Journal of Neurology and Experimental Neural Science
Groteklaes H, et al. J Neurol Exp Neural Sci 8: 172.
www.doi.org/10.29011/2577-1442.100072
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Research Article

Correlation of Hammersmith Neonatal Neurological Examination (HNNE) At Discharge and Long-Term Outcome in Very Preterm Infants

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Citation: Groteklaes A, Sina H, Kroll C, Demir S, Rösler B, et al. (2026) Correlation of Hammersmith Neonatal Neurological Examination (HNNE) At Discharge and Long-Term Outcome in Very Preterm Infants. J Neurol Exp Neural Sci 8: 172. DOI: 10.29011/2577-1442.100072.

Received Date: February 16, 2026; **Accepted Date:** 23 February, 2026 **Published Date:** 27 February, 2026

Abstract

Introduction: As the worldwide number of surviving very-low birthweight (VLBW) and extremely-low-birthweight (ELBW) preterm neonates is continuously rising, recognition and treatment of neurodevelopmental impairments is becoming increasingly important. Low-resource clinical examinations such as the Hammersmith Neonatal Neurological Examination (HNNE) could be of use to early identify neonates at risk for adverse neurological outcome and implement early neurorehabilitative treatments. However, the correlation between HNNE and long-term neurological outcomes has not been thoroughly investigated in VLBW and ELBW neonates, particularly in those with intraventricular hemorrhage (IVH). **Methods:** We analysed the correlation between HNNE scores at discharge and long-term neurodevelopmental outcomes, as assessed by the Bayley-III Scales of Infant Development (BS) at 2 years of age, in VLBW and ELBW children. **Results:** A total of 38 VLBW and 50 ELBW neonates were included in the study, of whom 16 were diagnosed with IVH. We found significant positive correlations between HNNE scores at discharge and long-term motor outcomes at 2 years of age, with the strongest correlations observed in neonates with IVH. Additionally, weak positive correlations were detected between HNNE scores at discharge and both language and cognitive outcomes. **Conclusion:** HNNE is a low-resource, simple-to perform clinical tool to detect VLBW and ELBW neonates at risk for adverse motor outcome, especially in VLBW and ELBW neonates with IVH. HNNE supports the implementation of early neurorehabilitative treatments in this patient population with the aim to improve their long-term outcome.

Keywords: HNNE; long-term outcome; IVH; ELBW, VLBW; Preterm

Introduction

Recognition and treatment of neurodevelopmental impairment is becoming increasingly important as the worldwide number of surviving very preterm neonates is continuously rising [6-29]. Thus, the recognition and treatment of morbidity influencing neurodevelopmental impairment is of increasing importance [1-4]. Therefore, low-resource clinical examinations such as the Hammersmith Neonatal Neurological Examination (HNNE) may help to identify neonates at risk for suboptimal neurological development and potentially help to improve their long-term outcome [12] . Preterm birth is associated with a higher risk for motor, learning and behavioural impairment [2, 24, 28, 30, 33]. Depending on gestational age, preterm children have by 40.5% elevated prevalence of mild to moderate motor impairment compared to term children [33]. Intraventricular hemorrhage (IVH) is a particularly common and clinically significant complication in very preterm infants, with an overall incidence of approximately

