A PILOT STUDY IN USING COMBINED STANDARDIZED DEVELOPMENTAL TESTING TO ASSESS DEVELOPMENTAL TRAJECTORY OF VERY LOW BIRTH WEIGHT PRETERM INFANTS UP TO TWO YEARS OF AGE

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Abstract. Very low birth weight (VLBW) preterm infants are at high risk for developmental delay, particularly that of language. Currently utilized standardized developmental tests for language development are those adopted or translated from English, which have limited utilization for Thai infants. An approach which can employ two different developmental tests, each appropriate for the child's stage of language development, may help circumvent this problem. We evaluated developmental progression of premature infants who had birth weight (BW) of ≤ 1,500 grams, or ≤ 32 weeks gestational age using The Bayley Scales of Infant Development (Third edition) at one year corrected age and Mullen Scales of Early Learning at 2 years of age. Of the 63 infants studied, the overall median (range) cognitive scores was 100 (55-130) at 1 year. At 2 years of age, the median (range) cognitive scores decreased to 90.5 (49-119). At 2 years of age, the stable/improved scores compared to the scores at 1 year of age were seen in 34 of 60 (56.7%) infants in cognitive, 47 of 57 (82.5%) in receptive language, and 35 of 58 (60.3%) in fine motor subtests. The infants with more GA and received ventilation support for less than 7 days after birth had better FM developmental progress (adjusted RR=1.12; 95%CI: 1.01-1.24, and 1.38; 95%CI: 1.03-1.85, respectively). There was no independent factor associated with better developmental trajectory for language development or motor skills.

Keywords: developmental progress, very preterm, low birth weight, factor

INTRODUCTION

Worldwide, the incidence of infants with premature birth was 9.6 % and 11.1% of all live births in 2005 and 2010 (Beck *et al*, 2010; Blencowe *et al*, 2012). Southeast Asian countries had a higher incidence rate (13.6%) than the global rate (Blencowe *et al*, 2012). According to the annual report by Siriraj Hospital, a referral tertiary care center in Bangkok, Thailand, preterm rate was even higher at 13.7% of live births in 2010 (Chawanpaiboon and Kanokpongsakdi, 2011). Infants with a lower gestational age (GA) or a lower birth weight (BW) were at higher risk for poor outcomes, including neonatal death and neurodevelopmental disabilities (Matthews *et al*, 2015). Sequelae reported include cerebral palsy, visual and auditory impairments, developmental coordination disorder and other neurodevelopmental dysfunctions such as cognitive deficits,

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academic underachievement and behavioral problems (Arpino *et al*, 2010; Arpi and Ferrari, 2013).

However, most studies evaluated the developmental outcomes in a cross-sectional manner, while longitudinal data would offer more predictive and better prognostic information. Moreover, the type of developmental test being performed had a direct bearing on the interpretation of its result. The Bayley Scales of Infant Development (Third edition)(Bayley-III) used 5 domains namely, cognitive, language, motor, socio-emotional behavior and adaptive behavior. This test assessed cognitive domain independently of language and fine motor abilities, making it more superior in assessing children who might have coexisting language and motor impairment such as early-preterm infants. However, while the first 3 domains of Bayley-III could be obtained through observation, the latter two behavioral domains necessitated the use of language and thus were prone to cultural influences. This limitation presented a challenge for using Bayley-III in non-English-speaking children beyond the age of 18 months. Thus, it had been the focal point of many researches. Hanlon *et al* (2016) conducted Bayley-III assessment in normal Ethiopian children and reported lower language scale scores than same-age norms. In a study among Japanese children, language scale scores obtained from Bayley-III were also lower than the age-average scores done by other developmental testing methods (Kono *et al*, 2016). These presented examples of Bayley-III used in non-Indo-European language cultures. The Thai language also differed dramatically from English in many aspects which were the focal point of Bayley-III language evaluation. In particular, Thai language lacked grammatical usage such as pronouns (Language scale: Receptive Item 30, 37, 38-Understands pronouns, Expressive Item 30-Uses pronouns), plurals (Language scale: Receptive Item 39-Understands plurals, Expressive Item 38 Uses plurals) and verb conjugation (Language scale: Receptive Item 34-Understands verb + *ing*, Item 44-Understands past tense, Expressive Item 34-Uses verb + *ing*, Expressive Item 45-Uses present progressive form, Expressive Item 47-Uses past tense, Expressive Item 48-Uses future tense). Instead of conjugating the verb to express temporal relationship, Thais normally added a variety of words, all meaning "already", to state that the action had already been performed Thus, one sentence with a present or past perfect tense in English could be translated to more than one form of sentence in Thai and conveying the correct question became an examiner-dependent task which undermined the purpose of a standardized testing method. In addition, non-verbal communication such as body language and facial expressions were not cultural norms in Thailand. This made generalization of Bayley-III assessment of language to the Thai population problematic.

