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Combined predictors of neurodevelopment in very low birth weight preterm infants

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ABSTRACT

Objective: To evaluate the combined prognostic value of neurological examination, head circumference and cranial ultrasound for neurodevelopmental delay (NDD) in very low birth weight (VLBW, < 1500 g) preterm infants.

Methods: Prospective follow-up study. Preterm infants with VLWB were assessed for NDD using the Mullen Scales of Early Learning test at 24 months of corrected age. Abnormal neurological examination (≥2 deviant items of Hammersmith neurological examination), microcephaly and major ultrasound abnormalities, each performed at term age, were evaluated as predictors of NDD in a multivariable Poisson model.

Results: 35/132 infants (26.5%) had NDD. In the multivariable analysis, microcephaly (RR, 3.2; 95% CI, 1.6–6.7) and major ultrasound abnormalities (RR, 2.7; 95% CI, 1.3–5.7) were associated to NDD. The combination of the two tests showed the highest positive predictive value (100%; 95% CI, 51%–100%), while the combination of normal neurological examination, no major US findings and normal head size at term showed the highest negative predictive value (89%; 95% CI, 78%–95%). The maximum under receiver operating characteristic curve area was for microcephaly or major ultrasound abnormalities (AUC 0.74 (0.65–0.83)).

Conclusion: The combination of head circumference, cranial ultrasound and neurological examination at term age is useful to predict NDD in VLBW preterm infants.

1. Introduction

Preterm birth is still a global health problem, especially in developing countries where access to optimal obstetric and neonatal care is not guaranteed [1,2]. In South America, mortality rates in very low birth weight (VLBW) infants reach 26% [3]. Preterm survival rates have increased in the last decades, making follow up essential. It is important not only to detect cerebral palsy and motor delay but also to timely recognize neurodevelopmental disorders, which can affect 50% of VLBW infants [4].

Prediction of neurodevelopment can be attempted with neurological examination at term age. Standardized tools have facilitated neurological assessment execution, though its capacity for prediction seems to be limited [5,6]. Head circumference is an easy-to-obtain parameter that correlates with brain volume and is a well-known predictor of neurodevelopment [7]. Cranial ultrasound, routinely performed at bedside, can detect brain abnormalities –such as severe intraventricular hemorrhage, ventriculomegaly, periventricular leukomalacia and brain infarction– which might influence future neurodevelopment [8]. It is especially useful in settings where magnetic resonance imaging (MRI) is

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not routinely obtained because of cost or limited access.

Low-cost, effective strategies which can improve detection of patients at risk of developmental abnormalities are of particular interest in developing countries [9]. Neurological examination, head circumference measurement and routine cranial ultrasound are easy to perform, inexpensive and routinely performed in VLBW babies. We hypothesized that the combination of these assessments could improve the prognostic value of each test alone to detect neurodevelopmental delay (NDD).

The aim of this study is to evaluate the combined prognostic value of neurological examination, head circumference and cranial ultrasound, each at term age, for NDD assessed at 24 months corrected age.

2. Methods

2.1. Study population

The NEOLACTO study was a multicenter clinical trial [10] which enrolled newborns with birth weights between 500 and 2000 g, and aimed to evaluate the efficacy of lactoferrin supplementation for sepsis prevention and its effect on neurodevelopment. Infants were enrolled at neonatal intensive care units of three large tertiary-care hospitals in Lima, Peru. Infants with conditions that profoundly affect growth and development such as chromosomal, congenital or brain abnormalities or infants with gastrointestinal problems were excluded from the clinical trial. Since lactoferrin showed no effect on neurodevelopment [10], all VLBW preterm infants followed up until 24 ± 1 months of corrected age with complete examinations at 40 ± 2 weeks of corrected age were included in this study. The clinical trial was approved by the Institutional Review Boards of Universidad Peruana Cayetano Heredia, University of Texas Health Science Center in USA and of each participating hospital. Both parents provided written informed consent.

