ARTICLE

Long-term neurodevelopmental outcomes at three years in preterm infants born before 29 Weeks gestation following Preterm Premature Rupture of Membranes (PPROM)

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OBJECTIVE: To determine the association between preterm premature rupture of membranes (PPROM) and neurodevelopmental impairment (NDI) at 3 years corrected age (CA) in infants born before 29 weeks of gestational age (GA).
DESIGN/METHODS: Infants born before 29 weeks GA between 2005 and 2017 were included. The primary outcome was a composite of death or NDI (full-scale intelligence quotient<85, cerebral palsy, vision or hearing impairment) at 3 years of CA. Infants were stratified by maternal PPROM status. Associations were explored using multivariate models.
RESULTS: Of 1231 participants, 481 were in the PPROM group, and 750 were in the No PPROM group. After adjusting for factors, the odds ratio of death or NDI for PPROM vs. No PPROM was 1.22 (95% Confidence Interval 0.93–1.59).
CONCLUSION: Our study suggests that PPROM was not associated with an increased risk of a composite outcome of death or NDI at 3 years CA.

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INTRODUCTION

Preterm premature rupture of membranes (PPROM) is the spontaneous rupture of fetal membranes before 37 weeks gestation and before labour onset [1]. About 3% of pregnancies are affected by PPROM, which is responsible for approximately one-third of preterm deliveries [2]. Approximately 0.4–0.7% of all pregnancies are complicated by PPROM before 28 weeks of gestation [3]. Complications of pregnancy that are commonly associated with PPROM include premature birth, fetal pulmonary hypoplasia, and intra-amniotic infection [4]. An extensive body of literature shows that gestational age (GA) at birth seems to be the strongest single predictor of morbidity and mortality in infants born after PPROM [5]. The degree of prematurity and its direct and indirect consequences are primarily responsible for the broad spectrum of neonatal and childhood adverse outcomes observed following PPROM. After PPROM, the latency period can range from hours to weeks, with most women giving birth within a week of the initial presentation [6]. The extended exposure to the intrauterine environment after PPROM increases the fetus's risk of developing chorioamnionitis and is thought to increase neurodevelopmental impairment (NDI), and cerebral palsy (CP). However, this period also offers a crucial window for administering interventions such as antibiotic prophylaxis, antenatal corticosteroids (ANCS), and magnesium sulfate ($MgSO_4$), which may reduce these risks. Research has indicated that longer latency periods are associated with negative impacts on both short-term neonatal and long-term neurodevelopmental outcomes [6–9]. When accounting for GA at delivery and other confounding factors, an earlier GA at the time of membrane rupture is significantly associated with an increased risk of neonatal death and higher rates of neonatal and childhood morbidity [10, 11]. A few cohort studies with limited follow-up rates comparing infants of a similar GA following preterm birth after PPROM versus other causes of preterm delivery have shown a similar risk of mortality, repeat hospitalizations, and developmental outcomes [12, 13], except few smaller studies which suggested a higher risk of adverse neurodevelopmental outcomes in infants born after PPROM [10, 14, 15].

We were unable to find any studies that examined the neurodevelopmental outcomes at 3 years in extremely low birthweight neonates born to mothers with PPROM. Therefore, our study aimed to explore the associations between PPROM and long-term neurodevelopmental outcomes at 3 years corrected age (CA) in preterm infants born at <29 weeks GA. We hypothesized that preterm infants born to mothers with PPROM have an increased risk of poor neurodevelopmental outcomes at 3 years CA.

METHODS

Study design and study participants

For this retrospective observational cohort study all infants born at < 29 weeks GA in Southern Alberta, Canada, between 2005 and 2017 who were admitted to the Foothills Medical Centre and enrolled in the Neonatal Follow-up Clinic (NFC) program were considered eligible. Study patients were divided into two groups: the PPROM and No PPROM groups.

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Infants with major congenital malformations, chromosomal disorders, complex congenital heart disease, moribund at birth, and those with unavailable follow-up data at 3 years CA were excluded. The term "moribund neonate" refers to a newborn who is critically ill and near death, with little or no chance of survival despite medical intervention. These infants are often in an extremely compromised physiological state due to severe illness, congenital anomalies, or extreme prematurity, where further medical treatment is considered futile. The term is used in clinical settings to describe the most severely ill neonates. We follow the *Strengthening The Reporting of Observational Studies in Epidemiology* (STROBE) reporting guideline [16].

