neonatal care have improved survival for premature and very low birth weight (VLBW) infants. Despite this, differences have been reported when comparing males and females. While the previously described concept of the "male disadvantage" asserts that there is a higher risk of mortality and morbidity for male infants, many studies have also found no sex differences in outcomes.

Aim: The objective of this study is to determine if the sex of VLBW premature infants is associated with survival and neurodevelopmental outcome in a regional Australian Neonatal Intensive Care Unit (NICU).

Methods: A retrospective cohort study was conducted for infants born at < 37 weeks gestation with VLBW (< 1,500 g) admitted to The Townsville Hospital NICU between 2010 and 2015. Comparisons for survival and neurodevelopment between males and females were made with Chi-square, Fisher's exact test and the Independent t-test. Multivariate logistic regression analysis was performed for the outcomes of death before NICU discharge and developmental delay assessed by the Bayley Scales of Infant and Toddler Development, the 3rd Edition.

Results: Data were collected for 430 infants. Fifty-three infants died before NICU discharge, with no sex difference in survival. Follow-up assessment was completed for 84 infants from the original cohort and demonstrated no sex differences in neurodevelopmental outcome. Male infants had a significantly higher prevalence of chronic lung disease (p = 0.009). Neither the logistic regression model for death by NICU discharge nor for neurodevelopmental delay identified sex as a significant predictor of outcome.

Conclusions: Male and female VLBW premature infants did not differ in survival or neurodevelopmental outcome at this center.

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Introduction

As a result of advancements in neonatal care during recent decades, there has been improved survival for premature and very low birth weight (VLBW) infants [1-3]. However, despite the overall increase in survival for VLBW premature infants, a difference has been reported when comparing males and females. The concept of the "male disadvantage" in neonatal care asserts that males tend to experience higher mortality than their female counterparts [4-6]. A recent systematic review [7] as well as many studies over the years have supported this concept [8-10], but some have confounded it by purporting no sex difference in survival [11-14].

Furthermore, premature infants are at greater risk of neurodevelopmental sequelae later in life [15-18], which have also shown sex differences [19-21]. Sex differences in short- and long-term outcomes continue to be of concern in recent years and may have clinical implications such as in counselling parents about the risks their children face [22]. The current study aimed to determine if sex is relevant to survival and neurodevelopmental outcome in an Australian regional Neonatal Intensive Care Unit (NICU).

Methods

Population

The Townsville Hospital (TTH) is the largest tertiary hospital in North Queensland and an academic institution of James Cook University (JCU). As the only level six tertiary referral center for newborns north of Brisbane, the TTH NICU services a wide geographical area of predominantly regional and rural communities, and receives patients from many smaller peripheral hospitals. Often, patients require retrieval or transfer to the TTH NICU and are later stepped-down to the hospitals that initially referred them. Also unique to North Queensland is the proportion of Aboriginal and Torres Strait Islander communities, which is nearly 3 and 4 times greater compared to Queensland as a whole and the national average, respectively [23]. There are more than 10,000 births per year in this region, and all high-risk pregnancies are managed in this center. This study, therefore, represents the demographically distinct characteristics of neonatal healthcare in North Queensland.

This is a retrospective cohort study of VLBW (< 1,500 g) premature infants (born at < 37 weeks gestation) admitted to TTH NICU. Data were collected from January 2010 to January 2015, a period in line with improved record-keeping in this unit and the establishment of a neurodevelopmental follow-up clinic.

Infants with ambiguous genitalia were excluded as they could not be used in sex comparisons, as well as those with syndromic or chromosomal abnormalities as this population has inherently different risks.

Early readmissions were excluded, along with outborn infants transferred to TTH late as they are managed predominantly at the original hospital and do not significantly reflect care delivered at TTH.

Approval for this study was granted by the Human Research Ethics Committee of TTH with reciprocal approval by the JCU Human Research Ethics Committee.

Data sources

NICU data

Data related to the infant's NICU admission was extracted from a prospectively maintained NICU database and de-identified, including gestational age (GA), birth weight (BW), sex, outborn status, antenatal steroid use, complications, and survival outcome. Data missing on extraction were followed-up by a review of original patient records.

Neurodevelopmental follow-up data

Ex-TTH NICU infants who survived admission and resided in the TTH geographic catchment attended a voluntary follow-up clinic for formal assessment of neurodevelopmental outcome at 2 years corrected age. The assessment was completed by a Clinical Psychologist (CD) using the Bayley Scales of Infant and Toddler Development® Third Edition (Bayley-III) [24]. The assessor was not blinded to neonatal history. To account for Bayley-III limitations of overestimation of the child's ability likely leading to underestimation of developmental delay [25, 26], norm cut-off scores generated from a Victorian cohort were used [26]. The retrospective nature of this study precluded using locally-specific control groups. Infants were classified with developmental delay as defined by scoring more than 1 SD below the mean for a domain, and moderate to severe delay as more than 2 SD below the mean. Assessment results were extracted from the clinic database for infants included in the study.