2.2. Data collection

Infants were enrolled in the first 72 h of life and followed until 24 months of corrected age. Gestational age was determined by first-trimester ultrasound, or in its absence by last menstrual period, or if both were absent by Ballard test. Child neurologists performed all examinations: neurological examinations, measurements of head circumference and cranial ultrasound at day 3–5 after birth, week 3–4 and 40 ± 2 weeks of corrected age. Results of examinations at 40 ± 2 weeks of corrected age were evaluated as potential predictors.

We used the Hammersmith Neurological Examination, consisting of 34 items which assesses posture and tone (ten items), tone patterns (five items), reflexes (six items), spontaneous movements (three items), abnormal signs (three items) and behavior (seven items). It has been standardized for preterm infants and has showed good intra and inter-observer reliability [11]. Scores of individual items outside the standardized 90th-centile range according to the gestational age at birth were considered deviants [12].

Head circumference was considered as the largest occipitofrontal circumference measurement taken with a non-distensible tape. Microcephaly was defined as a head circumference *Z*-score > 2 standard deviation (SD) below the mean according to age and sex of Fenton preterm growth charts [13]. Cranial ultrasound (US) was performed with 7.5 mHz transducers and portable sonography devices (Sonoscape S6, Sonoscape Co., China and Sonosite180, Sonosite Inc., USA). Brain infarction, parenchymal hemorrhage, severe intraventricular hemorrhage (grades 3 or 4), post-hemorrhagic hydrocephalus with ventricular index > 14 mm and periventricular leukomalacia (periventricular echogenicity persistent for ≥7 days and/or periventricular cysts) [14] were deemed as major US abnormalities if found in any of the 3 control dates. Minor cerebral abnormalities were intraventricular hemorrhage (grades 1 and 2), transitory periventricular echogenicity (as disappearance at 7 days or before), ventricular dilatation with ventricular index < 14 mm, lenticulostriatal vasculopathy and widened subarachnoid space.

2.3. Neurodevelopmental evaluation

Two trained pediatricians administered the Mullen Scales of Early Learning (MSEL) to assess neurodevelopmental outcomes at 24 ± 1 months of corrected age. This test assesses child's learning competencies among five domains: gross motor, visual reception, fine motor, receptive language and expressive language abilities, and shows moderate correlation with the scores from the Bayley Scores of Infant Development [15]. Scores of the last four domains yield the *Early Learning Composite Score* which has been standardized for infants from birth to 68 months with a mean ± SD score of 100 ± 15. Neurodevelopmental delay was defined as an Early Learning Composite *Z*-score ≥ 2 SD below the mean (standard score ≤ 70). All infants diagnosed with cerebral palsy [16] had such composite score < 70; hence our NDD definition included these infants.

2.4. Statistical analyses

For bivariate analysis, Fisher's exact test, Student's *t*-test and Mann-Whitney test were used as appropriate. Emphasizing clinical relevance, neurological examination was dichotomized. A proposed cutoff of ≥1 deviant items to define abnormal neurological examination [12] was not associated with NDD in our sample in a bivariate analysis, hence the immediately superior and associated cutoff of ≥2 was used to define it. Abnormal neurological examination, microcephaly and major US abnormalities entered into a multivariable Poisson linear model to assess their relative risks (RR) for NDD. Effect modification between these three tests was assessed. Abnormal neurological examination was not associated to NDD in the multivariable model nor showed effect modification on the other examinations, hence it was excluded from the final model.

Positive predictive (proportion of infants with NDD among those with positive tests) and negative predictive (proportion of infants with normal neurodevelopment among those with normal examinations) values and areas under receiving operating characteristic (ROC) curves (AUC) with confidence intervals (CI) were calculated for each examination and for different results of the three tests assessed in parallel. Multiple chi-squared tests on the equality of two AUC were used to assess the difference between the three combined predictors and each predictor alone. McNemar's test was used to assess the potential advantage of both head circumference and cranial US on neurological examination in determining more infants at risk of NDD. All reported *p*-values are two-sided and those < 0.05 are considered statistically significant. STATA v.14.0 (StataCorp LP, USA) was used.