Conversely, Mullen Scales of Early Learning (MSEL) contained less detailed assessments than Bayley-III, but also utilized less language-specific grammatical assessments and represented a more feasible alternative to longitudinal developmental assessment of Thai children. In addition, when looking at the itemized assessments for both methods, it became apparent that the two tests aligned in their overall concepts. For example, when assessing sentence formation in a 2-year-old, MSEL's criteria for a 'successful' sentence structure specified only that the subject, verb and object were present. Alternatively, Bayley-III required that the child was able to also correctly conjugate verbs to describe the action being shown. When translated into Thai, the child would simply add an adverb instead, since in the Thai language, verb conjugation was not possible. Therefore, using a combination of these two tests to assess and follow language trajectory in at-risk population of children would be ideal for the Thai population.

Siriraj Hospital's High Risk Preterm Clinic (HRPC) received over 511 children a year. In an attempt to obtain developmental status of these high risk infants, and limited by human resources, the clinic utilized Bayley-III for children younger than 1 year of age and MSEL for children older than 2 years of age. The true compatibility of these tests in gauging the developmental trajectories of these infants had not been determined.

The primary purpose of this study was to pilot a technique of using both Bayley-III and MSEL to longitudinally evaluate the developmental trajectory of VLBW, early preterm infants at first and second years of life. Secondarily, the study also described the factors correlated with the improvement or worsening of neurodevelopmental outcomes.

MATERIALS AND METHODS

This was a prospective study which evaluated developmental outcomes of preterm babies whose GA $\leq$32 weeks or whose BW were $\leq$1,500 grams who regularly attended high-risk preterm developmental clinic, Department of Pediatrics, Siriraj Hospital, Mahidol University. The infants born at Siriraj Hospital from January 1, 2012 to October 30, 2016 were recruited from the Intermediate Neonatal Intensive Care Unit. Parents of all participants provided written informed consent. The infants were excluded if they had any underlying conditions that could affect their development other than neonatal complications (such as genetic syndrome, congenital brain anomaly, uncontrolled epilepsy, congenital heart disease, hearing and visual impairment, and other congenital defects associated with developmental delay). Each infant completed a series of growth assessments, neurological examinations, developmental screenings and parents were provided with anticipatory guidance for developmental stimulation. A developmental assessment using the Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III) was performed at 1 year of corrected age, and with the Mullen Scales of Early Learning (MSEL) at 2 years of chronological age. The children's age was not corrected for prematurity at 2 years because of the catch-up theory of the preterm infants' growth and development.

The use of Bayley-III

There were 5 developmental domains in the Bayley-III which were independently assessed and scored, cognitive, language (subtests: receptive and expressive communication; RC and EC), motor (subtests: fine and gross motor; FM and GM), social-emotional, and adaptive behavior. The cognitive, language and motor domains of Bayley-III were used to assess children at 12 months corrected age. Using a table from the Bayley-III administration manual, the raw scores of each subtest were converted to a scaled score [range 1–19; the mean (Standard Deviation; SD) of the normative samples was 10 (3)] according to an individual child's age, and then to a composite score [range 40–160; the mean (SD) of the normative samples was 100 (15)] and a percentile rank.