Ethics approval

This study was conducted in accordance with the guidelines and regulations and approved by the Conjoint Health Research Ethics Board (CHREB) of the University of Calgary, Calgary, Canada (CHREB ID: REB23-0252). The collection of informed consent was waived by CHREB for the purposes of this study.

Data collection

Maternal and neonatal demographic and outcome date were collected by trained research assistants using standardized definitions from the Alberta Perinatal Health Program (APHP), Neonatal Intensive Care Unit (NICU) and NFC. NICU data were collected retrospectively, but neurodevelopmental outcome data were collected prospectively by trained data abstractors and recorded in the NFC. For missing data, maternal and infant charts were accessed to fill in maternal history or infant outcome data points. In addition, potential confounding variables such as GA, sex, birth weight, maternal age, ANCS, maternal pregnancy complications such as gestational diabetes, gestational hypertension, maternal infections, chorioamnionitis, site of birth, mode of delivery, APGAR scores, and the maternal highest level of education achieved were extracted for use in regression modelling.

Outcomes

The primary outcome was a composite of death or NDI at 3 years CA. Secondary outcomes included the individual components of the primary outcome - death before 36 months, any NDI, severe NDI, intellectual delay of >1 SD below the mean, CP, visual impairment, and hearing impairment.

Definitions

Any NDI was defined as full-scale intelligence quotient (IQ) composite score <85 (> 1 SD below the mean) as measured by the *Wechsler Preschool and Primary Scale of Intelligence – Third and Fourth Editions (WPPSI-III/IV)*, mild or moderate-severe CP, visual impairment (between 20/60 and 20/200 in the better eye, significant myopia, hypermetropia, or unilateral blindness) or bilateral blindness (corrected visual acuity of < 20/200 in the better eye) or sensorineural hearing loss not requiring or requiring amplification or cochlear implants. Severe NDI was defined as full-scale IQ composite score < 70 (> 2 SD below the mean) using WPPSI-III/IV, moderate-severe CP, bilateral blindness (corrected visual acuity of <20/200 in the better eye), and/or bilateral sensorineural hearing loss requiring amplification or cochlear implants.

Cerebral palsy (CP) was diagnosed by the neonatologist/developmental pediatrician based on a detailed neurological examination. Cerebral palsy is a permanent impairment consisting of a marked deficiency in muscle control and posture characterized by abnormal reflexes and muscle tone. Mild CP has characteristic deficits in muscle tone and reflexes without impairments in activities of daily living. Moderate-severe CP requires daily assistance or the use of specialized equipment. The functional classification of CP was defined using the Gross Motor Functional Classification (GMFC) System [17], with GMFCS 1-2 categorized as mild CP and GMFCS 3-5 categorized as moderate-severe CP.

Short-term neonatal outcomes and covariates

Short-term neonatal outcomes of interest included neonatal medical complications as defined by the Canadian Neonatal Network (CNN) Abstractor's manual [18], including bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA) requiring treatment, intraventricular hemorrhage (IVH) ≥grade III, severe neurologic injury (SNI), retinopathy of prematurity (ROP) (≥stage III or treatment), necrotizing enterocolitis (NEC), culture positive sepsis, and small for gestational age (SGA). BPD is defined as oxygen dependency at 36 weeks CGA [19]. PDA was considered

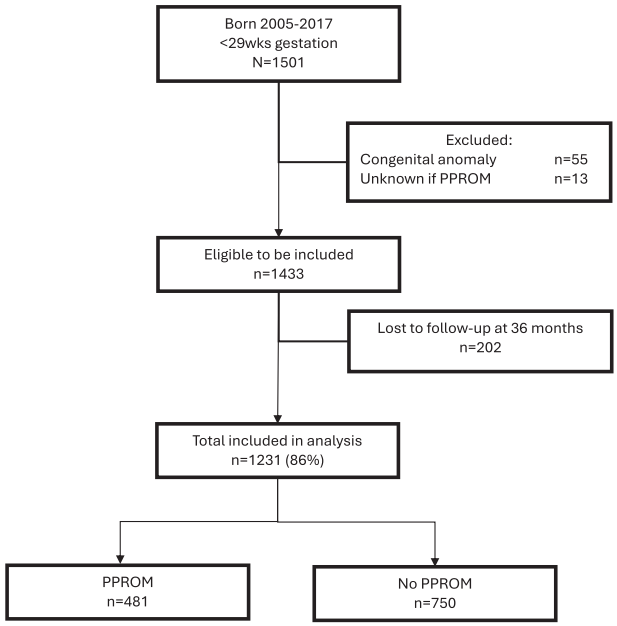

Fig. 1 Flow diagram of study cohort.