3. Results

From May 2012 to September 2014, 414 newborns with birth weights between 500 and 2000 g were enrolled in the clinical trial; 255 of them (61.6%) were preterms with birth weights between 500 and 1500 g. Of these 255 infants, 132 (51.8%) were followed-up until 24 months of corrected age and had complete examinations at 40 ± 2 weeks (Fig. 1). From the 123 infants not included in the analysis, 63 died, mainly of sepsis (Supplementary Table 1) and 42 had neurological examinations out of time (Fig. 1).

Baseline characteristics of the infants included in this study are depicted in Table 1. Compared to infants who were not included, included infants had higher gestational age (median 30 vs 29 weeks, $p < 0.001$), higher birth weight (median 1290 vs 1050 g, $p < 0.001$), less often use of mechanical ventilation (31.3% vs 70.7%, $p < 0.001$), less often necrotizing enterocolitis (6.8% vs 20.3%, $p < 0.001$) and intraventricular hemorrhage (11.4% vs 28.4%, $p < 0.001$; Supplementary Table 2). In the same way, relative to infants followed-up until

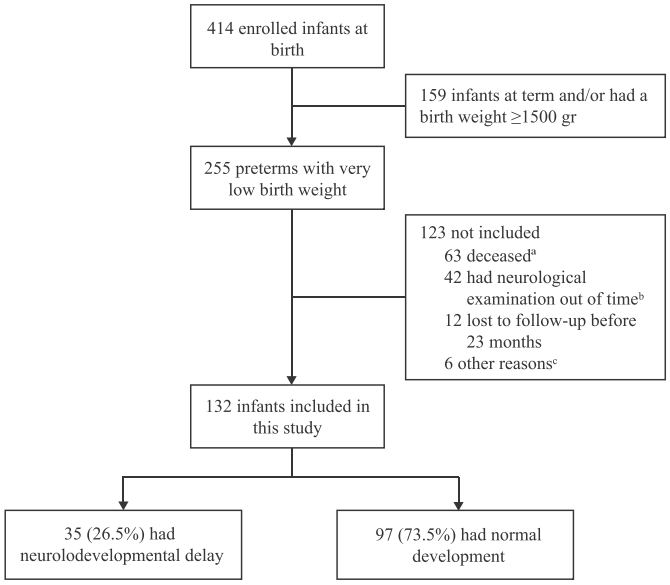

Fig. 1. Flow diagram of the prospective multicenter cohort study among VLBW infants.
[a] Causes of deceases are present in Supplementary Table 1.
[b] Infants with neurological evaluation before 38 weeks and/or after 42 weeks of corrected age but not between 38 and 42 weeks of corrected age as required.
[c] Three failed to comply the protocol, two declined to participate and one was transferred to another hospital.

24 months but without neurological examination at term age, included infants had higher birth weight (median 1290 vs 1171, $p = 0.02$), less often use of mechanical ventilation (31.1% vs 50.0%, $p = 0.04$), less often necrotizing enterocolitis (6.8% vs 19.1%, $p = 0.03$).

3.1. Neurodevelopmental delay and potential predictors

Thirty-five infants (26.5%) had NDD at 24 months of corrected age. Randomized, double-blind, placebo-controlled lactoferrin administration for eight weeks did not result in NDD prevention among this subgroup of infants from the parent clinical trial (17 infants had NDD among 35 who received lactoferrin [48.2%] versus 53/97 [54.6%] who received placebo; RR 0.84, 95% CI 0.5–1.5, $p = 0.54$). In a bivariate analysis, abnormal neurological examination with a cutoff of ≥2 deviant items was associated to NDD (RR, 2.0; 95% CI, 1.1–3.7) but not with the proposed cutoff of ≥1 [12] (RR, 0.9; 95% CI, 0.4–1.8). Most frequent deviant items were: visual orientation (58 infants [43.4%]), flexor head control (21.2%), leg traction (15.9%), alertness (14.4%), palmar grasp (12.1%) and arm recoil (10.6%).