Additional neurodevelopmental data were collected to identify any cerebral palsy (CP) in those discharged to the Townsville region who had subsequently presented for a TTH-linked health system follow-up. Presence of CP served as a surrogate marker of disability for children not assessed in the follow-up clinic, who therefore did not have Bayley-III data.

Outcomes

The primary and secondary outcomes were sex differences in survival to NICU discharge and neurodevelopment measured by Bayley-III or CP diagnosis, respectively. Birth characteristics and complications were also examined in relation to infant sex, such as necrotizing enterocolitis (NEC), chronic lung disease (CLD), retinopathy of prematurity (ROP), and intraventricular hemorrhage (IVH).

Definitions

GA was calculated using the expected due date based on the last menstrual period if known and/or first-trimester ultrasound. If the expected due date differed between the last menstrual period and the scan by > 14 days, then the GA was based on the scan dates. CLD was defined as oxygen dependency at 36 weeks postconceptional age [27].

Retinopathy of prematurity was schemed according to the International Classification of Retinopathy for Prematurity [28]. NEC was classified using Bell's staging criteria [29]. IVH was diagnosed by locally performed ultrasound scans and graded, as described by Papile et al. [30].

Statistical analysis

Statistical analysis was performed using SPSS® (Release 24.0.0.0). Sex comparisons were made using the Chi-square or Fisher's exact test for categorical variables and the Independent t-test for continuous variables [31]. Parametric methods were used without conducting tests of normality due to the sample size acquired [32]. Multivariate logistic regression analysis was performed for the dependent variable "death before NICU discharge" to identify any adjusted sex differences and other factors associated with survival [33]. Factors were included in the model for their clinical relevance and use in previous models. Adjusted odds ratios with 95% confidence intervals were calculated for each factor. Statistical significance was set at $p < 0.05$ using two-tailed comparisons for all analyses. Subgroup analysis was performed for children that presented for follow-up using the same univariate and logistic regression methods, with the dependent variable set as the presence of delay in any Bayley-III domain.

Sample size calculation

Sample size calculation for the primary outcome of survival was based on previous research, showing that 89 participants of each sex would be required to reject the null hypothesis of no sex difference with a power of 0.8 and alpha of 0.05 [34]. Similar calculations could not be done for the secondary outcome of neurodevelopment as the novel nature of study data meant that clinic follow-up rates could not be predicted and there were no comparable Australian studies with regional data to reference identified.

Results

A total of 438 infants with GA < 37 weeks, and BW < 1,500 g were admitted to the TTH NICU between January 2010 and January 2015 (**Fig. 1**). No infants had chromosomal or syndromic abnormalities. One infant had indeterminate sex
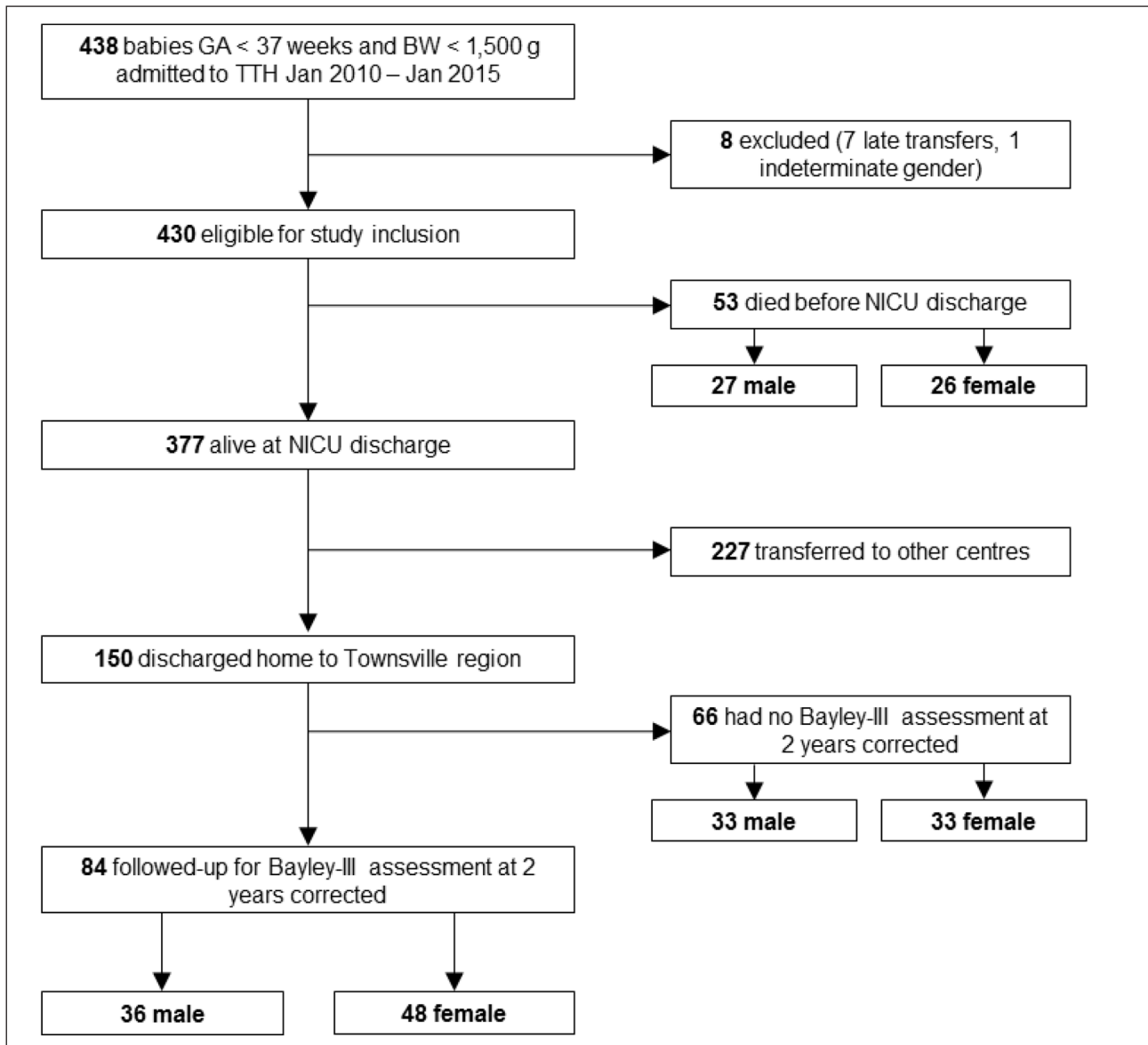
Figure 1. Flow chart of the study population.
NICU: Neonatal Intensive Care Unit; TTH: Townsville Hospital.