20-25% [22-27]. Preterm neonates with IVH are at increased risk for neurodevelopmental impairment [8-22]. While it is well established that high-grade IVH is associated with adverse long-term outcomes, such as the development of cerebral palsy (CP) [1,7,17-20]). Even low-grade IVH can have a significant impact on neurodevelopment impairment [20]. Early identification of those infants at risk for suboptimal neurological development in this vulnerable patient population helps to implement potential neuroprotective therapies and provide early neurorehabilitation and thus may improve neurodevelopmental long-term outcomes of preterm infants [3-31]. As the global survival rate of preterm neonates continues to rise, the associated morbidity is also increasing, making this issue of growing importance. Diagnostic approaches to identify neonates at risk for suboptimal neurological development include clinical, radiological, and instrumental assessments such as detailed clinical examination, cranial ultrasound, magnetic resonance imaging (MRI) and electroencephalography (EEG) [3-22]. The predictive value of cranial MRI in preterm infants is well established [3]. However, access to MRI remains severely limited, particularly in low- and middle-income countries which have the highest prevalence of preterm birth and perinatal brain injury [21-25]. Even in high-resource settings, MRI is often not performed routinely because of the substantial logistical and financial demands. Therefore, there is an urgent need for low-resource diagnostic tools to identify neonates at risk for suboptimal neurological development. Clinical neurological examinations at discharge represent a promising tool to identify neonates at risk for suboptimal neurological development in a non-invasive and low-resource manner and thus to provide them with early treatment [11]. The HNNE is a standardized clinical examination used to evaluate the neurobehavioral performance of preterm infants at term-equivalent age [11]. It consists of 34 items divided into six categories describing motor and behavioural functions [11]. The examination is easy to perform, can be performed by physiotherapists, physicians, or other trained clinical staff, and demonstrates high interrater reliability [14]. Originally designed for a cohort of term infants [11]. It has been also validated in preterm infants at term equivalent age [5-13]. In this study, we aim to investigate whether HNNE scores predict long-term outcome in preterm neonates with very low (VLBW)- and extremely low birth weight (ELBW) including a subgroup of preterms with IVH.

Methods

Data Collection and Measures

Data was retrospectively collected from preterm neonates born at or transferred to the neonatal intensive care unit (NICU) of the University Hospital Bonn (Germany) between February 2020 and December 2022. Preterm infants with a birth weight up to 1500 grams and a gestational age < 30 weeks of gestation were included in the study. Included preterm were categorized as very low birth infants (VLBW) with a birth weight <1500 g and extremely low birth (ELBW) with a birth weight<1000g. Information related to each neonate's medical history was collected from the clinical notes. Routine clinical parameters, as gestational age, birth weight, head circumference, gender, multiple birth, APGAR scores and birth pH were recorded. In addition, data on infection during hospitalization, management of persistent ductus arteriosus, mechanical ventilation and IVH were recorded. The study was approved by the local ethics committee (2024-188-BO).

Hammersmith Neonatal Neurological Examination (HNNE)

All included neonates were examined using HHNE before discharge by an experienced physiotherapist. Neonates were excluded if they showed a global developmental delay so that clinical examination at 18 to 24 months was not possible. HHNE was performed as already described in previous studies [11]. It consisted of 34 items divided into six categories. These were recorded on the standard proforma by t and scored as raw scores (1 to 5) which were later converted to optimality scores. Calculating the optimality score for HNNE was performed as previously described [11].

The Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley-III), German Edition

Long-term neurological outcomes were assessed using Bayley Scales of Infant Development, 3rd edition (BS) [4-15] between 18 and 24 months of corrected age. The cognitive, language, and motor composites of the Bayley-III were used as previously described.

Data Analysis

Statistical analysis was performed using GraphPad Prism version 10.0.0. Pearson correlation was used if the assessed sample size consisted of > 30 neonates, Spearman correlation was used if the assessed sample size consisted of <30 neonates to analyse the correlation between HHNE scores and the Bayley Scales composites. Strength of correlation (r value) was rated as follows: 0.0 to 0.2 (very weak to negligible correlation); 0.2 to 0.4 (weak, low correlation-not very significant); 0.4 to 0.7 (moderate correlation); 0.7 to 0.9 (strong correlation); and 0.9 to 1.0 (very strong correlation). Simple linear regression analysis was conducted to evaluate the extent to which HNNE could predict Bayley outcomes. Logistic regression was then used to evaluate whether HNNE allowed to predict adverse outcome as defined by Bayley Scales <70 or <85. Significance level was set at $p<0.05$.