In a multivariable analysis, only microcephaly (RR, 3.2; 95% CI, 1.6–6.7) and major US abnormalities (RR, 2.7; 95% CI, 1.3–5.7) were associated to NDD. Abnormal neurological examination was not associated to NDD nor showed effect modification on the other examinations, hence it was not included in the final model showed in Table 2.

3.2. Predictors' performance

Predictive values, sensitivity, specificity and AUC of each examination alone and combined are presented in Table 3. Comparing examinations individually, microcephaly showed the highest positive predictive value (80%; 95% CI, 55%–93%) and the highest AUC (0.66; 95% CI, 0.57–0.74), and normal neurological examination, the highest negative predictive value (83%; 95% CI, 71%–90%). Microcephaly and major US abnormalities had an AUC of 0.74 (95% CI, 0.65–0.83). The three examinations together showed an AUC of 0.78 (95% CI, 0.68–0.87) which was higher than abnormal neurological evaluation

Table 1
Baseline characteristics of infants from a prospective multicenter cohort study.

Characteristics	Total (n = 132)
Pregnancy and delivery	
Maternal age (years)	29.7 ± 6.2
Single mother[a]	8 (6.1%)
Mother with higher education[b]	60 (45.5%)
Monthly family income (US dollars)	422 (312–660)
Multiple pregnancy	36 (27.3%)
Cesarean delivery	108 (81.8%)
Neonatal	
Male sex	72 (54.6%)
Gestational age at birth (weeks)	30 ± 2.4
24–28 weeks	20 (15.2%)
28–29 weeks	38 (28.8%)
30–31 weeks	36 (27.3%)
32–36 weeks	38 (28.8%)
Birth weight (grams)	1290 (1103–1386)
5-min Apgar score	8.1 ± 1.4
Neonatal resuscitation needed	93 (70.5%)
Small for gestational age[c]	36 (27.3%)
Microcephaly at birth	17/114 (14.9%)
During hospitalization	
Use of total parenteral nutrition	118 (89.4%)
Time with total parenteral nutrition (days)[d]	10.5 (6.5–17)
Age at oral feeding initiation (days after birth)	4.0 ± 2.4
Age at establishment of full enteral feeding (days after birth)	15 (10 − 21)
Culture-proven late onset sepsis	16 (12.1%)
Culture-proven late onset sepsis or probable sepsis	29 (22.0%)
Use of mechanical ventilation	41 (31.1%)
Time with mechanical ventilation (days)[e]	7 (2–19)
Bronchopulmonary dysplasia	27 (20.5%)
Necrotizing enterocolitis (Modified Bell's stage ≥ 2)	9 (6.8%)
Intraventricular hemorrhage	15 (11.4%)
Grade 3 or 4	6 (4.6%)
Periventricular leucomalacia	8 (6.1%)
Growth restriction at discharge[f]	35/110 (31.8%)

Data are expressed in mean ± SD, median (P25–P75) or n (%) as appropriate.
[a] Unmarried or without a partner.
[b] Higher education defined as post-secondary education including college, university and/or institutes of technology.
[c] Defined as weight below the 10th percentile for the gestational age at birth.
[d] Frequency only among infants who were in total parenteral nutrition.
[e] Frequency only among infants who were in mechanical ventilation.
[f] Defined as a length below −2 standard deviation according the World Health Organization Child Growth Standards at hospital discharge [41].

Table 2
Potential predictors at term age of neurodevelopment delay assessed at 24 months of corrected age among VLBW infants from a prospective multicenter cohort study.

Potential predictors	Result	Neurodevelopmental delay, n/N (cumulative incidence[a])	Relative risk (95% CI)	
			Crude	*Adjusted*[b]
Abnormal neurological examination	No	11/63 (17.5)		
	Yes	24/69 (34.8)	2.0 (1.1–3.7)	
Microcephaly	No	23/117 (19.7)		
	Yes	12/15 (80.0)	4.1 (2.6–6.4)	3.2 (1.6–6.7)
Major brain abnormality	No	24/117 (20.5)		
	Yes	11/15 (73.3)	3.6 (2.2–5.7)	2.7 (1.3–5.7)

[a] Cases/100 infants/2 years.
[b] Calculated from a multivariable Poisson linear model in which the three potential predictors entered but then abnormal neurological examination was excluded because of lack of association.