while 7 were late transfers to TTH and excluded. One-hundred sixty-six infants (38.6%) were identified as Aboriginal or Torres Strait Islander. The final population was 430 infants; 215 males and 215 females.

Mortality and sex

Sex comparisons for mortality, complications, and clinical characteristics were performed (**Tab. 1**). Male infants overall had a significantly higher prevalence of CLD (p = 0.009). Neither GA nor BW was significantly different between the sexes. While more male than female infants were outborn, had ROP stage 3 or 4, IVH grade 3 or 4, and mothers who received antenatal steroids,

differences were not significant. The number of NEC was identical in both sexes.

Of the 430 infants admitted, 53 (12.3%) died before discharge. There was no sex difference in mortality (p = 0.88). The primary cause of death was identified in all infants: 24 cases of extreme prematurity and related complications, 7 of respiratory causes, 5 of NEC, 4 of IVH, 3 of sepsis/infection and 10 of other causes (hypoxic-ischaemic encephalopathy, hydrops, kidney disease, cardiorespiratory failure, multi-organ failure, bleeding). When analyzing by separate GA and BW groups (**Tab. 2**), there was no longer a difference in CLD, and there remained no differences in mortality or the other morbidities.

Table 1. Sex comparison of neonatal characteristics, mortality and complications.

Neonatal characteristics	Female	Male	p-value
GA, weeks, mean ± SD	28.1 ± 2.8	27.7 ± 2.7	0.21
GA < 26 weeks, n (%)	45 (20.9)	58 (27.0)	0.14
GA 26-27 weeks, n (%)	60 (27.9)	55 (25.6)	0.59
GA ≥ 28 weeks, n (%)	110 (51.2)	102 (47.4)	0.44
BW, g, mean ± SD	1,020.2 ± 269.2	1,019.1 ± 273.9	0.97
BW < 1,000 g, n (%)	99 (46.0)	105 (48.8)	0.56
BW 1,000-1,499 g, n (%)	116 (54.0)	110 (51.2)	0.56
Outborn, n (%)	43 (20.0)	44 (20.5)	0.90
Received antenatal steroids, n (%)	185 (86.1)	192 (89.3)	0.30
Died before NICU discharge, n (%)	26 (12.1)	27 (12.6)	0.88
CLD, n (%)	47 (21.9)	71 (33.0)	**0.009**
NEC, n (%)	16 (7.4)	16 (7.4)	1.0
ROP stage 3 or 4, n (%)	9 (4.2)	14 (6.5)	0.28
IVH grade 3 or 4, n (%)	11 (5.1)	15 (7.0)	0.42

n (%) expressed as percentage of total for females and males separately (n females = 215: n males = 215).
Significant values are bolded.
GA: gestational age; SD: standard deviation; BW: birth weight; g: grams; NICU: Neonatal Intensive Care Unit; CLD: chronic lung disease; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage.