The use of MSEL

The MSEL included measurements of visual reception (VR), FM, receptive language (RL), expressive language (EL), and GM skills. Using a table in the MSEL administration manual, the raw scores of each subtest were converted to standardized T score [the mean (SD) of the normative samples was 50 (10)], a percentile, and an age equivalence. Then, an Early Learning Composite (ELC) standardized score [mean (SD) of the normative samples was 100 (15)] was obtained from the combination of the T scores of the 4 cognitive subscales (*ie*, the VR, FM, RL and EL subtests). The ELC score was used to measure the global cognitive functioning.

The developmental progress of each infant was evaluated by comparing the results of the Bayley-III assessment at 1 year of corrected age with those of the MSEL at 2 years of chronological age. The following score-pairs were compared: the Bayley-III FM scaled score *vs* the

MSEL FM T score; the Bayley-III RC scaled score *vs* the MSEL RL T score; the Bayley-III EC scaled score *vs* the MSEL EL T score; and the Bayley-III cognitive composite score *vs* the MSEL ELC standard score.

Comparison of Bayley-III scores and MSEL. The infants' developmental trajectories from the Bayley-III scores at 1 year of age and the MSEL scores at 2 years of age were compared with normal infants of the same age. In order to make comparison possible between these 2 tests, we assigned the patient's Bayley-III and MSEL scores into categories according to where they fall in relationship to the standard deviation for that category. The trajectory was defined as declined (D), stable (S), or improved (I), depending on how the two tests compared. Detailed assignment of developmental progress can be found in Table 1.

Multiple linear regression analysis was used to evaluate factors associated with changes in developmental trajectories. Data were analyzed using PASW statistics 18.0 (IBM, Armonk, NY).

RESULTS

Of the 63 infants who completed both evaluations, 27 (42.9%) were male and 47 (74.6%) were singleton. The demographic data of the study populations were at Table 2. The median (range) GA was 29 (25-33) weeks, with 15 (23.8%) of infants were born before 28-weeks GA. The median (range) BW was 1,100 (670-2,350) grams, and 25 (39.7%) infants were born with BW less than 1,000 g. The most common perinatal complications were intraventricular hemorrhage (IVH) (49.9%) and bronchopulmonary dysplasia (BPD) (47.6%). The family histories revealed an advanced maternal age (≥ 35 years) associated with 28 (44.4%) of the infants, and an advanced paternal age (≥ 40 years) with 16 (25.4%). Thirty-four (54%) parents held a bachelor's degree or higher.

The Bayley-III and MSEL scores, including the subtest scores, were listed in Table 3. Four (6.3%) infants refused to do the entire tests. There was only one infant who had Bayley-III scores less than -2 SD of the normative samples at 1-year of corrected age. In contrast, 9 (14.3%) had an MSEL-ELC score of < - 2 SD at 2 years of chronological age. The median Bayley-III cognitive composite score was 100, ranging from 55-130, while the median (range) of the MSEL score was 90.5 (49–119). The two sets of developmental test scores for the same participants were compared at Table 4. A worsened performance in the cognitive subtest was found in of 43.3% of the participants. The receptive-language subtest had the highest number of participants (82.5%) with either stable or improved scores.

After adjustment for the confounding factors (namely, gender, GA, BW>1,000g, ventilator support less than 7 days during the neonatal period, multiple birth, family income, presence of BPD, IVH, and the Bayley-III scores demonstrated

Table 1
Categories of developmental levels according to Bayley III and MSEL scores.

Categories	Bayley III scaled score	Bayley III composite score	MSEL T-score	ELC
Superior	≥17	≥131	≥71	≥131
Above normal	14-16	116-130	61-70	116-130
Normal	7-13	85-115	40-60	85-115
Below normal	4-6	70-84	30-39	70-84
Delay	≤3	≤69	≤29	≤69

Table 2
Demographic data of the participants (N=63).