hemodynamically significant if the baby received medical or surgical treatment during the NICU stay. IVH was diagnosed radiographically and classified with the Papile classification [20]. SNI is defined as cranial ultrasound evidence of severe intraventricular hemorrhage (Grades III or IV) and/or periventricular leukomalacia (PVL). Ophthalmology diagnosed ROP according to the international classification of ROP [21]. NEC is defined using Bell's criteria [22] stage II or higher. Confirmed sepsis is defined as the isolation of pathogenic organisms from either blood or cerebrospinal fluid in the symptomatic neonate. SGA is defined as a birth weight less than the 10th percentile for gestational age on the Fenton preterm growth chart for gender [23]. Chorioamnionitis was diagnosed based on clinical findings by clinician and/or histologically confirmed by pathologist.

Sample size and statistical analysis

A sample size calculation was done a priori, assuming an α error probably of 0.05, power of 0.8, and moderate effect size of 0.2 based on previous studies [15]. The sample size required to estimate this effect size for a 2 × 2 table with two PPROM groups and a binary outcome was 197 (calculated using G*Power 3.1.9.4). With planned multivariate logistic regression analysis, we selected a birth year cohort of at least 1000 infants to allow for adjustment for confounders.

Demographic, perinatal, and neonatal characteristics, and outcomes for the PPROM and no PPROM groups were compared using the chi-square test or Fisher's exact test for categorical variables, the t-test for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. Multivariate logistic regression models were fit to explore the association between PPROM and 3-year outcomes after adjusting for maternal antihypertensives, ANCS, c-section, chorioamnionitis, inborn, sex, birth weight, and maternal education. Maternal education was excluded from the models for outcomes involving death as this data were unavailable. Confounders were chosen based on the observed differences between groups in the univariate analysis and clinical importance. Post-hoc propensity score matching was also used to control for differences in baseline characteristics between groups. Propensity scores were estimated using a logistic regression model with PPROM as the response variable and maternal antihypertensives, ANCS, c-section, chorioamnionitis, inborn, sex, and birth weight as predictors. The SAS GMATCH macro was used to perform one-to-one matching using nearest neighbour greedy matching without replacement with a calliper width of 0.2 standard deviations of the logit of the propensity score. Balance between groups in the matched sample was assessed by examining standardized differences in the covariates. The matched sample's odds ratios and 95% confidence intervals (CI) were calculated by fitting generalized estimating equations using the logit link function and an unstructured correlation matrix.

Table 1. Demographic, Perinatal and Neonatal Characteristics.

Characteristic	No PPROM $N = 750$	PPROM $N = 481$	p-value[a]
Mean maternal age, years (SD)	31 (SD 8)	31 (SD 5)	0.518
Maternal education any post secondary, n/N (%)	459/652 (70)	274/405 (68)	0.347
Smoking during pregnancy, n/N (%)	126/745 (17)	88/478 (18)	0.501
Gestational diabetes, n/N (%)	42/632 (7)	30/412 (7)	0.692
Maternal antihypertensives, n/N (%)	156/742 (21)	18/479 (4)	< 0.001
Maternal antibiotics, n/N (%)	383/742 (52)	420/480 (88)	< 0.001
Antenatal steroids, n/N (%)	660/744 (89)	452 (94)	0.002
C-Section, *n* (%)	456 (61)	240 (50)	< 0.001
Chorioamnionitis, n/N (%)	108/734 (15)	176/465 (38)	< 0.001
Median gestational age, weeks, (IQR)	26 (22–28)	26 (22–28)	0.458
Mean birth weight, g, (SD)	869 (231)	905 (223)	0.007
Inborn, *n* (%)	632 (84)	448 (93)	< 0.001
Male, *n* (%)	418 (56)	270 (56)	0.890
Multiple birth, *n* (%)	221 (29)	147 (31)	0.682
5 min APGAR < 7, n/N (%)	267/746 (36)	183/477 (38)	0.363
SGA <10th percentile, n/N (%)	58/729 (8)	45/457 (10)	0.261
Median duration of hospital stay, days, (IQR)	93 (29–412) Missing=2	91 (42–441) Missing=5	0.207
BPD, n/N (%)	416/719 (58)	260/445 (58)	0.848
RDS, n/N (%)	709/749 (95)	441 (92)	0.039
Nitric oxide, *n* (%)	66 (9)	48/480 (10)	0.479
Postnatal steroids[c], *n* (%)	146 (19)	94/480 (20)	0.960
Caffeine, *n* (%)	704 (94)	450/480 (94)	0.934
Spontaneous pneumothorax, n/N (%)	30/749 (4)	25 (5)	0.324
Persistent pulmonary hypertension, *n* (%)	65 (9)	52 (11)	0.211
NEC stage 2 and higher, *n* (%)	89 (12)	64 (13)	0.455
Confirmed sepsis, n/N (%)	160/748 (21)	93/480 (19)	0.394
IVH grade III or IV, n/N (%)	121/749 (16)	61 (13)	0.094
IVH grade III or IV or PVL, n/N (%)	135/749 (18)	72 (15)	0.162
ROP stage III or higher or treated ROP[b], n/N (%)	144/595 (24)	72/377 (19)	0.062
PDA requiring treatment, n/N (%)	402/748 (54)	204 (42)	< 0.001