Table 2. Sex comparison of mortality and morbidity by gestational age (GA) and birth weight (BW).

			GA at birth (weeks)			Total
			< 26	26-27	≥ 28	
Died before NICU discharge [a]	BW 1,000-1,499 g	Male	0	1	4	12
		Female	0	1	6	
	BW < 1,000 g	Male	18	3	1	41
		Female	16	2	1	
CLD [a]	BW 1,000-1,499 g	Male	0	8	11	30
		Female	0	6	5	
	BW < 1,000 g	Male	32	17	3	88
		Female	20	11	5	
NEC [a]	BW 1,000-1,499 g	Male	0	0	1	6
		Female	0	2	3	
	BW < 1,000 g	Male	11	2	2	26
		Female	8	3	0	
ROP stage 3 or 4 [a]	BW 1,000-1,499 g	Male	0	2	0	4
		Female	0	1	1	
	BW < 1,000 g	Male	10	1	1	19
		Female	4	2	1	
IVH grade 3 or 4 [a]	BW 1,000-1,499 g	Male	0	1	1	5
		Female	0	2	1	
	BW < 1,000 g	Male	10	3	0	21
		Female	6	2	0	

[a] No significant difference in males vs. females for any gestation or birth weight subgroup.
GA: gestational age; NICU: Neonatal Intensive Care Unit; BW: birth weight; g: grams; CLD: chronic lung disease; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage.

The multivariate logistic regression model for death before NICU discharge included sex, GA, BW, outborn status, antenatal steroid use (included as only 3 infants had GA > 35 weeks, the cut-off for steroid use at TTH), CLD, NEC and IVH grade 3 or 4 as independent variables (**Tab. 3**). Variables found to be significant included CLD (p < 0.001), grade 3 or 4 IVH (p = 0.002), receiving antenatal steroids (p = 0.002), NEC (p = 0.004) and BW (p = 0.036). Sex, outborn status, and GA were not significant in the model.

Table 3. Multivariate logistic regression analysis for factors associated with death before NICU discharge.

Variable	OR (95% CI)	p-value
Male sex	1.26 (0.62-2.57)	0.518
Outborn	0.74 (0.31-1.75)	0.492
Received antenatal steroids	0.20 (0.08-0.55)	**0.002**
GA (weeks)	0.80 (0.63-1.00)	0.057
BW (g)	0.998 (0.995-0.999)	**0.036**
CLD	0.11 (0.04-0.30)	**< 0.001**
NEC	4.27 (1.58-11.51)	**0.004**
IVH grade 3 or 4	5.28 (1.83-15.28)	**0.002**

Significant differences are bolded.
OR: odds ratio; CI: confidence interval; GA: gestational age; BW: birth weight; g: grams CLD: chronic lung disease; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage.

Neurodevelopment and sex

Of the original NICU cohort who survived to discharge and eligible for follow-up, 84 (56%) children comprising 48 females and 36 males underwent Bayley-III assessment. There were no significant sex differences in the clinical characteristics of this group.

Comparing the number of males and females with delay assessed by Bayley-III, 65 children (77.4%) had a developmental delay in at least one domain (**Tab. 4**). However, overall, there were no significant sex differences in the number of children with delay. The multivariate logistic regression model for the dependent variable "delay in any Bayley-III domain" indicated that male sex, GA, BW, antenatal steroid use, CLD, ROP stage 3 or 4, IVH grade 3 or 4 did not predict a neurodevelopmental delay in this cohort.

The review of TTH medical records identified 5 children as having a diagnosis of CP, all of whom were male. The review also identified an additional 6 children who did not attend for Bayley-III assessment to have diagnoses of other developmental delays, and among these 5 were male, and 1 was female.

Discussion

This retrospective study of VLBW premature infants is the first to examine the role of infant sex in neonatal outcomes in a regional setting of Queensland. The sex of neonates was compared by survival at NICU discharge, and long-term neurodevelopment with few differences identified, possibly due to the lowering of the mortality rate.

Table 4. Sex comparison of neurodevelopmental delay on Bayley-III assessment at two year follow-up.