Results

We included 88 neonates into the study, who underwent both HHNE before discharge and BS at 18 to 24 months of corrected age. Characteristics of the study cohort are displayed in (Table 1). 38 VLBW neonates and 50 ELBW neonates were included in this

study. 16 of the neonates included were diagnosed with IVH (5 Grade I, 4 Grade II, 6 Grade III, 1 Grade IV). Characteristics of the included neonates are shown in (Table 1) both for the entire cohort as well as specified for VLBW and ELBW neonates and neonates with IVH.

Entire cohort	**n=88**
Gestational age at birth	27+6 WOG, IQR 26+4- 29+4 WOG
Birth weight	967 g (IQR 785g-1222,5g)
Gestational age at HHNE examination	36+3 WOG (IQR 35+1-37+5 WOG)
VLBW neonates	**n=38**
Gestational age at birth	29+4 WOG, IQR 28+0-31+4 WOG
Birth weight	1265 (IQR 1880-1440) g
Gestational age at HHNE examination	35+7 WOG, IQR 34+5-37+1 WOG
ELBW neonates	**n =50**
Gestational age at birth	26+5 WOG (IQR 24+6-27+5 WOG)
Birth weight	790 g (IQR 640- 900g)
Gestational age at HHNE examination	36+5 WOG (IQR 35+1-37+5 WOG)
IVH	**n=16**
Gestational age at birth	25+5 WOG (IQR 24+4-27+3 WOG)
Birth weight	745 g (IQR 650-920 g)
Gestational age at HHNE examination	37+3 WOG (IQR 37+1-39+0 WOG)

Table 1: Characteristics of the study cohort. WOG= weeks of gestation, VLBW= very low birth weight; ELBW= extremely low birth weight; IVH= intraventricular hemorrhage; WOG= weeks of gestation; IQR= interquartile range.

All neonates included underwent HNNE and BS. In one child, the cognitive BS was not performed due to lack of cooperation by the infant. Results of HNNE at discharge and BS at 18-24 months are shown in (Table 2). While HNNE at discharge primarily did not reveal pathological findings, the 2-year follow- up examination in ELBW and VLBW children already revealed a significant proportion with noticeable developmental delay. In ELBW and VLBW neonates with IVH, there was already a significant proportion with pathological HHNE at discharge. ELBW and VLBW neonates with IVH showed a marked developmental delay with significantly below-average results at 18-24 months BS- follow-up (Table 2).

	HHNE at discharge (median, IQR)	Gestational age at HHNE (median, IQR)	Cognitive BS BS at 18-24 months (median, IQR)	Motor BS at 18-24 months (median, IQR)	Language BS at 18-24 months (median, IQR)
Entire cohort (n=88)	31 (28.75-33)	36+3 WOG (35+1 WOG-37+5 WOG)	100 (75-112.5)	96 (76.75-106)	91 (70.5-106)
VLBW (n=38)	30 (29-32)	29+4 WOG, IQR 28+0-31+4 WOG	100 (85-135)	100 (79-113)	91 (75-109)
ELBW (n=50)	32 (28-33)	37+0 WOG (36+0-38+0WOG)	92.5 (70-110)	92 (73-100)	87 (66-106)
IVH (n=16)	28.5 (26-31.25)	38+0 WOG (37+1-39+0WOG)	65 (55-110)	62 (51.25-96)	66 (55.5-104.5)

Table 2: HNNE at discharge and long-term outcome at 18-24 months using BS.

Results of correlation analysis as well as for the entire cohort as for subgroups are shown in (Table 3) as well as in Figure 1. Correlation analysis revealed a positive, significant correlation (r=0,313, p=0,003) between HNNE at discharge and the BS motor scale at 18-24 months and a weak significant correlation between HNNE and BS language scale at 18-24 months (r=0,313, p=0,035). No statistically significant correlation could be found between HNNE and cognitive BS. Simple linear regression showed that HNNE predicts motor and

language outcome at 18-24 months (Table 4). A significant regression was found between HHNE and motor and language BS. Table 4 shows that for each point increase in HNNE, the predicted motor BS increases by approximately 2.1 points and the predicted language BS increases by approximately 1.7 points. Logistic regression analysis (Table 5) further showed that HNNE does not only predict BS results but also allows to predict whether infants have adverse outcome as defined by BS<85 or <70 points. Each missing point in HNNE leads to a 1.16 x increased risk of adverse cognitive outcome as defined by BS<85 and an 1.23x increased risk of adverse cognitive outcome as defined by BS <70. Each missing point in HNNE leads to a 1.23x increased risk of adverse motor outcome as defined by BS <85 and a 1.26x increased risk of adverse motor outcome as defined by BS <70.