Table 3
Performance of three examinations alone and combined to predict neurodevelopmental delay in VLBW infants from a prospective multicenter cohort study.

Potential predictors	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under ROC curve (95% CI)
Abnormal neurological exam	69 (52–81)	54 (44–63)	35 (25–47)	83 (71–90)	0.61 (0.52–0.70)
Microcephaly	34 (21–51)	97 (91–99)	80 (55–93)	80 (72–87)	0.66 (0.57–0.74)
Major US abnormality	31 (19–48)	96 (90–99)	73 (48–89)	79 (71–86)	0.64 (0.56–0.72)
Microcephaly + major US abnormality					
Microcephaly or major US abnormality	54 (38–70)	93 (86–97)	73 (54–86)	85 (77–91)	0.74 (0.65–0.82)
Microcephaly and major US abnormality	11 (5–26)	100 (95–100)	100 (51–100)	76 (68–82)	0.56 (0.50–0.61)
Abnormal neurological exam + microcephaly + major US abnormality					
Abnormal neurological exam or microcephaly or major US abnormality	83 (67–92)	51 (41–60)	38 (28–49)	89 (78–95)	0.67 (0.59–0.75)
Abnormal neurological exam and microcephaly and major US abnormality	11 (4–26)	100 (95–100)	100 (51–100)	76 (68–82)	0.56 (0.50–0.61)

Data are presented as % (95% CI) except for area under ROC curve which is presented as area (95% CI).

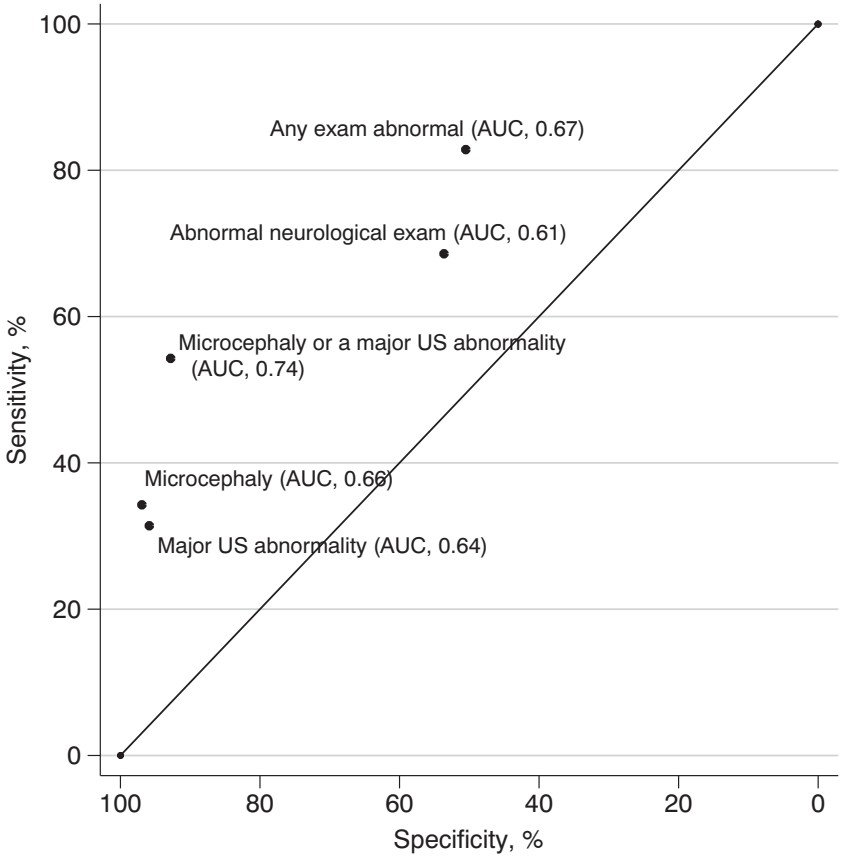

Fig. 2. Sensitivity versus specificity plot of five results among three examinations to predict neurodevelopmental delay in VLBW infants from a prospective multicenter cohort study.
AUC, area under receiver operating characteristic curve; US, ultrasound.

alone (0.17 points of AUC higher, 95% CI 0.06–0.28, $p < 0.001$), microcephaly alone (0.12 points of AUC higher, 95% CI 0.01–0.23, $p = 0.004$), and major US abnormalities alone (0.14 points of AUC higher, 95% CI 0.03–0.25, $p = 0.001$; Fig. 2).

