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Original Article

Motor skills as early indicators for cognitive development in preterm infants with very low birth weight

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ABSTRACT

Background: Preterm babies born with very low birth weight (VLBW, birth weight <1500 g) have inferior long-term neurodevelopmental outcomes to term babies. This study aimed to identify early predictive neuro-developmental factors for future cognitive outcomes that could serve as indicators for early intervention strategies.
Methods: This longitudinal cohort study enrolled 146 VLBW preterm infants, identified between 2011 and 2020. Each child underwent four neurodevelopmental assessments (at ages 6,12, 24, and 60 months) using the Bayley-III and Wechsler Preschool and Primary Scale of Intelligence-IV examinations. Correlation and linear regression analyses were performed to determine the correlation between early neurodevelopmental status and late cognitive outcomes. We concurrently considered neonatal medical complications and socioeconomic variables as risk factors to develop a prediction model of cognitive outcomes at five years old.
Results: A total of 146 VLBW children, born with a mean weight of 1090.4 ± 229.6 g and a mean gestational age of 28.2 ± 2.0 weeks, were evaluated. At 6 months of age, motor outcome was the only factor that exhibited a significant correlation with cognitive development at 5 years of age ($p < 0.01$, $r = 0.242$). The strength of the correlation between motor and cognitive function increased with age, reaching greater significance at 12 and 24 months ($p < 0.001$, $r = 0.409$ and 0.472, respectively). The linear regression model demonstrated that neonatal medical conditions and Bayley motor score at six months old predicted 26% of the variance in the Full-Scale Intelligence Quotient (FSIQ) at five years old.
Conclusion: The results of the present study show that motor function was the earliest and persistent predictor of FSIQ. This underscores the importance of prioritizing motor development in interventions as early as six months of age, which could substantially advance the timing of early intervention programs.

1. Introduction

Preterm babies born with very low birth weight (VLBW, birth weight <1500 g) have inferior long-term neurodevelopmental outcomes to term babies [1–3]. Early detection of poor future developmental outcomes is thus crucial for early intervention. Some studies have demonstrated that VLBW preterm infants show catch-up at school age [4–6]. However, while the stability of cognitive performance from ages two to five years has been reported in some cohorts [7,8], others have shown that most delayed participants performed worse over time [9,10]. In the present study, we aimed to discover the situation in Taiwan, to provide an important indication of the starting time and detection strategies for early intervention projects. Furthermore, although some risk factors, including neonatal medical complications and socio-economic status have been identified, few quantitative predictive models have been proposed [9,11–14]. One prior cohort study presented a model at 12 months of age, but only considered early cognitive performance as a persistent prediction variable [13]. In contrast, although few studies have presented conflicting results, one recent review proposed a link between motor function before 12 months of age and future cognitive development, consistent with our clinical experience [15]. We therefore hypothesized that there is an earlier prediction model, starting from 6

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months of age, encompassing a comprehensive domain of neurodevelopmental assessments, including motor and language assessments, that could provide an extensive direction for early intervention strategies.

In this context, the primary aim of this study was to determine the correlation between neurodevelopmental assessments at 6, 12, and 24 months of age and cognitive performance at five years old to identify the earliest and most persistently predictive neurodevelopmental factors. Second, we aimed to develop a predictive model starting at 6 months of age, encompassing neurodevelopmental assessment with social and biological factors, to predict cognitive outcomes at five years old.

2. Methods

2.1. Participants

This longitudinal study was conducted between 2011 and 2020, enrolling 146 candidates from a medical center located in Taichung, Taiwan. Fig. 1 presents a flowchart of enrollment of the study participants. All neonates were included based on the following inclusion criteria: (1) birth weight from 500 g to 1500 g; (2) gestational age before 32 weeks; and (3) neurodevelopmental assessment results available at 6, 12, 24, and 60 months. Participants who did not complete all four assessments were excluded to obtain accurate prediction results. This study was approved by the hospital (CMUH111-REC2-089), while the ethics committee of the hospital approved ethical considerations. We regularly collected clinical assessment results from medical centers. The sample size was determined on the basis of the number of cases during the study period.

2.2. Assessment of neurodevelopment

All participants completed the Bayley Scales of Infant Development (BSID) assessment at 6, 12, and 24 months and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at 60 months. A correlation analysis was subsequently conducted between the BSID and WPPSI results.