	HNNE- outcome	**Correlation (significance)**
Entire cohort	mental BS	0.1877 (0.0817)
	language BS	0.2263 (0.0351*)
	Motor BS	0.3133 (0.0033*)
VLBW	Mental BS	0.003 (0.985)
	language BS	0.170 (0.307)
	Motor BS	0.249 (0.137)
ELBW	mental BS	0.3374 (0.0166*)
	language BS	0.2715 (0.0591)
	motor BS	0.3649 (0.0099*)
IVH	mental BS	0.4175 (0.1216)
	language BS	0.3333 (0.2053)
	motor BS	0.5411 (0.0394*)

Table 3: Correlation analysis between HHNE at discharge and long-term outcome as measured by BS at 18-24 months of corrected age. Correlation analysis was performed using Pearson's correlation in neonates with VLBW and ELBW and Spearman's correlation in neonates with IVH. *= statistically significant results.

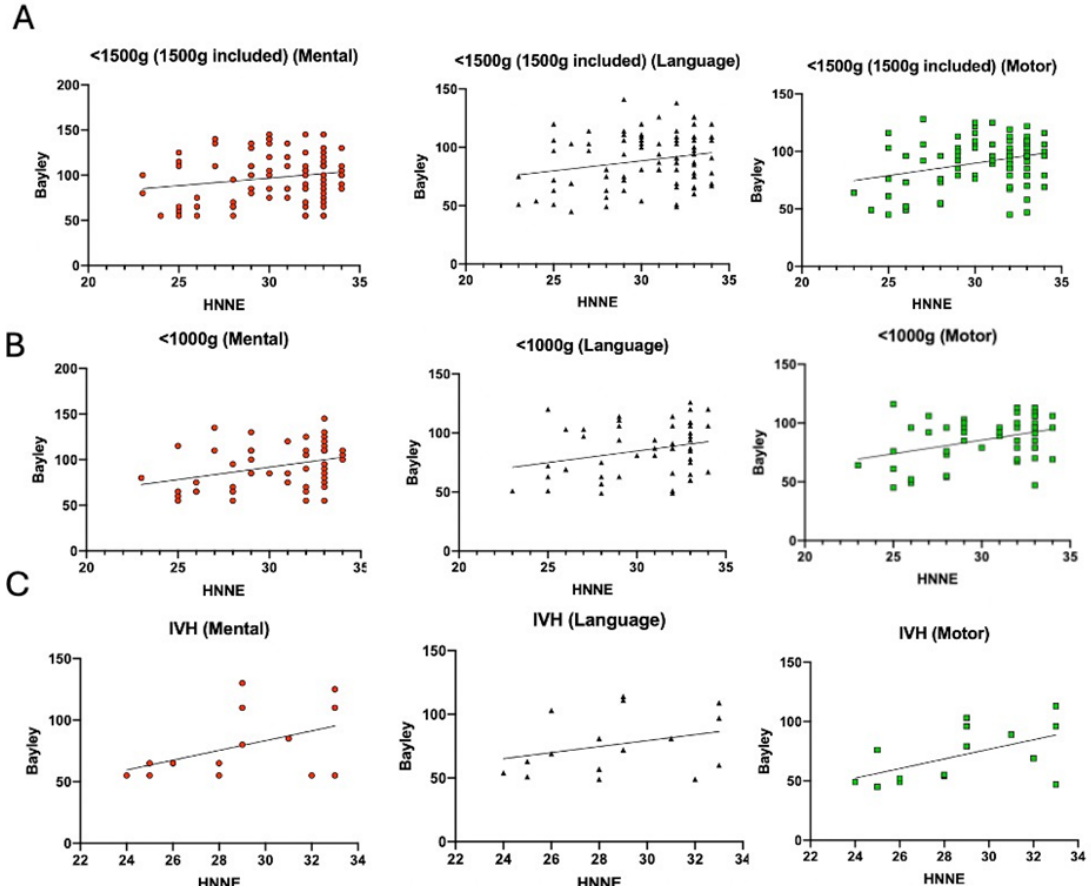

Figure 1: Correlations between HHNE at discharge and BS at 2 years of age. A, entire cohort, B, ELBW neonates (<1000g), C, VLBW/ELBW neonates with IVH. A significant correlation between HHNE at discharge and BS at 2 years of age can be observed between HHNE and motor outcome in all cohorts, HHNE and mental BS in ELBW neonates and HHNE and language outcome in all neonates.

VLBW/ELBW infants with IVH

VLBW and ELBW neonates with IVH have a lower median HNNE score (median: 28.5, IQR 26-31.25, range 24-33) and lower BS motor scale (median: 69, IQR 50.5-92.5, range 45-113) than those VLBW/ELW neonates without IVH. In this subgroup, we found a significant strong positive correlation between HNNE and BS motor scale (p=0,039, r= 0.5411) using the Spearman correlation. No significant correlation was found between HNNE and mental/language BS in this sub cohort. Simple linear regression showed that HNNE significantly predicts