Considering the three examinations assessed in parallel, microcephaly and major US abnormalities, regardless of the neurological examination, showed the highest positive predictive value (100%; 95% CI, 51%–100%). The combination of normocephaly, no major US abnormalities and normal neurological examination showed the highest negative predictive value (89%; 95% CI, 78%–95%). The combination of normocephaly and no major US abnormalities showed a similar predictive value (85%; 95% CI, 77%–91%) ($p = 0.06$). In our sample, neurological examination missed 11 of 35 (31%) infants who developed NDD which were reduced to six infants (17%) with the combination of neurological examination, head circumference and cranial ultrasound.

3.3. Infants with cerebral palsy

Eight infants had cerebral palsy and NDD. They had similar gestational age (28.3 ± 2.5 weeks), birth weight (1117 ± 237 g) and proportion of male gender (50%) than other infants with neurodevelopmental impairment. Major US abnormalities were found in six infants (75%), microcephaly at term age in five (62.5%) and seven (87.5%) had abnormal neurological examinations. All infants with cerebral palsy had two or more abnormal tests, except one infant who had only one predictor which was a grade IV intraventricular hemorrhage. Infants

with cerebral palsy had a median of three deviant items (interquartile range 2–6.5) compared to two deviant items (interquartile range 0–3) among infants with NDD but no cerebral palsy.

4. Discussion

In this study we used the Hammersmith neurological examination [11], a tool originally designed for term infants. The authors revisited the scale and eliminated certain items that were too difficult to measure in NICU settings, were too variable or had too little capacity to discriminate between normal and abnormal [17]. Some authors have evaluated its use in preterms, and found that ranges of normal values are wider in this population, specifically in the areas of behavior and muscle tone [18–20]. Comparing scores for preterm and term babies, items outside 90% are similar in both groups, which suggest that some neurological signs are infrequent at 40 weeks corrected age regardless of gestational age at birth [21].

The ability of a systematic neurological examination to predict neurodevelopmental abnormalities in preterms has been widely explored, and showed variable results. One study found that a non-optimal neurological status at term correlates with lower performances in standard neurodevelopment tests [5]. On the contrary, other studies showed that the mayority of preterm babies with non-optimal evaluations at term age have normal development. These findings might suggest that exam abnormalities might be due to transient postural disturbances or maturation delay patterns in otherwise healthy preterms [22]. Our findings coincide with this observation, which could explain the very low positive predictive and high negative predictive values found for abnormal neurological examination at term.

Microcephaly is associated with a reduction of brain tissue volumes, especially deep nuclear gray matter [7]. Microcephaly at birth is frequent, affecting 7–12% of VLBW infants, whereas suboptimal head circumference (defined as a *Z*-score > 1 SD below the mean) can be detected in 25–30% preterms [7,24]. Percentages of microcephaly in our population of low birth weight preterms were higher and reached 17% at birth and 29% at discharge [10]. In large cohorts of VLBW infants, proportions of babies with microcephaly or suboptimal head circumference increased significantly at 2 year follow up evaluations and correlate with impaired developmental outcomes [25–27], as found in our study. Greater head growth in preterms from birth to term age is associated with higher cognitive and motor scores at 18 months [28]; however, some studies suggest that head growth at post-discharge might be a better predictor of cognitive outcomes [29,30].

