ORIGINAL RESEARCH

Evaluation of a Cranial Ultrasound Scoring System for Prediction of Abnormal Early Neurodevelopment in Preterm Infants

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Abstract

Aim: To evaluate and compare a cranial ultrasound (cUS) scoring system to conventional reporting of cranial ultrasound abnormalities (CUAs) for prediction of early neurodevelopmental outcomes in preterm infants.

Materials and methods: This retrospective, single-center study compared cUS scores to results from late ultrasound examination reports for any cUS abnormality (CUA) (any hemorrhage or white matter lesion) or severe CUA [severe intraventricular hemorrhage (IVH)], cystic periventricular leukomalacia (PVL), parenchymal or cerebellar hemorrhage) for predicting early signs of cerebral palsy (CP) or developmental delay in preterm infants.

Results: Six-weeks postnatal cUS examinations were analyzed against early neurodevelopmental outcomes at 3–4-months corrected age of 242 preterm infants (median gestational age, 26.5 weeks; interquartile range [IQR, 4 weeks] and median body weight 880 grams [IQR, 356.5 grams]). We did not find any statistically significant differences between cUS score and any CUA for sensitivity (57% vs 57% [95% confidence interval (CI): from −19 to 19]) and specificity (68% vs 64% [95% CI: from −3 to 10]) for predicting CP. Similarly, there was no difference in sensitivity (44% vs 46% [95% CI: from −12 to 7]) and specificity (74% vs 70% [95% CI: from −5 to 13]) for predicting any developmental delay. However, in comparison to severe CUA, cUS score had significantly higher sensitivity (57% vs 27% [95% CI: from 12 to 49]) but significantly lower specificity (68% vs 96% [95% CI: from −21 to −34]) for predicting CP. There was higher sensitivity (44% vs 12 % [95% CI: from 23 to 41]) but lower specificity (74% vs 98% [95% CI: from −15 to −32]) for any delay.

Conclusions: Cranial ultrasound score was similar to any reported CUA for predicting neurodevelopmental outcomes; however, when compared to severe CUA, it had better sensitivity but poor specificity for predicting early neurodevelopmental outcomes.

Clinical significance: Objective scoring of cUS examinations on late neonatal scans was found to be similar to conventional reporting of any CUA for the prediction of early neurodevelopmental outcomes in this retrospective study. This indicates that scoring does not value add to the diagnosis of these infants.

Keywords: Brain injury, Cerebral palsy, Cranial ultrasound, Early intervention, Neurodevelopmental outcome, Preterm infants, Prognosis.

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Introduction

Cranial ultrasound (cUS) is widely used for the screening of preterm neonates to detect brain injury due to prematurity.[1,2] Infants found to have brain abnormalities on cUS are followed up with further imaging,[3] focused neurodevelopment assessments,[4] and early intervention provided when indicated.[5,6] Brain injuries that are predictive of early neurodevelopmental impairment in preterm infants include any grade of intraventricular hemorrhage (IVH), cerebral or cerebellar hemorrhage, white matter injury (WMI), ventriculomegaly and hydrocephalus, cystic changes, and signs of brain atrophy after any injury.[7,8]

Late screening cUS examinations are performed at various time points in different institutions;[9] 6-weeks, term–equivalent age (TEA) or discharge may be used as the last screening examinations. The late cUS examination is important to detect any evidence of WMI.

The use of a cUS scoring system (Appendix 1) for the quantification of brain injury in preterm neonates has been reported as a useful tool to consider using in the prediction of neurological outcome.[10,11] The scoring system includes measurements of the lateral ventricle, interhemispheric fissure, thickness of the corpus callosum and subarachnoid space. Several subjective assessments of injury are also included in the score items indicating signs of white matter loss, the presence of any cysts and deep gray matter injury. These assessments

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were obtained from a TEA cUS performed on the neonates. The cUS score provides a systematic approach to quantifying brain abnormality in a single score and the higher the score the more likely the expected outcome of adverse neurodevelopment. However, the data was limited on the validity of this technique as a reliable method of predicting neurological outcome and we, therefore, studied a group of high-risk neonates to assess its usefulness in predicting adverse early neurodevelopmental outcomes at 3–4-months corrected age (age from the original due date).