2.2.1. Bayley Scales of Infant Development, third edition (BSID III)

The BSID III was used to assess neurodevelopment in all participants at 6, 12, and 24 months of age. The total cognitive, motor (including fine and gross motor), and language (including receptive and expressive domains) scores were used as continuous variables to indicate participant performance at each age. Based on previous studies and consensus, the score was defined as normal if the Bayley III cognitive or motor score was ≥85, borderline deficit as a score between 70 and 84, and developmental delay as a score <70 [9,14].

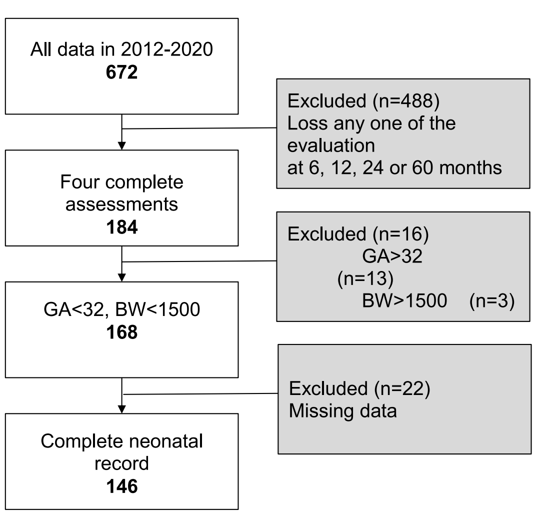

Fig. 1. Flowchart of participants selection through the study.
Abbreviations: Birth Weight(BW), Gestational Age(GA).

2.2.2. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV)

The Chinese version of the WPPSI-IV was applied for the cognitive assessment of all participants at a corrected age of 5 years [16]. The Full-Scale Intelligence Quotient (FSIQ) outcome contains five subscales: verbal comprehension, visual spatial, fluid reasoning, working memory, and processing speed. Based on previous studies and consensus, cognitive function was defined as normal if FSIQ was ≥85, borderline cognitive deficit as a score between 70 and 84, and abnormal cognitive outcomes as FSIQ <70 [9,14].

2.3. Other potential predictors

We identified several candidate variables from prior studies that may have a high predictive value for 5-year-old children's cognitive development [9,11–14]. Variables were divided into two categories. Neonatal conditions included birth weight, sex, gestational age, multiple births, intraventricular hemorrhage (IVH), ventriculomegaly, periventricular leukomalacia (PVL), sepsis, retinopathy of prematurity (ROP), chronic lung disease (CLD), seizure, and respiratory distress syndrome (RDS). The variables were defined as follows: IVH was graded according to the criteria of Papile et al. [17] Ventriculomegaly was diagnosed when the atrial diameter is ≥ 10 mm, which is 2.5–4 standard deviations above the mean [18]. PVL was defined as a categorical variable (0 or 1), and was diagnosed under brain ultrasound. Seizures were defined based on clinical observation [19]. ROP was graded from stage 1–5, according to the criteria of Brown et al. [20] CLD was defined as the use of supplemental oxygen at 36 weeks of gestation age [21]. Infants with PVL, seizures, and ventriculomegaly, as well as those with IVH grades III and IV, RDS grades III and IV, and Apgar scores of 1–5, were considered serious cases. The second category involved paternal and maternal education along with socioeconomic status (SES), which was represented by a single SES factor. SES classification took education and occupational norms in Taiwan into consideration, as well as the methodologies adopted from previous research based on a Taiwan cohort [22,23].

2.4. Statistical analysis

Correlation and regression analyses were performed to determine early functional status and late cognitive outcome using R-language. Fig. 2 presents a flowchart of the statistical analyses.

After integrating the VLBW data from the China Medical University Hospital (CMUH) outpatient system, we cleaned the dataset using a rule-based outlier detection procedure. We were interested in the scale assessment at different ages, which included three BSID III tests and a WPPSI-IV test.

We predicted FSIQ at 5 years of age by building a linear regression model with candidate variables, including sex, birth weight, gestational age, gravidity and parity, multiple births, IVH, ventriculomegaly, PVL, sepsis, ROP, CLD, seizure, RDS, Apgar scores at 1 and 5 min, and BSID III scores. Birth weight, Apgar scores at 1 and 5 min, and BSID-III scores were considered continuous variables, whereas other neonatal medical factors were categorical variables graded by disease severity.

We performed a two-stage procedure for model establishment because of the model complexity and strong correlation between the candidate variables. First, the least absolute shrinkage and selection operators (LASSO) is adopted. Using the L1-norm penalty and MSE-Optimization, variables that were more important for prediction were obtained. Following variable selection, some relationships between the dependent variables remained. The Ridge trick at 2nd stage to reduce collinearity. Finally, the shrinkage regression coefficients were estimated.