BPD Bronchopulmonary dysplasia, *IQR* Interquartile range, *IVH* Intraventricular hemorrhage, *NEC* Necrotising enterocolitis, *PDA* Patent ductus arteriosus, *RDS* Respiratory distress syndrome, *SD* Standard deviation, *SGA* Small for gestational age, *ROP* Retinopathy of prematurity.
[a]χ^2 test for categorical variables; T-test for maternal age, Mann-Whitney U test for GA, birth weight, duration of hospital stay, duration of ventilation, and duration of respiratory support.
[b]Diagnosed in NICU or up to 8 months adjusted age, includes "plus disease".
[c]Includes dexamethasone, hydrocortisone, or inhaled steroids.

Within the PPROM group, the association between the duration of ROM and outcomes was explored using the chi-square or Fisher's exact test and multivariate logistic regression models. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) with a significance level of 0.05.

RESULTS

A total of 1501 eligible infants were born at < 29 weeks' GA in Southern Alberta and admitted to Foothills Medical Center NICU between 2005 and 2017. Of these, 270 infants were excluded because they had major congenital anomalies, PPROM data were unavailable, or they were lost to follow-up (Fig. 1). 1231 (86%) eligible infants had complete follow-up information, of whom 481 (39%) were in the PPROM group, and 750 (61%) were in the No PPROM group. Of the 477 infants in the PPROM group for whom duration of PPROM was known, 205 (43%) had duration of ≤ 48 h, 202 (42%) had duration of 2–14 days, 61 (13%) had duration more than 14 days, and 9 (2%) had duration of at least > 24 h but exact extent unknown. The demographic, perinatal and neonatal characteristics are shown in Table 1. Mothers in the PPROM group had higher rates of chorioamnionitis (38% vs 15%, $p < 0.001$) and use of intrapartum antibiotics (88% vs 52%, $p < 0.001$) compared to the No PPROM group. The ANCS coverage was also higher in the PPROM group (94% vs 89%, $p = 0.002$). Infants in both groups were similar in terms of demographic characteristics and short-term neonatal outcomes. More infants in the No PPROM group were treated for hemodynamically significant PDA (54% vs 42%, $p < 0.001$). The demographic characteristics of the infants lost to follow-up and those included in the study were similar (Supplementary Table 1).

After adjusting for confounders, the odds of the composite outcome of death or any NDI (primary outcome) in the PPROM group were not significantly different from the No PPROM group [adjusted odds ratio (aOR)] 1.22 (95% confidence interval [CI] 0.93–1.59)] in the logistic regression analyses (Table 2).

The secondary outcomes, including odds of death before 36 months (aOR 1.15 [95% CI 0.73–1.81]), any NDI (aOR 1.12 [95% CI 0.84–1.50]), severe NDI (aOR 0.85 [95% CI 0.54–1.34]), intellectual

Table 2. Outcomes at 36 Months Corrected Age‡ - includes those who died or were seen at 36 months.