Demographic data	*n* (%)
Maternal characteristics	
Maternal age (years), median (range)	34 (16-44)
Teenage mother	5 (7.9)
Advanced maternal age; > 35 years	28 (44.4)
Mother as a primary caregiver	40 (63.5)
Single mother	2 (3.2)
Maternal prenatal drug use	3 (4.8)
No antenatal care	3 (4.8)
Maternal education	
Primary school	7 (11.1)
Secondary school	14 (22.2)
College	8 (12.7)
Bachelor Degree	30 (47.6)
Master Degree	4 (6.3)
Paternal characteristics	
Paternal age (years), median (range)	36 (18-49)
Teenage father	1 (1.6)
Advanced paternal age; > 40 years	16 (25.4)
Paternal education	
Primary school	9 (14.3)
Secondary school	9 (14.3)
College	11 (17.5)
Bachelor Degree	26 (41.3)
Master Degree	5 (7.9)
Doctor	3 (4.8)
Family income (Thai Bahts), Median (minimum, maximum)	39,000 (9,000-300,000)
Child characteristics	
Male gender	27 (42.9)
Age in months at Bayley-III evaluation, median (range)	12 (8-15)
Age in months at MSEL evaluation, median (range)	24 (21-37)
Twins	10 (15.9)
Triplets	6 (9.5)
Cesarian section	39 (61.9)
Gestational age (weeks), median (range)	29 (25-33)
Extremely preterm (<28 weeks)	15 (23.8)
Very preterm (28- <32 weeks)	43 (68.3)
Moderate preterm (32- <34 weeks)	5 (7.9)
Birth weight (grams), median (range)	1,100 (670-2,350)
Extremely low birth weight (<1,000 g)	25 (39.7)
Very low birth weight (<1,500 g)	25 (39.7)

Table 2 (Continued)

Demographic data	*n* (%)
Low birth weight (≥ 1,500 g)	13 (20.6)
Small for gestational age	10 (15.9)
Perinatal complications	
Brain ultrasound performed (*n*=51)	
Normal	26 (50.1)
IVH grade I	14 (27.5)
IVH grade II	6 (11.8)
IVH grade III	1 (2.0)
IVH grade IV	0 (0)
Cystic change	3 (5.9)
Hydrocephalus	1 (2.0)
Need ventilator support longer than 7 days (*n*=58)	22 (37.9)
BPD	30 (47.6)
NEC	19 (30.2)
Sepsis with positive blood culture	14 (22.2)
ROP	14 (22.2)
Birth asphyxia	4 (6.3)
Meningitis	2 (3.2)
Hearing impairment	1 (1.6)

Birth asphyxia is defined as the Apgar score at 5 minutes < 7, or cord blood gas at birth demonstrated that pH < 7.2, or base excess over -12. BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage.

at 1year of corrected age), we found that a higher GA (adjusted RR = 1.12; 95% CI: 1.01-1.24; $p = 0.03$) and ventilation support of less than 7 days during the neonatal period (adjusted RR = 1.38; 95% CI: 1.03-1.85; $p = 0.03$) were associated with improved FM developmental progress (Table 5).

Infants with a higher GA tended to make better progress in their RL development (adjusted RR = 1.08; 95% CI: 1.00-1.17; $p = 0.06$). Progress in the development of the FM skills of children with a BW > 1,000 g tended to outstrip that of children with a BW of < 1,000 g (adjusted RR = 0.70; 95% CI: 0.48-1.03; $p = 0.07$). The developmental scores at 1 year of corrected age was not a significant predictor of scores at 2 years of corrected age.

DISCUSSION

This is the first longitudinal study of the developmental trajectory of very preterm infants in Thailand that has used standardized tools for developmental assessment. Overall, children in our study exhibit delayed language trajectory when using the Bayley-MSEL combined longitudinal testing. While normal language testing is the norm for low-birth weight infants in the US, our patients show normal language at one year and a subsequent decline at 2 years. This is particularly true in expressive language, despite

Table 3
The Bayley Scales of Infant and Toddler Development, Third edition (Bayley-III) scores at 1 year corrected age and the Mullen Scales of Early Learning (MSEL) at 2 years of age.