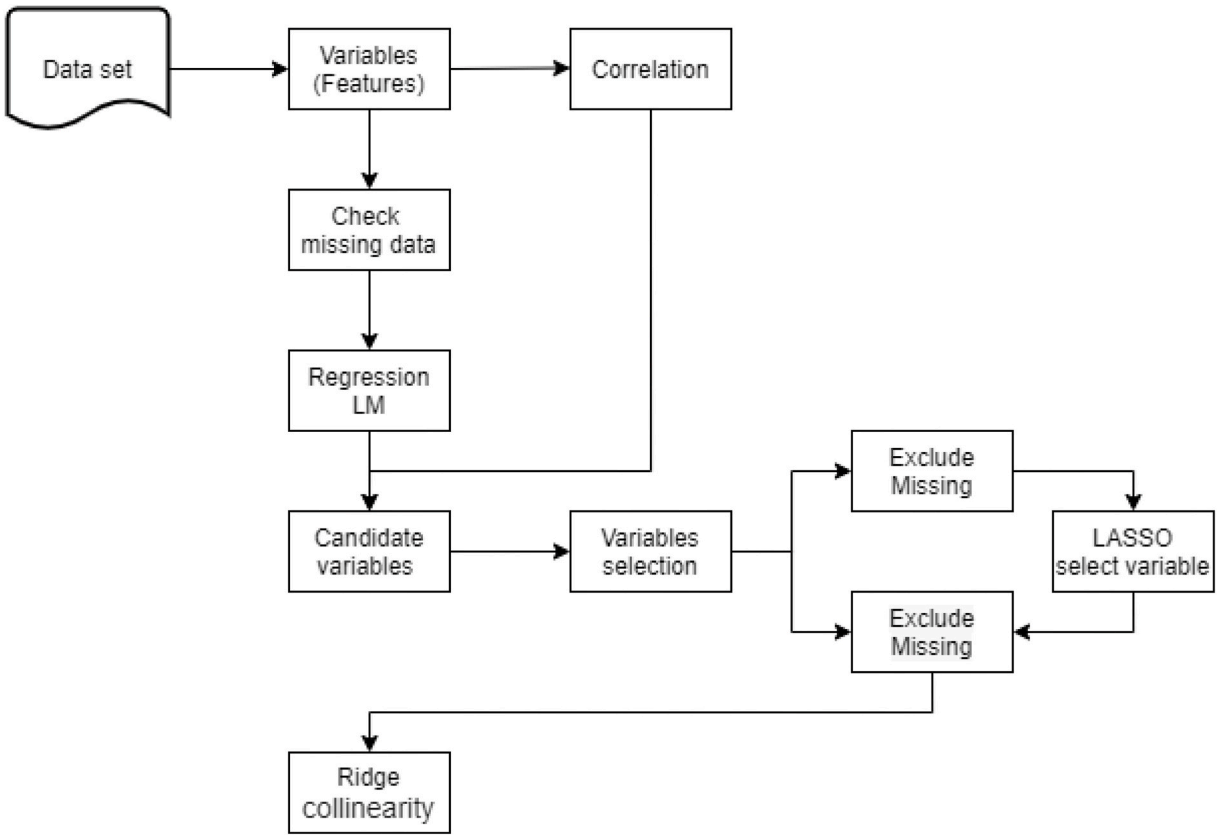

Fig. 2. Flowchart of statistical analysis through the study.
Abbreviations: Liner Model (LM), Least Absolute Shrinkage and Selection Operator (LASSO).

3. Results

3.1. Demographic characteristics

Among the 146 infants included in the study, the sample mean (SD) birth weight was 1090.4 (229.6) g, while the mean gestational age was 28.2 (2.0) weeks. The average follow-up period was five years. The mean (SD) of the FSIQ of the cohort was 95.0 (14.4). Table 1 provides an overview of the infants' birth conditions.

Our investigation revealed that 96.6% of the infants demonstrated normal cognitive function (Bayley III cognitive score >85) at 6 months of age, decreasing to 80.3% by 5 years. Furthermore, in the cognitive delay group at five years of age, 71.4% of the participants demonstrated normal cognitive function at six months, which substantially decreased to 14.3% by two years of age.