motor BS at 18-24 months in VLBW/ELBW neonates with IVH (Table 4). Table 4 shows that for each point increase in HNNE, the predicted motor BS increases by approximately 4.04 points. Logistic regression analysis (Table 5) could show no statistically significant prediction of adverse outcome as defined by BS<70/<85 points by HNNE.

Entire cohort								
Dependent	**Independent**	**B**	**SE**	**Beta**	**T**	**p**	**95%CI for B**	
							Lower bound	**Upper bound**
CBS	**HNNE**	1.659	0.942	0.188	1.762	0.082	-0.231	3.531
MBS	**HNNE**	2.168	0.717	0.313	3.024	0.003*	0.742	3.595
LBS	**HNNE**	1.728	0.807	0.226	2.142	0.035*	0.124	3.332

VLBW								
CBS	**HNNE**	-0.031	1.597	-0.003	-0.019	0.985	-3.273	3.212
MBS	**HNNE**	1.786	1.174	0.249	1.52	0.137	-0.599	4.17
LBS	**HNNE**	1.332	1.285	0.17	1.037	0.307	-1.273	3.989
ELBW								
CBS	**HNNE**	2.712	1.092	0.337	2.484	0.017*	0.516	4.908
MBS	**HNNE**	2.316	0.862	0.365	2.687	0.010*	0.582	4.05
LBS	**HNNE**	1.975	1.021	0.272	1.934	0.059	-0.079	4.029
IVH								
CBS	**HNNE**	3.968	2.143	0.457	1.851	0.087	-0.662	8.598
MBS	**HNNE**	4.045	1.832	0.544	2.336	0.036*	0.304	7.786
LBS	**HNNE**	2.365	1.991	0.303	1.189	0.254	-1.903	6.636

Table 4: Linear regression between cognitive (CBS), motor (MBS) and language (LBS) BS at 18-24 months and HNNE. Linear regression analysis reveals a significant prediction of MBS and LBS results at 18-24 months in the entire cohort. In ELBW neonates, HHNE allows to predict CBS and MBS results at 18-24 months. In VLBW neonates, regression analysis showed no significant prediction of BS by HHNE. In neonates with IVH, HHNE allows to predict MBS at 18-24 months. *= statistically significant results