Early neurodevelopment assessment provides screening for early features of cerebral palsy (CP) or early developmental delay in infants who are born preterm and require intervention.[12]

The aim of this study was to evaluate and compare the parameters of two methods (cUS scoring vs conventional cUS reporting) to characterize abnormal cUS findings for early adverse neurodevelopmental outcomes—any CP or any adverse neurodevelopment assessed at 3–4-months corrected age.

Materials and Methods

The cUS screening is routinely performed on preterm infants, who are born in less than 32 weeks gestational age (GA) or below 1500 gm in our unit. The screening includes a *late* or last cUS examination when neonates are 6-weeks postnatal age (PNA). Our unit does not perform a TEA cUS as part of the screening protocol. Infants born before 29 weeks GA or with a birth weight of less than 1000 gm were selected for inclusion in this retrospective cohort study as they were the group who had routine inpatient and outpatient neurodevelopmental assessments in our unit. The data available for the study was obtained from the time of the establishment of the neurodevelopment clinic in 2018 until 2022. This includes screening for early features of CP or developmental delay at 3–4-months corrected age.[4,12] Neonates were excluded from the study if they did not have a 6-weeks PNA cUS examination prior to their early neurodevelopment clinic assessment. Ultrasound examinations were performed to routine screening standards of our unit at the time and neurological examinations performed on each neonate in the study in a dedicated early neurodevelopment clinic.[12,13]

The cUS score was calculated retrospectively by two investigators (GM and KVH) from the ultrasound examination reports using the cUS scoring system reported previously,[10,11] and both scorers were blinded to the early neurodevelopment clinic outcomes. In this study, a cUS score of 10 or lower was considered normal or test negative, whereas a score of more than or equal to 11 was considered abnormal or test positive.[10] If the scores were different and one scorer considered the cUS examination was normal, while the other scorer scored as abnormal (10 vs ≥11) a consensus was reached after deliberation. Any cUS abnormality was considered positive if there was the presence of any abnormality, such as IVH, periventricular leukomalacia (PVL), cerebral or cerebellar hemorrhage and negative if the cUS examinations demonstrated no abnormality,[8] Similarly, the severe CUA test was considered positive if there was IVH grade 3 or above present,[14,15] cystic PVL,[16] cerebral (parenchymal) or cerebellar hemorrhage. Otherwise, the test outcome was considered negative.

The cUS examinations included static coronal and sagittal images obtained through the anterior fontanelle and axial plane images were obtained through the mastoid fontanelle.[1,17,18] All examinations were performed by in-house trained and credentialled sonographers and the examinations were reported by consultant pediatric radiologists. No extra projections were required to calculate the cUS scores and it was, therefore, possible to use available images and imaging reports.

The neurodevelopment assessments included a video assessment of general movements [general movements assessment (GMA) at fidgety age],[19] Hammersmith Infant Neurological Examination (HINE),[20] and medical examination for the outcomes of early features of CP, high risk of CP, developmental delay, abnormal GMA, and suboptimal HINE.

Statistical Analysis

Statistical analyses were performed using STATA, version 17.0 (StataCorp LLC, College Station, Texas, USA). The sensitivities and specificities were calculated for the index diagnostic tests (cUS score, any CUA, and severe CUA) against the reference outcomes of an infant with CP (clinic diagnosis of early features of CP or high risk of CP), and a composite of any developmental delay (any abnormality in development, early features of CP, or high risk of CP). Absolute differences in the test accuracy with 95% confidence interval (CI) were calculated to compare the differences between the sensitivities and specificities of the index diagnostic tests accuracy using the McNemar's test. Although cUS score above 10 was considered as abnormal based on the previous literature, the receiver operating characteristic (ROC) analysis was also performed to determine the cut-off value for cUS score that most accurately predicts CP and for any developmental delay.

Results

Two hundred and forty-two preterm infants were included in the study with the median GA being 26.5 weeks (IQR, 4 weeks). The median body weight was 880 grams (IQR, 356.5 gm). Any CUA was reported in 93/242 (38%) infants and 17/93 (18%) had severe CUAs. Furthermore, 85/242 (35%) infants had an abnormal score of more than or equal to 11. The median score was similar between the two scorers (medial 10 vs 10) and there was no disagreement ($\kappa = 1$). At the early neurodevelopment clinic assessments, there were 33/242 (14%) infants diagnosed with CP/high risk of CP and 124/242 (51%) had some form of developmental delay.