	Bayley-III scores	MSEL scores
	Cognitive CS (*N*=61)	
Median (range)	100 (55-130)	NA
No. with scores < -2 SD: *n* (%)	1 (1.6%)	NA
No. with scores between -1 and -2 SD: *n* (%)	6 (9.8%)	NA
		ELC scores (*N*=62)
Median (range)	NA	90.5 (49-119)
No. with scores < -2 SD: *n* (%)	NA	9 (14.3%)
No. with scores between -1 and -2 SD: *n* (%)	NA	5 (7.9%)
		Visual reception T score (*N*=62)
Median (range)	NA	43 (20-71)
No. with scores < -2 SD: *n* (%)	NA	5 (8.1%)
No. with scores between -1 and -2 SD: *n* (%)	NA	13 (21.0%)
	Motor CS (*N*=59)	
Median (range)	94 (46-118)	NA
No. with scores < -2 SD: *n* (%)	4 (6.8%)	NA
No. with scores between -1 and -2 SD: *n* (%)	7 (11.9%)	NA
Fine motor scores	Fine motor SS (*N* = 59)	Fine motor T score (*N*=62)
Median (range)	9 (1-13)	40 (20-56)
No. with scores < -2 SD: *n* (%)	1 (1.7%)	11 (17.7%)
No. with scores between -1 and -2 SD: *n* (%)	5 (8.5%)	17 (27.4%)
	Gross motor SS (*N* = 59)	
Median (range)	8 (1-13)	NA
No. with scores < -2 SD: *n* (%)	4 (6.8%)	NA
No. with scores between -1 and -2 SD: *n* (%)	8 (13.6%)	NA
	Language CS (*N*=59)	
Median (range)	86 (50-127)	NA
No. with scores < -2 SD: *n* (%)	6 (10.2%)	NA
No. with scores between -1 and -2 SD: *n* (%)	19 (32.2%)	NA
	Receptive communication SS (*N*=59)	Receptive language T score (*N*=61)
Median (range)	7 (1-16)	50 (20-68)
No. with scores < -2 SD: *n* (%)	6 (10.2%)	7 (11.5%)
No. with scores between -1 and -2 SD: *n* (%)	17 (28.8%)	7 (11.5%)
	Expressive communication SS (*N*=59)	Expressive language T score (*N*=61)
Median (range)	7 (1-13)	41 (20-63)
No. with scores < -2 SD: *n* (%)	1 (1.7%)	9 (14.8%)
No. with scores between -1 and -2 SD: *n* (%)	15 (25.4%)	20 (32.8%)

CS, composite score; SS, scaled score; ELC scores, Early Learning Composite scores.

Table 4
Developmental outcomes comparing the performance at 1 year corrected age and 2 years of age.

	n (%)
Cognitive composite score *vs* ELC standard score (*N*=60)	
Stable/Improved	34 (56.7)
Declined	26 (43.3)
FM scaled score *vs* FM T score (*N*=58)	
Stable/Improved	35 (60.3)
Declined	23 (39.7)
RC scaled score *vs* RL T score (*N*=57)	
Stable/Improved	47 (82.5)
Declined	10 (17.5)
EC scaled score *vs* EL T score (*N*=58)	
Stable/Improved	39 (67.2)
Declined	19 (32.8)

ELC, Early Learning Composite; FM, Fine Motor; RC, Receptive Communication; RL, Receptive Language; EC, Expressive Communication; EL, Expressive Language.

Table 5
Independent factors affecting positive developmental trajectories of preterm infants (*N*=41).