Cranial ultrasound (US) is the preferred neuroimaging study at NICU because of its feasibility and availability [31]. In low-resource settings, its cost represents a great advantage over MRI. The predictive value of cranial US has been addressed by several studies. Sensitivity and specificity were 43–44% and 82–87% respectively to predict cerebral palsy when sonograms were performed within the first five days of life. Predictive accuracy is better with additional sonograms, especially if the additional study is performed between 36 and 40 weeks corrected age [8,23,32]. In our study we performed three US evaluations until term age, and the specificity and negative predictive value for developmental impairment were high (96% and 79% respectively). Out of infants with cerebral palsy, 75% had major abnormalities in brain US. Ultrasound might show less sensitivity for less severe white matter lesions [33]; therefore, its capacity to predict non-motor disabilities is yet to be determined [34], although ventriculomegaly (with or without IVH) is associated with increased risk of cognitive impairment [35,36]. In some studies, cranial US showed higher predictive capacity for neurodevelopmental abnormalities at one year of age when compared to neurological examination [22].

Predictive values of tests performed in parallel might be statistically higher than predictive values of each test. Maas [37] compared predictive values of several tests alone and in combination with other tools (brain ultrasound, generalized movements test, sleep organization test) in 100 babies with gestational age < 30 weeks. They found that Prechtl neurological test at term corrected age had the highest predictive value, comparable to that of cranial US, but they could not find an additive effect on prediction power of either test. Other authors compared generalized movement evaluation and brain ultrasound and found high predictive value. [38] Although it is a proven predictive tool for NDD, especially at 4 months corrected age [39], general movements evaluation is not routinely performed in our country because of the lack of trained personnel. Sëtanen found that neurological examination at term age combined with brain MRI or cranial US findings improved the predictive value of either neuroimaging test alone when considering neurosensory outcome at 2 years corrected age [12].

To our knowledge it is the first study to combine these specific three predictors of neurodevelopment in VLBW preterms. We evaluated this unique combination of three tests to improve prediction, and found excellent positive predictive values when all three tests were abnormal, and high negative predictive values when either of the tests was normal. The combination of tests already in use for the evaluation of preterms in hospitals could be a useful tool for health care practitioners in charge of preterm follow up. We used serial brain sonography tests, a strategy that helps increasing the predictive value of this tool.

Our study has limitations. Our sample size was not large, and although not a significantly different population, our study had a great loss of patients because of untimely evaluation. Also, neurological evaluation was performed by four different trained pediatric neurologists, and as such this could lead to greater interrater variability. However, we used a standardized examination to prevent this from happening. The tool we chose for neurodevelopmental evaluation (MSEL) is widely used in preterm population and has close correlation with Bayley's psychomotor and mental indexes [40], but its use limits comparisons with results of similar studies.

5. Conclusion

Our study shows that the combination of findings on neurological examination at term, head size at term, and presence of major abnormalities in serial brain ultrasound is a good predictor of neurodevelopmental impairment in VLBW infants at 2 years corrected age. They can be a useful tool for selection of patients in low-resource settings for early intervention strategies.

Conflict of interest statement

None to declare.

Financial disclosure

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Potential conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

Clinical trial registration

Lactoferrin for Prevention of Sepsis in Infants (NEOLACTO), NCT01525316, https://clinicaltrials.gov/ct2/show/NCT01525316

CRediT authorship contribution statement

Pilar Medina-Alva: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Kevin R. Duque:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing, Formal analysis. **Alonso Zea-Vera:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Sicilia Bellomo:** Data curation, Writing - original draft, Writing - review & editing. **César Cárcamo:** Data curation, Formal analysis. **Daniel Guillen-Pinto:** Data curation, Writing - original draft, Writing - review & editing. **Maria Rivas:** Data curation, Writing - original draft, Writing - review & editing. **Alfredo Tori:** Data curation, Writing - original draft, Writing - review & editing. **Jaime Zegarra:** Data curation, Writing - original draft, Writing - review & editing. **Luis Cam:** Data curation, Writing - original draft, Writing - review & editing. **Anne Castañeda:** Data curation, Writing - original draft, Writing - review & editing. **Aasith Villavicencio:** Data curation, Software, Supervision, Writing - original draft, Writing - review & editing. **Theresa J. Ochoa:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing, Resources, Funding acquisition.

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Appendix A. Supplementary data

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