	No PPROM $N = 750$	PPROM $N = 481$	*p*-value*	Crude OR (95%CI) PPROM vs. No PPROM	Adjusted OR (95%CI)[a] PPROM vs. No PPROM	Propensity Score-Matched OR (95%CI)[b] PPROM vs. No PPROM
Primary Outcomes						
Death or any NDI, n/N (%)	313/731 (43)	218/474 (46)	0.278	1.09 (0.87–1.37)	1.22 (0.93–1.59)	1.08 (0.81–1.44)
Secondary Outcomes						
Death before 36 months, n/N (%)	77 (10)	45 (9)	0.602	0.90 (0.61–1.33)	1.15 (0.73–1.81)	1.20 (0.70–2.07)
Any NDI, n/N (%)	238/656 (36)	173/429 (40)	0.179	1.19 (0.92–1.52)	1.12 (0.84–1.50)	0.99 (0.73–1.36)
Severe NDI, n/N (%)	77/656 (12)	48/429 (11)	0.782	0.95 (0.65–1.39)	0.85 (0.54–1.34)	0.70 (0.43–1.13)
Intellectual Delay >1 SD below mean, n/N (%)	205/652 (31)	150/428 (35)	0.217	1.18 (0.91–1.52)	1.11 (0.83–1.50)	1.00 (0.73–1.38)
Cerebral Palsy, n/N (%)	59/674 (9)	33/435 (8)	0.491	0.86 (0.55–1.33)	0.91 (0.55–1.51)	0.92 (0.52–1.61)
Visual Impairment/Blindness, n/N (%)	33/675 (5)	18/437 (4)	0.549	0.84 (0.47–1.50)	0.97 (0.47–1.99)	0.70 (0.30–1.59)
Hearing Impairment/Deafness, n/N (%)	14/671 (2)	13/435 (3)	0.342	1.45 (0.67–3.12)	†	1.03 (0.39–2.71)

NDI Neurodevelopmental Impairment, *SD* Standard deviation.
*χ^2 test or Fisher's exact test.
‡The outcomes have different denominators because not all children had all outcomes available.
†Model does not fit due to a small number of events.
[a]Adjusted for maternal antihypertensives, antenatal steroids, c-section, chorioamnionitis, inborn, sex, and birth weight. For outcomes not involving death, also adjusted for maternal education (because data is not available for those who died before hospital discharge).
[b]Propensity score estimated from maternal antihypertensives, antenatal steroids, c-section, chorioamnionitis, inborn, sex, and birth weight. The matched models also adjusted for maternal education for outcomes not involving death. There were 387 matched pairs in each group.

delay >1 SD below the mean (aOR 1.11 [95% CI 0.83–1.50]), CP (aOR 0.91 [95% CI 0.55–1.51]), visual impairment/blindness (aOR 0.97 [95% CI 0.47–1.99]), and hearing impairment/deafness (Crude OR 1.45 [95% CI 0.67–3.12]), were also similar in both groups (Table 2).

Similar results were shown in the post-hoc propensity score-matched analyses based on 387 matched pairs (Table 2).

When compared to the No PPROM group, infants with PPROM duration of > 48 h had similar composite outcomes of death or any NDI (aOR 1.14[95% CI 0.82–1.58]) (Supplementary Table 2). Within the PPROM group, we divided infants into three groups based on the duration of ROM before delivery: ROM ≤ 48 h, 2–14 days and > 2 weeks (Supplementary Table 3). The three groups also did not differ in primary (Composite of death or any NDI, aOR 0.90[95% CI 0.48–1.70] for ROM > 2 weeks vs. ≤ 48 h) or secondary outcomes.

DISCUSSION

This study is representing a large single-center investigation comparing neurodevelopmental outcomes of preterm infants born before 29 weeks GA to mothers with and without PPROM at 3 years CA. Our findings indicate that PPROM is not associated with NDI or death at 3 years. Furthermore, we found no significant correlation between PPROM and individual components of secondary outcomes, including CP, intellectual impairment, visual impairment, or hearing impairment at 3 years CA.