3.2. Correlation between neurodevelopment at 6, 12, and 24 months and cognitive performance at 5 years old

Table 2 presents the associations between BSID motor, language, and cognitive scores at 6, 12, and 24 months, and WPPSI scores at 5 years of age. At 6 months, motor performance exhibited the strongest correlation with FSIQ, reaching statistical significance ($p \leq 0.01$). Notably, this result was significantly correlated with the subscale of the processing speed index ($p < 0.01$), visual-spatial index, and fluid reasoning index ($p < 0.05$). In contrast, cognitive and language scores at six months of age did not correlate with the FSIQ score at five years of age. Starting at 12 months of age, all domains of the BSID showed a significant correlation ($p < 0.001$) with FSQI. Overall, motor function was the earliest and most strongly correlated with neurodevelopmental factors. The correlation between motor function and FSIQ score at 5 years of age was significant and persistent from 6 months of age, surpassing the

Table 1
Characteristics of the participants Abbreviations.

Characteristics	N (%)/mean ± SD
Gestational age (weeks)	28.2 ± 2.0
Birth weight (gram)	1090.4 ± 229.6
Sex (female)	74(50.6%)
Maternal age (years)	32.9 ± 4.7
Paternal age (years)	35.2 ± 4.8
Multiple birth	31(21.2%)
single	115 (78.8%)
twins	29 (19.9%)
triplets	2 (1.4%)
IVH grade III/IV	7(4.8%)
PVL	8(5.5%)
RDS grade III/IV	29(19.9%)
Apgar <6 at 1 min	21(14.4%)
Apgar <6 at 5 min	2(1.4%)
Ventriculomegaly	42(28.8%)
Sepsis	14(9.6%)
CLD	52(35.6%)
ROP	72(49.3%)
Bayley	
Cog_6 m	97.8 ± 9.3
Lag_6 m	99.8 ± 9.3
Motor_6 m	98.5 ± 13.4
Cog_12 m	98.9 ± 11.9
Lag_12 m	94.9 ± 10.3
Motor_12 m	95.9 ± 13.2
Cog_24 m	92.7 ± 10.9
Lag_24 m	92.2 ± 13.5
Motor_24 m	92.7 ± 12.3
WPPSI_FSIQ_60 m	95.0 ± 14.4

Chronic Lung Disease(CLD), Cognitive(Cog), Full-Scale Intelligence Quotient (FSIQ), Intraventricular Hemorrhage (IVH), Periventricular Leukomalacia (PVL), Retinopathy of Prematurity (ROP), Respiratory Distress Syndrome (RDS), Language(Lag).

Table 2
The correlation between BSID-III at 6,12,24 months and WPPSI-IV at 60 months.

	Cog 2y	Lag 2y	Motor 2y	Cog 1y	Lag 1y	Motor 1y	Cog 6 m	Lag 6 m	Motor 6 m
FSIQ	0.588***	0.528***	0.472***	0.369***	0.387***	0.409***	0.204*	0.169*	0.242**
VCI	0.500***	0.564***	0.378***	0.322***	0.378***	0.262**	0.150	0.108	0.153
VSI	0.526***	0.310***	0.409***	0.362***	0.312***	0.409***	0.112	0.167	0.214*
FRI	0.488***	0.371***	0.407***	0.357***	0.317***	0.322***	0.150	0.112	0.190*
WMI	0.276**	0.195*	0.148	0.175*	0.170	0.217*	0.108	0.066	0.122
PSI	0.465***	0.394***	0.475***	0.240**	0.213*	0.400***	0.138	0.025	0.248**

Note: Full-Scale Intelligence Quotient (FSIQ), Fluid Reasoning Index(FRI), Processing Speed Index(PSI), Verbal Comprehension Index(VCI), Visual Spatial Index(VSI), Working Memory Index(WMI).
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

association with cognition score at the time.

3.3. Predictive equation for cognitive outcome at five years old

Using a multivariate regression analysis, we identified several crucial influencing factors. Table 3 presents the variables correlated with 5-year-old cognitive development, with each column representing an independent predictive model at six, 12, and 24 months. The included factors were the results of the LASSO and Ridge trick to mitigate collinearity among neonatal medical conditions and eliminate non-essential variables. First, Apgar score at 1 min and SES consistently emerged as positive predictive factors, with positive coefficients of 1.124 and 2.2599, respectively. In contrast, sepsis and ROP were identified as negative predictive factors, with the influence of ROP diminishing by the age of two years. Second, the effect of sex on later cognitive outcomes, which showed that girls performed better than boys, was observed only at 6 and 12 months of age. Finally, at six months of age, only motor function was included as a crucial neurodevelopmental variable.