Cranial Ultrasound Score vs Any Cranial Ultrasound Abnormalities

There was no difference in sensitivity (57% vs 57% [95% CI: from −19 to 19]) and specificity (68% vs 64% [95% CI: from −3 to 10]) for predicting CP. There was no difference in sensitivity (44% vs 46% [95% CI: from −12 to 7]) and specificity (74% vs 70% [95% CI: −5 to 13]) for predicting any delay (Table 1).

Cranial Ultrasound Score vs Severe Cranial Ultrasound Abnormalities

There was significantly higher sensitivity (57% vs 27% [95% CI: from 12 to 49]) but lower specificity (68% vs 96% [95% CI: from −21 to −34]) for predicting CP. There was higher sensitivity (44% vs 12% [95% CI: from 23 to 41]) but lower specificity (74% vs 98% [95% CI: from −15 to −32]) for any delay (Table 2).

The ROC curve (Fig. 1) demonstrated that a cUS score of above or equal to 10.5 had a sensitivity of 52% for predicting CP with a specificity of 19% (Area under the curve (AUC): 0.66; 95% CI: from 0.55 to 0.77).

The ROC curve (Fig. 2) demonstrated that a cUS score of above or equal to 10.5 had a sensitivity of 23% for predicting any adverse

Table 1: Diagnostic test accuracy of abnormal cUS score vs any CUA for predicting adverse early neurodevelopmental outcomes

	cUS score	*Any CUA*	*Absolute difference in the test accuracy (95% CI) (%)*	*p-value*
Outcome: CP/ high risk of CP				
Sensitivity (%) (TP/TP + FN)	57 (19/33)	57 (19/33)	0 (−19, 19)	1.00
Specificity (%) (TN/TN + FP)	68 (143/209)	64 (135/209)	4 (−3, 10)	0.25
Outcome: Any delay or CP/ high risk of CP				
Sensitivity (%) (TP/TP + FN)	44 (55/124)	46 (58/124)	−2 (−12, 7)	0.60
Specificity (%) (TN/TN + FP)	74 (88/118)	70 (83/118)	4 (−5, 13)	0.31

CP = cerebral palsy; CUA = cranial ultrasound abnormality reported on cranial ultrasound examination; any delay = any neurodevelopmental delay at 3–4 months corrected age

Table 2: Diagnostic test accuracy of abnormal cUS score vs severe CUA for predicting adverse early neurodevelopmental outcomes

	cUS score	*Severe CUA*	*Absolute difference in the test accuracy (95% CI) (%)*	*p-value*
Outcome: CP/ high risk of CP				
Sensitivity (%) (TP/TP + FN)	57 (19/33)	27 (9/33)	30 (12, 49)	0.002
Specificity (%) (TN/TN + FP)	68 (143/209)	96 (201/209)	−28 (−21, −34)	0.0000
Outcome: Any delay or CP/high risk of CP				
Sensitivity (%) (TP/TP + FN)	44 (55/124)	12 (15/124)	32 (23, 41)	0.0000
Specificity (%) (TN/TN + FP)	74 (88/118)	98 (116/118)	−24 (−15, −32)	0.0000

CP = cerebral palsy; severe cranial ultrasound abnormality = severe intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL), parenchymal or cerebellar hemorrhage; any delay = any neurodevelopmental delay at 3–4 months corrected age

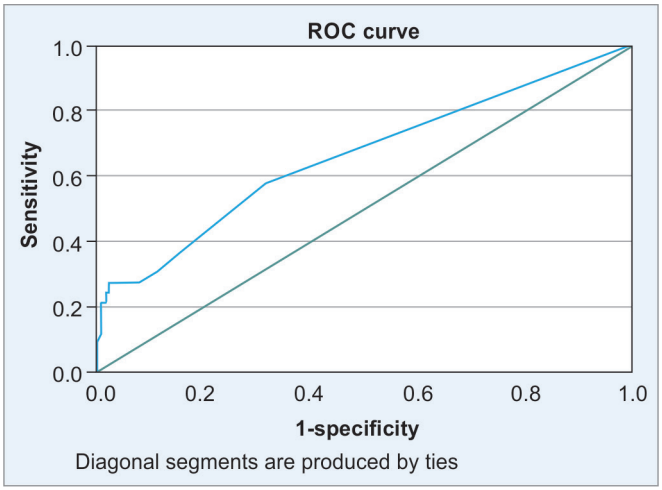

Fig. 1: An ROC curve demonstrating that cUS score of above or equal to 10.5 had a sensitivity of 57% for predicting CP with a specificity of 31% (AUC: 0.66; 95% CI: from 0.55 to 0.77)