	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*p*	Adjusted RR (95% CI)	*p*
RL				
GA	1.07 (1.01-1.13)	0.02*	1.08 (1.00-1.17)	0.06
FM				
GA	1.05 (0.98-1.11)	0.15	1.12 (1.01-1.24)	0.03*
BW >1,000g	1.13 (0.86-1.49)	0.38	0.70 (0.48-1.03)	0.07
Ventilator support < 7 days	1.31 (0.98-1.74)	0.07	1.38 (1.03-1.85)	0.03*

The analysis adjusted for gender, GA, birth weight >1,000g, ventilator support less than 7 days, multiple birth, family income, presence of BPD, IVH, and Bayley-III scores (cognitive scores for ELC outcome, RL scores for RL outcome, EL scores for EL outcome, and FM scores for FM outcome).

by-passing the grammatical differences by using MSEL at 2 years of age. On the other hand, receptive language seems to be spared as are fine motor and cognitive developments. It is important to bear in mind that data show that Thai children are already prone to language delay (NSO and UNICEF, 2016). Culture and child-rearing practices may play a role in this phenomenon. A study in Taiwan, a country with similar language culture, has observed that a more reserved parent-child interaction and lack of expressive gesture are possible explanations (Yu *et al*, 2013). And while this technique of combined standardized testing to negate the need for grammatical evaluation is feasible, this study raises more questions regarding the validity of such method.

In this study, cognitive skill worsens at 2 years of chronological age. In contrast, the majority of the infants have stable or improved RL outcomes. At our institution, speech and occupational therapy are available which specific target FM, RL and EL. However, no integrated program exists which collectively offer cognitive intervention. In addition, Bayley-III testing at 1 year of age assesses cognitive function directly through observed problem-solving tasks. MSEL, conversely, assesses cognition through cumulative evaluation of RL, EL, FM, and visual reception tasks. Therefore, poorer performance on language tasks negates worsening of the overall score. Furthermore, child-rearing practices play an integral role in developmental trajectory and must be accounted for in the analysis and more data collection on child-rearing practices is needed to assess its impact on child development.

It is not surprising to see the effects of GA and BW on the developmental outcomes. The children who have a higher GA and BW display better developmental progress**.** Longer ventilator support is also found to be associated with poorer cognitive and fine motor developmental progress. This finding is consistent with a previous study which states that prolonged mechanical ventilation is a strong risk factor for motor development of preterm infants (Bozynski *et al*, 1987).

Although previous studies that show a relationship between intraventricular hemorrhage, especially if followed by ventricular dilatation, and poorer developmental progression, no such correlation was found in our study and 2 previous studies (Bozynski *et al*, 1987; Palmer *et al*, 1982. While the proportion (50%) of the children who has intraventricular hemorrhage in this study was comparable to a previous study, the proportion of severe intraventricular hemorrhage (*ie*, grades III and IV) and ventricular dilatation was found to be 5%, much less than the 20–35% being reported elsewhere (Brouwer *et al*, 2008). We found no correlation between the developmental performance at 1 and 2 years. This is similar to the findings of a previous study on preterm infants and toddlers in which only 15% of the children demonstrate a stable performance from 6, 12 and 24 months (Janssen *et al*, 2011).

There are limitations in this study. The small number of participants may have resulted in missing potential factors for developmental outcomes. Moreover, an evaluation of GM skills was not performed at the 2-chronological-year-old follow-up as the assessment was focused on the ELC scores. Although the complete developmental progress on GM is missing, the overall scores could provide an indication of the infants' developmental progress. Finally, the results of this study may be subjected to a selection bias towards poorer developmental progression. This is because the more severely impaired an infant's cognitive ability, the more likely that the parents would come for follow-up and early interventions.

In conclusion, the very low birth weight preterm infants displayed a worsening of cognitive ability from 1 year of corrected age to 2 years of chronological age. However, they tended to have stable or improved fine motor and language skills. The factors significantly correlated with the poorer outcomes were a lower GA and the provision of ventilation support for more than 7 days during the neonatal period. Future research with a larger sample size and a longer follow-up period is warranted.

The approach of using combined Bayley-III at one year and MSEL at 2 years represents a novel solution to the problem of validity of language testing in Thailand. Exploration of this concept using linguistic principles can yield a more 'standardized' testing method that can be validated.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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