The correlations between the predicted value and the true score of the FSIQ at five years old were 0.516, 0.612, and 0.625 at 6, 12, and 24 months, respectively. The prediction model can be interpreted as follows: the model at six months old is y(prediction of the cognitive outcome at five years old) = 64.99 + 1.12*Apgar 1 min - 9.8 * sepsis - 1.27 *ROP + 0.15 * Bayley motor score at 6 months of age - 3.15 * sex category - 0.96 * gravity. Notably, at 6 months of age, 26% of the variance in 5-year-old cognitive outcomes can be explained by the combination of neonatal medical conditions and a single motor outcome from the Bayley Scale. As age increased, neurodevelopmental outcomes at 12 and 24 months enhanced the predictive accuracy to 36% and 38%, respectively.

Table 3
The prediction model and variables for 5-year-old cognitive development at different ages.

Candidates _ Age	6 months	12 months	24 months
Intercept	64.9906	29.0102	30.5908
Apgar_1min	1.124	1.0133	0.7269
Sepsis	−9.8097	−8.5591	−5.5244
ROP	−1.2751	−1.2644	a
SES	2.2599	2.0010	1.2434
Bayley Cog_6 m	a	b	b
Bayley Lag_6 m	a	b	b
Bayley Motor_6 m	0.1549	b	b
Bayley Cog_12 m	b	0.1801	b
Bayley Lag_12 m	b	20.202	b
Bayley Motor_12 m	b	2.1545	b
Bayley Cog_24 m	b	b	0.304
Bayley Lag_24 m	b	b	0.1716
Bayley Motor_24 m	b	b	0.1030
Sex	−3.1569	−2.9588	a
Gravity	−0.9629	a	a
Correlation(FSIQ, FSIQ)	0.516	0.612	0.625
R^2 [c]	0.2607	0.3660	0.3822

Abbreviations: Full-Scale Intelligence Quotient (FSIQ), Retinopathy of Prematurity (ROP), Socioeconomic Status (SES).
Note.
[a] The variable is deleted via variable-selection(Least Absolute Shrinkage and Selection Operator, Lasso).
[b] The variable is not in covariates. According to 3 evaluation time points (6 months, 12 months, and 24 months), Bayley scales are respectively involved in the model.
[c] The R^2 in the table represents the proportion of variance in the dependent variable that is explained by the independent variables in the model. R^2 ranges from 0 to 1, with a higher R^2 value suggesting that the model's predictions closely match the actual data.

4. Discussion

In the present study, we found that, at six months of age, motor function was the only neurodevelopmental factor that correlated with cognitive performance at five years of age. Furthermore, we advanced the predictive model to six months of age, identifying predictive factors that could provide early detection of poor neurodevelopmental outcomes in the high-risk group.

In this study, 28 of 146 (19%) VLBW patients had abnormal cognitive outcomes at five years old. The proportion of abnormal cases was consistent with that of a large national cohort study enrolling 1427 participants from Taiwan [14]. In other comparable studies with smaller cohorts, the prevalence of cognitive disability ranged from 33.8% to 38%, which was higher than our demographic data [9,13]. The incidence rates of severe IVH (grades 3 or 4) and PVL in our study were similar to those reported in other studies [9,13]. Compared with another study, the proportion of severe cases of ROP (grades 3 or 4) was slightly higher in our cohort [9].

Overall, our study revealed a decline in the proportion of VLBW preterm infants exhibiting normal cognitive function between the ages of two and five years. This finding aligns with prior research indicating cognitive deterioration in VLBW preterm infants at five years of age [10]. However, it contrasts with other Taiwanese studies that reported either a stable (64.1% and 66.2%) or increased (43.4%–72.1%) proportion of children maintaining normal cognitive function over the same period [9,14]. These discrepancies may be attributed to demographic differences, particularly the lower incidence of severe cognitive delay in our cohort. This indicates that, even among populations with fewer initial cognitive impairments, there is a notable risk of cognitive decline between two and five years of age. Additionally, our findings are consistent with studies reporting that a subset of children (2.58% and 18.4%, respectively) who exhibited normal neurodevelopment at two years ultimately developed abnormalities by five years [9,14]. In our study, 14.3% of children who were developmentally normal at two years experienced delays by the age five. These results underscore the critical importance of long-term follow-up in identifying and addressing emerging developmental issues in this population.