Entire cohort								
Dependent	**Independent**	**B**	**SE**	**Wald**	**P**	**Odds ratio**	**95%CI for Odds ratio**	
							Lower bound	**Upper bound**
CBS<85	Missing points HNNE	0.153	0.076	4.041	0.044*	1.165	1.004	1.353
CBS<70	Missing points HNNE	0.208	0.086	5.808	0.016*	1.231	1.04	1.458
MBS<85	Missing points HNNE	0.207	0.079	6.769	0.009*	1.23	1.052	1.437
MBS<70	Missing points HNNE	0.237	0.092	6.591	0.010*	1.267	1.058	1.518
LBS<85	Missing points HNNE	0.146	0.076	3.729	0.053	1.157	0.998	1.343
LBS<70	Missing points HNNE	0.152	0.081	3.486	0.063	1.164	0.992	1.365
VLBW								
CBS<85	Missing points HNNE	-0.005	0.125	0.002	0.965	0.995	0.779	1.27
CBS<70	Missing points HNNE	0.115	0.153	0.562	0.454	1.122	0.831	1.515
MBS<85	Missing points HNNE	0.275	0.135	4.135	0.042*	1.317	1.01	1.716
MBS<70	Missing points HNNE	0.285	0.168	2.876	0.09	1.33	0.957	1.85
LBS<85	Missing points HNNE	0.111	0.117	0.906	0.341	1.118	0.889	1.405
LBS<70	Missing points HNNE	0.083	0.146	0.319	0.572	1.086	0.816	1.446
ELBW								
CBS<85	Missing points HNNE	0.264	0.108	6.019	0.014*	1.303	1.055	1.609
CBS<70	Missing points HNNE	0.257	0.11	5.424	0.020*	1.293	1.042	1.505
MBS<85	Missing points HNNE	0.166	0.1	2.766	0.096	1.181	0.971	1.437
MBS<70	Missing points HNNE	0.215	0.112	3.706	0.054	1.24	0.996	1.544
LBS<85	Missing points HNNE	0.172	0.101	2.915	0.088	1.187	0.975	1.446
LBS<70	Missing points HNNE	0.19	0.528	7.698	0.065	1.21	0.988	1.48
IVH								

CBS<85	Missing points HNNE	0.404	0.254	2.532	0.112	1.498	0.911	2.463
CBS<70	Missing points HNNE	0.428	0.235	3.319	0.068	1.535	0.968	2.433
MBS<85	Missing points HNNE	0.464	0.254	3.329	0.068	1.691	0.966	2.62
MBS<70	Missing points HNNE	0.248	0.192	1.681	0.192	1.282	0.881	1.867
LBS<85	Missing points HNNE	0.235	0.201	1.362	0.243	1.265	0.853	1.876
LBS<70	Missing points HNNE	0.27	0.195	1.92	0.166	1.31	0.894	1.92

Table 5: Logistic regression between missing points in HNNE and adverse outcome at 18-24 months as defined by cognitive (CBS), motor (MBS), and language (LBS) BS <70/<85. HNNE allows to predict adverse cognitive and motor outcome in all neonates included. Looking particularly at VLBW neonates, HNNE allows prediction of adverse motor outcome as each missing point in HNNE increases the risk to have adverse motor outcome as defined by MBS<85 by 1.3 times. In ELBW neonates, each missing point in HNNE increases risiko of adverse cognitive outcome as defined by CBS <70 points by 1.29, as defined by CBS <0.85 by 1.3 times. In neonates with IVH, logistic regression analysis showed no statistically significant results. *= statistically significant results.