	Female	Male	p-value
Delay in any Bayley-III domain, n (%)	38 (79.2)	27 (75.0)	0.65
Cognitive, n (%)			
Developmental delay, < 1 SD	10 (20.8)	8 (22.2)	0.88
Moderate-severe developmental delay, < 2 SD	2 (4.2)	3 (8.3)	0.65
Total cognitive delay	12/48 (25.0)	11/36 (30.6)	NA
Language, n (%) [a]			
Developmental delay, < 1 SD	17 (35.4)	12 (33.3)	0.92
Moderate-severe developmental delay, < 2 SD	7 (14.6)	4 (11.1)	0.75
Total language delay	24/48 (50.0)	16/35 (45.7)	NA
Motor, n (%)			
Developmental delay, < 1 SD	34 (70.8)	21 (58.3)	0.23
Moderate-severe developmental delay, < 2 SD	3 (6.3)	4 (11.1)	0.46
Total motor delay	37/48 (77.1)	25/36 (69.4)	NA

n (%) expressed as percentage of total for females and males separately (n females = 48, n males = 36).
[a] Language assessment not completed for 1 child due to exhaustion and inattentiveness.
SD: standard deviation; NA: not applicable.

Although clinically notable that more male infants died before discharge and a smaller proportion of male children experienced a neurodevelopmental delay, these differences were not statistically significant. The predictors of survival identified are consistent with other researches [22, 35-39]. Infant's sex did not influence either survival or neurodevelopment.

Survival at NICU discharge was not influenced by sex in this study, and this observation has been noted elsewhere [11, 13, 14, 40-42]. With the abundance of literature highlighting the male disadvantage, this study raises questions about the sex difference in survival concerning what factors may be conducive to the appearance of a sex difference and what factors may mask or eliminate it. One thought in the literature is that the sex difference becomes irrelevant at certain GA and BW. Numerous studies have found that sex differences in survival disappear after certain GA or BW ranges have been reached [22, 43, 44]. These patterns might be explained by the idea that there

are sex differences in maturation at certain stages of gestation [11, 45]. After these maturation points, there might be a catch-up of male development, thereby reducing the constitutional differences contributing to the sex gap in survival overall. In this study, there were wide GA inclusion criteria, and the initial univariate analysis of the whole cohort did not detect a sex difference in survival. Perhaps the combination of low-GA high-risk and high-GA low-risk infants in the same cohort clouded the sex differences that might have only occurred for the highest risk infants.

Further analysis by separate GA and BW categories then found no sex difference in survival for any gestation or weight. It is therefore arguable that, contrary to the idea above, maturational discrepancies were minimal in this cohort. The lack of a sex difference might also be attributed to the actual mortality rate recorded in this study being lower than that used in the sample size calculation. While low mortality represents positive outcomes for this center, a larger sample size may have been required to demonstrate a sex difference in survival. It is also debatable whether the absence of a male disadvantage reflects an attenuation of the sex difference in survival by the routine administration of maternal steroids and postnatal surfactant [21].

There were no sex differences in the number of children with developmental delay as assessed by Bayley-III. While many studies of ex-premature infants have indicated poorer male neurodevelopment [17, 19, 21, 22, 46, 47], this is not the only one to lack sex differences in Bayley-III, whether in some or all developmental domains [48-50]. The absence of a sex difference in this cohort may in part reflect the reduced sample size acquired at the follow-up clinic. Follow-up was a significant challenge, as many in the study population were transferred or discharged home to sites outside of Townsville. In this regional population characterized by many inter-hospital transfers within the large referral catchment area for Townsville Hospital, complete follow-up is a difficult barrier to overcome.

Additionally, the cohort followed-up may not have represented the high-risk group for the developmental delay; only one-fifth of all children who had CLD as infants attended this clinic while over 60% of attendees were born at lower risk gestations ≥ 28 weeks. Logistic regression analysis for predictors of Bayley-III delay found none of the neonatal factors, including sex, to be significant, suggesting that the factors available in this cohort did not influence the neurodevelopmental outcome. The regression model should be viewed with caution and may serve as an example of the ongoing importance and challenge of identifying key predictors for childhood neurodevelopmental delay [47, 51]. Indeed, studies report that many neonatal factors may not be significant in predicting the neurodevelopmental outcome, instead of pointing towards an inherent role of male physiology [19, 21, 44]. There have also been reports of differential effects whereby a factor influences neurodevelopment differently in each sex [52, 53]. For example, sepsis and multiple gestations have been associated with poorer neurodevelopment in males but not females, whereas CLD and lower education in the child's caregiver have shown the opposite [19].

Among those with CP identified from the TTH database, all were male. The identification of more children with CP in this study is limited by the search being restricted to data available in the TTH records, the reliability of such on-site data, as well as clinical hesitation or delay in making a CP diagnosis. Still, in those for whom data were obtained, there was the suggestion of a trend towards a male disadvantage in CP. Male disadvantage in CP has been reported [54], and a recent Victorian paper reported a male excess in CP, emphasizing that there appeared a gestation-specific association between sex and CP [55].