This study identified a significant correlation between motor development, as assessed by the Bayley-III Motor Scale at 6 months of age, and FSIQ, surpassing the correlation observed between cognitive function, measured by the Bayley-III Cognitive Scale at the same age, and FSIQ [15]. This finding aligns with a longitudinal observational study indicating that preterm infants exhibiting school performance problems at 10 years of age demonstrated delayed motor development as early as 6 months, with this trend persisting up to 30 months of age [9,13,24,25]. In contrast, one study identified a correlation solely between the Alberta Infant Motor Scale at 12 months and cognitive function at five years of age, with no association identified with the Bayley motor score [13]. This discrepancy may stem from the inclusion of gross, fine motor, and cognitive skills in the Bayley-III Motor Scale, which may not be stable at 12 months of age. Another study further demonstrated a significant correlation between the Bayley motor score at two years of age and cognitive outcomes [9]. Two underlying mechanisms have been proposed to explain this association between early motor development and later cognitive outcomes: a predisposition to general brain impairment in preterm infants affecting both motor and cognitive domains, and a perception-action cycle enabling cognitive skill development through environmental interaction facilitated by early motor function [15]. Overall, our findings confirm the hypothesis of an early and longitudinal link between motor and cognitive functions, thus underscoring the importance of prioritizing motor development in interventions as early as six months of age. This approach could substantially advance the timing of early intervention programs and suggests that interdomain training may serve as a novel intervention strategy.

Several medical and socioeconomic risk factors were identified. Consistent with previous studies, socioeconomic status, Apgar score at 1 min, and ROP were all identified as significant risk factors [9,11–14]. Additionally, we identified sepsis during the neonatal period as a novel risk factor that demonstrated a sustained influence from 6 months to 2 years of age. Although factors associated with brain injury, such as PVL, IVH of all grades (1–4), and ventriculomegaly, were initially included in the regression model, they were excluded from the prediction equation after adjusting for collinearity through LASSO regularization. This result was different from previous studies [9,14], while this may be attributed to several reasons. Firstly, adjustment of the LASSO is necessary to mitigate potentially high correlations with neonatal medical complications. This adjustment stabilized the parameters estimated in the multivariate regression analyses and avoided compromising the explanatory power of the model. Using this approach, the predictive factors included in our model were purer than those used in other studies.

Our study advances the prediction model for 5-year-old cognitive development to the earliest time of six months, elucidating up to 26% of the variance in predicting outcomes at five years of age. While another cohort study achieved predictive capabilities of 39% at 12 months and 54% at 24 months for 5-year cognitive development, our study distinguishes itself by comprehensively considering motor and language scores [13]. Furthermore, instead of utilizing a single Neonatal Medical Index as a categorical variable for medical conditions, we specifically analyzed the predictive value of each preterm neonatal disease, to provide more precise and detailed information to caregivers and physicians.

The strengths of this study lie in the statistical method we applied, which eliminated collinearity between variables to attain a more precise model. In addition, every participant underwent four complete assessments with consistent measurement tools, ensuring a robust database for correlation studies and comparison of the three continuous timing prediction models at 6, 12, and 24 months of age. However, the following limitations were identified. First, it was conducted at a single medical center. Although the sample size was limited compared to that of cohorts from the Taiwanese National Health Insurance database, this approach afforded access to more detailed medical records and clinical data. This enabled the identification and inclusion of sepsis as a risk factor for the first time. Second, we did not include a term control group, as a significant proportion of term infants did not undergo follow-up assessments until the age of five years. The lack of complete data for the four assessment points (6, 12, 24, and 60 months) may have affected the precision of our predictive model.

Based on these findings, future studies investigating the correlation between motor function as early as 6 months of age and subsequent cognitive skills should be conducted. First, randomized controlled trials are required to determine whether early intervention in motor training can enhance cognitive performance. Second, by analyzing the WPPSI subscales, we aim to further elucidate the underlying mechanism linking the levels of motor development, postural control, and motor behavior using the FSIQ. Overall, these findings provide valuable and detailed guidelines for developing early intervention strategies.

5. Conclusion

This study validated the persistent link between motor function and the FSIQ at five years old from six months of age. Our study further advances the early prediction model of cognitive outcomes at six months of age by collectively considering medical complications, comprehensive domains of neurodevelopmental outcomes, and socioeconomic factors. These findings inspired us in two directions: 1) Early motor intervention at six months of age is highly recommended for children with neurodevelopmental delays. 2) Substantial data could be used to develop further AI-predictive model training to achieve higher predictive accuracy.

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Declarations of competing interest

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