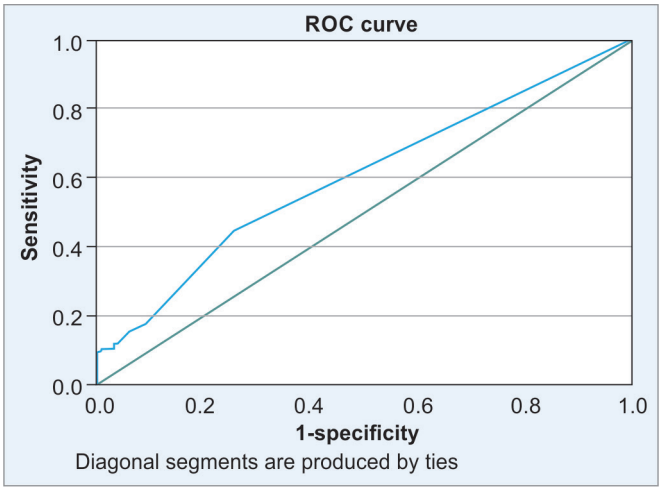

Fig. 2: An ROC curve demonstrating that cUS score of above or equal to 10.5 had a sensitivity of 44% for predicting any adverse neurodevelopment delay with a specificity of 25% (AUC: 0.6; 95% CI: from 0.53 to 0.67)

neurodevelopment delay with a specificity of 25% (AUC: 0.60; 95% CI: 0.53 to 0.67).

Discussions

We report the practical use of a cUS scoring system[10] to predict early neurodevelopmental outcomes in a cohort of extremely preterm neonates. The cUS score in our study had no difference in sensitivity for the prediction of CP but lower sensitivity for any neurodevelopment delay, as compared to CUA. However, the specificity of using the cUS score was higher for both CP and any delay. Compared to severe CUA, the score had significantly higher sensitivity for predicting CP and any delay but had significantly lower specificity for CP and any delay. Overall, the cUS score performed the same when compared to any CUA but had higher sensitivity and lower specificity when compared to severe CUA when predicting abnormal early neurodevelopment in extremely preterm infants.

The literature reporting the use of cUS scoring is sparse and our study adds to the evidence on this emerging technique. The scoring system is the only cUS scoring system documented. The study by Skiöld et al. carried out on 84 infants found that

agreement between the cUS scoring system and MRI scores was good. Sensitivity was the same for cUS and MRI in predicting CP (75%) and severe cognitive delay (100%). Specificity for CP was the same for MRI compared with cUS (97% vs 90%).[10] Our study in comparison had lower sensitivity than theirs for predicting CP (57% vs 75%). The specificity to predict CP in our study was lower than Skiöld et al. (68% vs 90%), although the ultrasound examinations were performed at different time points with our infants examined at 6-weeks PNA while the Skiöld et al. infants were all TEA when the cUS score was calculated. The sample size of the Skiöld was however smaller than our study (84 vs 242).

This cUS score has been reported as having similar sensitivity to MRI brain in a study on infants at TEA.[10] The score includes an expanded list of brain injuries compared with other studies[21,22] and is therefore more in line with MRI scoring systems.[23–25] This includes subtle abnormalities like corpus callosum thinning and delayed folding of the cortex as well as the sequelae of IVH, periventricular hemorrhagic infarction (PVHI), ventriculomegaly and injury to the white matter including any signs of atrophy. Although their study used the cUS score to compare cUS findings at TEA with MRI, it is reasonable to suggest that it could also be of value when comparing cUS examinations. Unlike the MRI and cUS studies on infants at TEA, our study evaluated data from ultrasound examinations performed at 6-weeks PNA, as this is the final screening examination performed at our unit. We acknowledge that further white matter volume loss could have occurred in the infants after the 6-weeks cUS examination and therefore not captured by the study. Further studies to assess later cUS score at TEA should be therefore investigated in a similar group of infants.