Male infants in this cohort had a significantly higher prevalence of CLD overall. Studies have demonstrated a sex difference in CLD with female infants generally experiencing less CLD than males [9, 43, 52, 56], although there are some exceptions [41, 57]. Avoiding hyperoxia in neonates is associated with decreased risk of CLD, while higher oxygenation targets and long-term ventilation increase the risk [58, 59]. A study exploring this showed that when oxygen saturation targets were reduced, female infants responded significantly better, as evidenced by a greater decrease in CLD than males [60]. The increased CLD in males of the current study may be related to this, as it may be possible that because of inherently reduced tolerance to lower oxygenation targets [56] males required more intensive oxygenation. It is important to further clarify reasons for the sex difference in CLD, as this condition has long-term implications for surviving infants [47, 61].

This study is not without limitations. Incomplete follow-up of children at 2 years reduced study power for the secondary outcome. The frequency of follow-up found in this study, though, can be used to inform and power future similar research. Further investigation in this region with improved sample size is recommended and may demonstrate a male disadvantage in line with other national research. Additionally, CP status in children was determined by using the general TTH database, so information was reliant on there being subsequent TTH-linked follow-ups or admissions. These issues relate to the ongoing complexities of a regional population and mean that records of infants discharged to sites outside Townsville or followed-up outside the public system could not be accessed. A larger prospective scale study with improved resources may assist in accessing follow-up data of those infants treated in this NICU and not captured in the Townsville clinic. Although Australian reference data were used for Bayley-III analyses, the data were generated from a Victorian cohort and may not reflect a population of infants in North Queensland entirely.

Conclusion

This study concludes that in this specific NICU setting and regional population, sex had a limited role in the survival and neurodevelopmental outcome. No significant sex difference in survival for VLBW premature infants nor in neurodevelopmental delay was identified. More males were identified with CP, and this may tentatively suggest a slight trend towards male disadvantage. While low power restricted further conclusions, the strength of this study is in demonstrating the evolving trends of neonatal outcomes within a modern, regional, population-based cohort and providing a new study group for further elucidation of sex differences in survival and neurodevelopmental outcome in similar settings. Future studies in this region should consider prospective analysis with local control cohorts to enhance results.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Bennett FC, Robinson NM, Sells CJ. Growth and development of infants weighing less than 800 grams at birth. Pediatrics. 1983;71(3):319-23.

2. Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. Semin Perinatol. 2003;27(4):281-7.

3. Rüegger C, Hegglin M, Adams M, Bucher HU; Swiss Neonatal Network. Population based trends in mortality, morbidity and treatment for very preterm- and very low birth weight infants over 12 years. BMC Pediatr. 2012;12:17.

4. Brothwood M, Wolke D, Gamsu H, Benson J, Cooper D. Prognosis of the very low birthweight baby in relation to gender. Arch Dis Child. 1986;61(6):559-64.

5. Naeye RL, Burt LS, Wright DL, Blanc WA, Tatter D. Neonatal mortality, the male disadvantage. Pediatrics. 1971;48(6):902-6.

6. Tandoi F, Agosti M. Gender differences: are there differences even in Pediatrics and Neonatology? J Pediatr Neonat Individual Med. 2012;1(1):43-8.

7. Vu HD, Dickinson C, Kandasamy Y. Sex Difference in Mortality for Premature and Low Birth Weight Neonates: A Systematic Review. Am J Perinatol. 2018;35(8):707-15.

8. La Pine TR, Jackson JC, Bennett FC. Outcome of infants weighing less than 800 grams at birth: 15 years' experience. Pediatrics. 1995;96(3 Pt 1):479-83.

9. Stevenson DK, Verter J, Fanaroff AA, Oh W, Ehrenkranz RA, Shankaran S, Donovan EF, Wright LL, Lemons JA, Tyson JE, Korones SB, Bauer CR, Stoll BJ, Papile LA. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. Arch Dis Child Fetal Neonatal Ed. 2000;83(3): F182-5.

10. Upadhyay K, Pourcyrous M, Dhanireddy R, Talati AJ. Outcomes of neonates with birth weight ≤ 500 g: a 20-year experience. J Perinatol. 2015;35(9):768-72.

11. Battin M, Ling EW, Whitfield MF, Mackinnon M, Effer SB. Has the outcome for extremely low gestational age (ELGA) infants improved following recent advances in neonatal intensive care? Am J Perinatol. 1998;15(8):469-77.

12. Ray B, Platt MP. Mortality of twin and singleton livebirths under 30 weeks' gestation: a population-based study. Arch Dis Child Fetal Neonatal Ed. 2009;94(2):F140-3.

13. Vanhaesebrouck P, Allegaert K, Bottu J, Debauche C, Devlieger H, Docx M, François A, Haumont D, Lombet J, Rigo J, Smets K, Vanherreweghe I, Van Overmeire B, Van Reempts P; Extremely Preterm Infants in Belgium Study Group. The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. Pediatrics. 2004;114(3):663-75.

14. Verloove-Vanhorick SP, van Zeben-van der Aa DM, Verwey RA, Brand R, Ruys JH. The male disadvantage in very low birthweight infants: does it really exist? Eur J Pediatr. 1989;149(3): 197-202.

15. Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990s. Semin Neonatol. 2000;5(2):89-106.

16. McCormick MC. Has the prevalence of handicapped infants increased with improved survival of the very low birth weight infant? Clin Perinatol. 1993;20(1):263-77.

17. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. Pediatrics. 2005;116(3):635-43.

18. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics. 2005;115(4):997-1003.

19. Hintz SR, Kendrick DE, Vohr BR, Kenneth Poole W, Higgins RD; Nichd Neonatal Research Network. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. Acta Paediatr. 2006;95(10):1239-48.

20. Lind A, Korkman M, Lehtonen L, Lapinleimu H, Parkkola R, Matomäki J, Haataja L; PIPARI Study Group. Cognitive and neuropsychological outcomes at 5 years of age in preterm children born in the 2000s. Dev Med Child Neurol. 2011;53(3):256-62.

21. Peacock JL, Marston L, Marlow N, Calvert SA, Greenough A. Neonatal and infant outcome in boys and girls born very prematurely. Pediatr Res. 2012;71(3):305-10.

22. Kent AL, Wright IM, Abdel-Latif ME; New South Wales and Australian Capital Territory Neonatal Intensive Care Units Audit Group. Mortality and adverse neurologic outcomes are greater in preterm male infants. Pediatrics. 2012;129(1):124-31.

23. Kandasamy Y, Tanchi PP, Edmonds LK. Small for gestational age and low birth weight term admissions to a tertiary perinatal centre in northern Queensland, Australia. J Immigr Minor Health. 2015;17(1):227-31.

24. Bayley N. Bayley Scales of Infant and Toddler Development, Third Edition. San Antonio: Pearson, 2006.

25. Anderson PJ, Burnett A. Assessing developmental delay in early childhood – concerns with the Bayley-III scales. Clin Neuropsychol. 2017;31(2):371-81.

26. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW; Victorian Infant Collaborative Group. Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med. 2010;164(4):352-6.

27. Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, Everette R, Peters N, Miller N, Muran G, Auten K, Newman N, Rowan G, Grisby C, Arnell K, Miller L, Ball B, McDavid G; National Institute of Child Health and Human Development Neonatal Research Network. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004;114(5):1305-11.

28. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991-9.

29. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, Brotherton T. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1-7.

30. Papile LA, Munsick-Bruno G, Schaefer A. Relationship of cerebral intraventricular hemorrhage and early childhood neurologic handicaps. J Pediatr. 1983;103(2):273-7.

31. http://science-network.tv/choosing-statistical-analysis/, last access: February 2017.

32. Ghasemi A, Zahediasl S. Normality tests for statistical analysis: a guide for non-statisticians. Int J Endocrinol Metab. 2012;10(2):486-9.

33. http://science-network.tv/choosing-statistical-analysis/, last access: February 2017.

34. Ingemarsson I. Gender aspects of preterm birth. BJOG. 2003;110(Suppl 20):34-8.

35. Chye JK, Lim CT. Very low birth weight infants – mortality and predictive risk factors. Singapore Med J. 1999;40(9):565-70.

36. Garg P, Abdel-Latif ME, Bolisetty S, Bajuk B, Vincent T, Lui K. Perinatal characteristics and outcome of preterm singleton, twin and triplet infants in NSW and the ACT, Australia (1994-2005). Arch Dis Child Fetal Neonatal Ed. 2010;95(1):F20-4.

37. Itabashi K, Horiuchi T, Kusuda S, Kabe K, Itani Y, Nakamura T, Fujimura M, Matsuo M. Mortality rates for extremely low birth weight infants born in Japan in 2005. Pediatrics. 2009;123(2):445-50.

38. Kugelman A, Bader D, Lerner-Geva L, Boyko V, Levitzki O, Riskin A, Reichman B. Poor outcomes at discharge among extremely premature infants: a national population-based study. Arch Pediatr Adolesc Med. 2012;166(6):543-50.

39. Shankaran S, Fanaroff AA, Wright LL, Stevenson DK, Donovan EF, Ehrenkranz RA, Langer JC, Korones SB, Stoll BJ, Tyson JE, Bauer CR, Lemons JA, Oh W, Papile LA. Risk factors for early death among extremely low-birth-weight infants. Am J Obstet Gynecol. 2002;186(4):796-802.

40. Binet ME, Bujold E, Lefebvre F, Tremblay Y, Piedboeuf B; Canadian Neonatal Network™. Role of gender in morbidity and mortality of extremely premature neonates. Am J Perinatol. 2012;29(3):159-66.

41. Neubauer V, Griesmaier E, Ralser E, Kiechl-Kohlendorfer U. The effect of sex on outcome of preterm infants – a population-based survey. Acta Paediatr. 2012;101(9):906-11.