Given the paucity of comparable studies or contradictory findings regarding neurodevelopmental outcomes at 3 years CA in preterm infants, our study provides new insights. Although there was one small study reporting NDI at 24 months CA in premature infants born between 24 and 34 weeks GA, our research fills a critical gap by extending the follow-up to 3 years CA and focusing on a more specific cohort of infants born before 29 weeks GA [15]. Another study by Patkai et al. examined 29 infants born to mothers who experienced PPROM before 25 weeks GA [14]. These infants were followed up by pediatricians at 2 years of age, although without the use of standardized tests. The study identified an increased risk of mortality and morbidity, along with significant delays in motor acquisitions such as walking, running, learning to eat, maintaining cleanliness, stacking cubes, embedding puzzles, and language acquisition. In the context of this findings, it is crucial to address the prevailing assumption that chorioamnionitis is inherently associated with PPROM. This uterine inflammation, triggered by bacterial endotoxins, is widely believed to initiate a cascade of inflammatory mediators that can significantly impact brain development. These mediators influence cerebral blood flow and contribute to white matter destruction, particularly PVL leading to neurodevelopmental impairment [24–27]. In contrast to this study result, at 3 years of age despite higher rates of chorioamnionitis in the PPROM group, our study opposes this assumption by demonstrating no significant association between PPROM and NDI or CP at 3 years CA. This suggests that the relationship between chorioamnionitis, PPROM, and adverse neurodevelopmental outcomes may not be as straightforward as previously thought. Possibly a time window to administer antibiotics, ANCS and $MgSO_4$ may counteract any adverse consequences of PPROM. Due to economic constraints, many perinatal centers in North America do not have longitudinal follow-up beyond 24 months CA. The outcomes at 2 years are not always predictive of long-term outcomes at 3 years. Our study fills this crucial knowledge gap by providing comprehensive data on neurodevelopmental outcomes at 3 years CA. This can significantly enhance the counseling of parents in the NICU.

Studies comparing different latency periods did not report on neonatal long-term neurodevelopmental outcomes. Our study is the first to report the impact of latency (the interval from PPROM to the end of pregnancy) on long-term neurodevelopmental outcomes at 3 years CA. Interestingly, our findings reveal no

significant differences in the risk of NDI, mortality, or other secondary outcomes, including CP and cognitive delay, based on latency. This may be attributed to improved obstetric care and management such as transport to a perinatal center during latency. Additionally, we found that the incidence of early or late sepsis did not significantly differ across groups based on the latency of PPROM. This finding may help explain the lack of significant differences in neurodevelopmental outcomes at 36 months of CA among the infants. Furthermore, while severe oligohydramnios is commonly associated with pulmonary hypoplasia, which could potentially lead to hypoxic respiratory failure, recurrent apnea, and adverse effects on brain development, our analysis revealed no significant difference in the risk of lung hypoplasia across the groups. In contrast, Drassinower et al. [7] conducted a secondary analysis of the BEAM (Beneficial Effects of Antenatal Magnesium Sulfate) trial, which highlighted those infants born to mothers who experienced PPROM for more than 3 weeks faced independent risks of motor and mental delays. Their findings indicated that a duration of PPROM exceeding 3 weeks was associated with a significantly increased risk of motor delays (aOR: 2.12; 95% CI [1.29–3.49]) and mental delays (aOR: 1.83; 95% CI [1.13–3.00]), with Bayley scores of less than 70 at 2 years. However, this prolonged duration of PPROM did not correlate with an increased risk of CP. In contrast, the outcome of the 61 preterm infants within our cohort with PPROM > 14 days was also reassuring.

Strengths and limitations

Our study has several strengths. It is a large study that explore the association between PPROM and neurodevelopmental outcomes at 3 years CA in preterm infants born before 29 weeks GA. Additionally, a multidisciplinary team in the NFC clinic assessed all premature children using reliable and standardized assessment tools, including the WPPSI-III/IV. Also, our cohort had a high follow-up rate of 86% at 3 years CA. The study was conducted at a regional population-based perinatal center, enhancing the generalizability of our findings.

The main limitation of our study is its retrospective design, which introduces potential selection bias. Our study included births over a 13-year period, during which there may have been variations in neonatal care. Additionally, the unblinded status of the multidisciplinary team during assessments may contribute to measurement bias.

CONCLUSION

Our study demonstrates that PPROM is not associated with an increased risk of a composite outcome of death or neurodevelopmental impairment at 3 years CA in preterm infants born before 29 weeks gestation.

DATA AVAILABILITY

Under the Alberta Health Services Data Disclosure Agreement, we cannot provide or make the data available for any purpose to a third party without the prior written consent of Alberta Health Services, Calgary, Alberta. A custom-generated SAS code used for data analysis is available upon reasonable request to the authors.

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AUTHOR CONTRIBUTIONS

HB drafted the initial version of the manuscript. AL and AS were involved in critical review and revision of the manuscript. AL and AS conceptualized and designed the study and were involved in the acquisition and interpretation of the data and the

critical review and revision of the manuscript. ST, AL was involved in data acquisition, statistical analysis and interpretation of the data and the critical review and revision of the manuscript. ST and SM were involved in the acquisition and interpretation of the data and the critical review and revision of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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