A strength of our study was the 100% agreement between the two scorers when deciding if a score was normal or abnormal (abnormal ≥ 11) and our study had a considerable larger cohort compared to the previous Skiöld study. Although our study has a relatively big sample size, compared with the Skiöld study, some CI are very wide and the study would benefit from a larger patient group. As the cUS score was possible to be calculated at a later date than when the examination was performed, it could be calculated by an independent operator in an auditing or research setting.

Another limitation of the study was assessing the cUS score in a dichotomous way to calculate the diagnostic accuracy parameters. The cUS score is a continuous measure with a score of 10 being normal and any score above 10 abnormal—the higher the score the more likely there is brain injury. However, we have used it as a categorical variable as a distinction between normal and abnormal is required to calculate the sensitivity and specificity. Therefore, we also performed an ROC analysis, which shows that the cut-off used in the study agrees with the previous study.[10] The AUC of the ROC curve of 0.5 indicates that the performance of the tests are not significantly different for predicting early abnormal neurodevelopment and is of very limited value.

The late cUS examinations at our institution were performed at 6-weeks PNA, according to our protocol, rather than at TEA as described by Skiöld et al. This meant that the age of the neonates in our study was varied unlike those in the published study. It may indicate that this scoring system is only predictive when used for term-aged neonates. We plan to conduct future studies, which look at late screening time points to evaluate this further.

All infant's neurodevelopment was assessed early at 3–4-months corrected age. The infants will also be undergoing later neurodevelopment assessments at two years of age. Early diagnosis allows for early intervention and treatment,[5,13] and any adverse neurodevelopment would be confirmed with longer term follow-up. As the study shows the overall cUS scores are quite low and therefore ultrasound poor at predicting abnormal neurodevelopment it is crucial there is follow-up in all early preterm infants. Severe CUA has good specificity but very poor sensitivity and therefore it is important it is not considered as sufficient to use alone.

Conclusions

The use of a cUS scoring system to predict early neurodevelopmental outcome is similar to any reported CUA for predicting outcomes, however, when compared to severe CUA, it had better sensitivity but poor specificity for predicting abnormal early neurodevelopmental in extremely preterm neonates.

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Appendix 1: Cranial ultrasound scoring system.[1]

		Subjective assessment				
Scoring item		*Score 1*	*Score 2*	*Score 3*	*Score 5*	*Score 10*
I	Cysts or cavity	None		Focal cyst or cavity but not involving cortico-spinal tract	Unilateral cyst or cavity involving more than one region but not cortico-spinal tract or optic radiation	Cyst or cavity involving cortico-spinal tract or bilateral cystic PVL
II	Cortical gray matter abnormality	None	One focal abnormality		Extensive abnormality	
III	Deep gray matter abnormality	None			Unilateral atrophy/cysts	Bilateral atrophy/cysts
IV	Maturation of gyral fold	Normal	Frontal reduction of gyral folding	Global reduction of complex gyral folding/ delayed gyration for gestational age		
V	Cerebellar abnormality	None	Small focal hemorrhage	Unilateral extensive lobar hemorrhage	Bilateral extensive lobar hemorrhage	
Measured items						
VI	Size of frontal horns Ventricular index Anterior horn width	Normal <13 mm <3 mm	Moderate dilatation 13–16 mm 3–6 mm		Severe dilatation or shunt without dilatation >16 mm >6 mm	Shunt with persistent dilatation
VII	Size of ventricular midbody	Normal <10 mm	Mild-moderate enlargement 10–15 mm	Severely enlarged >15 mm		
VIII	Subarachnoid space size	Normal <4 mm	Mildly enlarged 4–6 mm	Severely enlarged >6 mm		
IX	Size of inter-hemispheric fissure	Normal <3 mm	Mildly enlarged 3–6 mm	Severely enlarged >6 mm		
X	Thickness of Corpus callosum	Normal >1.5 mm		Marked thinning <1.5 mm		