Discussion

In this study, we demonstrate that the Hammersmith Neonatal Neurological Examination (HNNE) performed at discharge not only correlates with but also predicts long-term neurodevelopmental outcomes in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants. In particular, HNNE scores were significantly associated with motor outcomes at 18-24 months of corrected age across the entire cohort, with the strongest associations observed in infants with intraventricular hemorrhage (IVH). These findings support the value of early structured neurological assessment as a low-resource tool for identifying preterm infants at risk for adverse neurodevelopmental outcomes. Our results are consistent with previous studies demonstrating associations between early neurological examinations and later motor development in very preterm infants [18,19,32]. However, to our knowledge, this is the first study to specifically investigate the predictive value of HNNE in a cohort of VLBW and ELBW infants with a dedicated subgroup analysis of neonates with IVH. Given the high vulnerability of this population, our findings add important evidence supporting the clinical utility of HNNE in routine neonatal care. Subgroup analyses revealed that in ELBW infants, HNNE scores were also significantly associated with cognitive outcomes. This observation aligns with earlier reports showing that early neurological performance and brain integrity are linked to later cognitive development in very preterm infants [16,18,19,32]. Importantly, our study extends these findings by demonstrating that HNNE not only correlates with but also predicts adverse cognitive outcomes in ELBW infants, as shown by both linear and logistic regression analyses. This highlights the potential role of HNNE as an early screening tool for identifying infants at risk for later cognitive impairment. In infants with IVH, HNNE scores showed a strong and significant correlation with motor outcomes at 18–24 months. Linear regression analysis confirmed that HNNE at discharge predicts later motor performance in this subgroup, with a larger effect size compared to the overall cohort. These findings are clinically relevant, as IVH-particularly moderate to severe grades-is well known to be associated with adverse motor outcomes, including cerebral palsy [1,7,17,20,22]. Logistic regression analysis did not demonstrate a statistically significant prediction of adverse outcomes defined by Bayley scores <70 or <85 in the IVH subgroup. This is most likely due to the limited sample size. Larger multicenter studies are needed to further explore the prognostic value of HNNE in this high-risk population. Our study further underscores that infants with IVH are at particularly high risk for neurodevelopmental impairment. Compared to infants without IVH, they showed lower median HNNE scores at discharge and substantially poorer motor, cognitive, and language outcomes at follow-up. Early identification of these infants using a standardized clinical tool such as HNNE may facilitate timely referral to early intervention and neurorehabilitative programs, which have been shown to improve functional outcomes in preterm populations [3,31].

As the global burden of preterm birth continues to rise, particularly in low- and middle-income countries, there is an increasing need for reliable, low-resource screening tools to identify infants at risk for neurodevelopmental impairment [21,23,26]. While neonatal MRI and EEG provide valuable prognostic information, their availability is limited by costs, infrastructure, and the need for specialized personnel [3,21,25]. In contrast, HNNE is inexpensive, easy to perform, requires minimal equipment, and can be administered by trained healthcare professionals in a wide range of clinical settings. Moreover, HNNE has been adapted and validated in different populations, supporting its broader applicability [9]. Nevertheless, studies from low-resource settings suggest that neurological examinations developed in high-income countries may overestimate the number of at-risk infants, emphasizing the need for contextual validation [20]. The median HNNE score in our cohort was higher than those reported in previous studies assessing infants earlier in the postmenstrual period or strictly at term-equivalent age [18,19]. This may be explained by the timing

of assessment at discharge, when infants are often more clinically stable. Previous work suggests that HNNE performed at discharge provides comparable predictive value to assessments conducted at term-equivalent age, while reducing loss to follow-up and allowing for earlier identification of at-risk infants [32,33]. Earlier detection may enable earlier initiation of targeted interventions and improve parental counselling during a critical period. Several limitations of this study should be acknowledged. First, the sample size was relatively small, particularly in the IVH subgroup, which may have limited statistical power in some analyses. Second, neurodevelopmental outcomes were assessed at 18-24 months of corrected age; it is well recognized that certain cognitive, behavioural, and executive function impairments may only become apparent at school age or later. Future studies with larger, multicenter cohorts and long-term follow- up into childhood and adolescence are required to validate and extend our findings.

Conclusion

In this study, we show that early clinical neurological assessment at discharge even before term- equivalent age using HHNE allows to detect ELBW and VLBW neonates at risk for adverse motor outcome. We show that neonates with IVH are at higher risk for neurodevelopmental impairments. We suggest that HHNE is a low-resource diagnostic tool to detect ELBW and VLBW neonates at risk for adverse neurodevelopmental outcome in both high – and low resource settings and to implement neuro-rehabilitative strategies at an early point in order to improve outcome in these patients.

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