42. Olugbuyi O, Samms-Vaughan M, Trotman H. Mortality of very-low-birth-weight infants in Jamaica. Trop Doct. 2006;36(3):169-71.

43. Jones HP, Karuri S, Cronin CM, Ohlsson A, Peliowski A, Synnes A, Lee SK; Canadian Neonatal Network. Actuarial survival of a large Canadian cohort of preterm infants. BMC Pediatr. 2005;5:40.

44. 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 centres. Part 2: infant survival. Acta Paediatr. 2004;93(8):1081-9.

45. Tyson JE, Younes N, Verter J, Wright LL. Viability, morbidity, and resource use among newborns of 501- to 800-g birth weight. National Institute of Child Health and Human Development Neonatal Research Network. JAMA. 1996;276(20):1645-51.

46. Hoffman EL, Bennett FC. Birth weight less than 800 grams: changing outcomes and influences of gender and gestation number. Pediatrics. 1990;86(1):27-34.

47. Månsson J, Fellman V, Stjernqvist K; EXPRESS Study Group (authors). Extremely preterm birth affects boys more and socio-economic and neonatal variables pose sex-specific risks. Acta Paediatr. 2015;104(5):514-21.

48. Janssen AJWM, Oostendorp RAB, Akkermans RP, Steiner K, Kollée LAA, Nijhuis-van der Sanden MWG. High variability of individual

longitudinal motor performance over five years in very preterm infants. Res Dev Disabil. 2016;59:306-17.

49. Serenius F, Källén K, Blennow M, Ewald U, Fellman V, Holmström G, Lindberg E, Lundqvist P, Maršál K, Norman M, Olhager E, Stigson L, Stjernqvist K, Vollmer B, Strömberg B; EXPRESS Group. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. JAMA. 2013;309(17):1810-20.

50. Valcamonico A, Accorsi P, Sanzeni C, Martelli P, La Boria P, Cavazza A, Frusca T. Mid- and long-term outcome of extremely low birth weight (ELBW) infants: an analysis of prognostic factors. J Matern Fetal Neonatal Med. 2007;20(6):465-71.

51. Skiöld B, Alexandrou G, Padilla N, Blennow M, Vollmer B, Adén U. Sex differences in outcome and associations with neonatal brain morphology in extremely preterm children. J Pediatr. 2014;164(5):1012-8.

52. Christmann V, Roeleveld N, Visser R, Janssen AJ, Reuser JJ, van Goudoever JB, van Heijst AF. The early postnatal nutritional intake of preterm infants affected neurodevelopmental outcomes differently in boys and girls at 24 months. Acta Paediatr. 2017;106(2):242-9.

53. Frondas-Chauty A, Simon L, Branger B, Gascoin G, Flamant C, Ancel PY, Darmaun D, Rozé JC. Early growth and neurodevelopmental outcome in very preterm infants: impact of gender. Arch Dis Child Fetal Neonatal Ed. 2014;99(5):F366-72.

54. Australian Cerebral Palsy Register Group. Report of the Australian Cerebral Palsy Register, Birth Years 1993-2009. Sydney: Cerebral Palsy Alliance Research Institute, 2016.

55. Reid SM, Meehan E, Gibson CS, Scott H, Delacy MJ; Australian Cerebral Palsy Register Group. Biological sex and the risk of cerebral palsy in Victoria, Australia. Dev Med Child Neurol. 2016;58(Suppl 2):43-9.

56. Elsmén E, Hansen Pupp I, Hellström-Westas L. Preterm male infants need more initial respiratory and circulatory support than female infants. Acta Paediatr. 2004;93(4):529-33.

57. Shinwell ES, Reichman B, Lerner-Geva L, Boyko V, Blickstein I; Israel Neonatal Network. "Masculinizing" effect on respiratory morbidity in girls from unlike-sex preterm twins: a possible transchorionic paracrine effect. Pediatrics. 2007;120(3):e447-53.

58. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med. 2003;349(10):959-67.

59. Geary C, Caskey M, Fonseca R, Malloy M. Decreased incidence of bronchopulmonary dysplasia after early management changes, including surfactant and nasal continuous positive airway pressure treatment at delivery, lowered oxygen saturation goals, and early amino acid administration: a historical cohort study. Pediatrics. 2008;121(1):89-96.

60. Deulofeut R, Critz A, Adams-Chapman I, Sola A. Avoiding hyperoxia in infants < or = 1250 g is associated with improved short- and long-term outcomes. J Perinatol. 2006;26(11):700-5.

61. Hoekstra RE, Ferrara TB, Couser RJ, Payne NR, Connett JE. Survival and long-term neurodevelopmental outcome of extremely premature infants born at 23-26 weeks' gestational age at a tertiary center. Pediatrics. 2004;113(1 Pt 1):e1-6.