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Predicting the developmental outcomes of very premature infants via ultrasound classification

A CONSORT - clinical study

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Abstract

Objective: This study aimed to assess the accuracy of ultrasonic grading in determining brain injury in very premature infants and analyze the affecting factors of these neonatal morbidity and mortality, and to investigate the relationship between serial cranial ultrasound (cUS) classification and Mental Developmental Index (MDI)/Psychomotor Developmental Index (PDI) in premature infants.

Methods: A total of 129 very preterm infants (Gestational Age $\leq$ 28 weeks) were subjected to serial cUS until 6 months or older and classified into 3 degrees in accordance with classification standards. The MDI and PDI (Bayley test) of the infants were measured until the infants reached the age of 24 months or older. The consistency between Term Equivalent Age (TEA)-cUS and TEA- magnetic resonance imaging (MRI) was calculated. Ordinal regression was performed to analyze the relationship among severe disease, early cUS classifications, psychomotor and mental development, and death. Operating characteristic curve were used to analyze the relationship between serial cUS grades and MDI/PDI scores.

Results: The mortality and survival rates of 129 very preterm infants were 32.8% and 67.3%, respectively. Among the 86 surviving infants, 20.9% developed mild cerebral palsy (CP) and 5.8% to 6.9% developed severe CP. The consistency between TEA-cUS and TEA-MRI was 88%. Grades 2 and 3 at first ultrasound were associated with adverse mental (OR = 3.2, OR = 3.78) and motor (OR = 2.25, OR = 2.59) development. cUS classification demonstrated high sensitivity (79%–96%). Among all cUS classifications, the specificity of the first cUS was the lowest and that of TEA-cUS was the highest (57% for PDI and 48% for MDI).

Conclusions: Moderate and severe brain injury at first ultrasound is the most important factor affecting the survival rate and brain development of very premature infants. The cUS classification had high sensitivity and high specificity for the prediction of CP, especially in TEA-cUS.

Abbreviations: ARDS = acute respiratory distress syndrome, CHD = congenital heart disease, CPD = chronic pulmonary dysplasia, c-PVLs = cystic periventricular leukomalacias, cUS = cranial ultrasound, DEHSI = diffuse excessive high signal intensity, DIC = disseminated intravascular coagulation, GA = gestational age, GMH–IVH = germinal matrix, MDI = Mental Developmental Index, MRI = magnetic resonance imaging, NEC = neonatal necrotizing enterocolitis, PDI = Psychomotor Developmental Index, PVE = periventricular echodensities, PWMLs = punctate white-matter lesions, ROC = operating characteristic curve, sMA = severe metabolic acidosise, TEA = term equivalent age, WM = white matter, CP = cerebral palsy.

Keywords: classification, cranial ultrasound, Mental Development Index, Psychomotor Development Index, very preterm infant

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

The incidence of premature birth is approximately 12% and is increasing annually.[1] Given the high incidence of brain injuries in premature infants, the improved detection and characterization of these pathologies in early life may help with prognosis and in anticipating needs for appropriate early interventions. Premature infants mainly exhibit 2 kinds of brain injuries: hemorrhage and white matter (WM) damage.[2,3] In premature infants, these injuries usually cause poor outcomes, such as cerebral palsy (CP) and mental deficiencies. In general, ultrasound is used for the diagnosis of brain injury in premature infants but provides a poor prognosis. In contrast to previous studies that performed qualitative ultrasound methods, this work quantitatively analyzed the brain injuries of participants by introducing quantization parameters as diagnostic criteria and classification standards. The criteria and standards were used to quantify the type and degree of early, TEA, and later brain injuries in very premature infants. These scales could be used to evaluate the prognostic development of infants in terms of movement and intelligence. This study analyzed the clinical data of 129 cases of very premature infants to discuss the relationship of basic data, serious diseases, and serial cUS characteristics with the prognosis of nervous system development and death. This analysis attempted to determine the relationship between ultrasound classification and a prognostic index in clinical prognostic evaluation of craniocerebral injuries in premature infants.

2. Materials and methods

2.1. Patients

One hundred twenty nine very preterm infants of gestational age (GA) $\leq$ 28 weeks that were admitted to the neonatal intensive care unit of Hunan children's hospital between January 2012 and November 2014 were assessed for brain maturation and brain injury through cUS and MRI, and followed up till January 2017. The study was approved by the Medical Ethics Committee of Hunan Children's Hospital, and informed consent was obtained from the parents. The exclusion criteria included congenital anomalies of the central nervous system, other severe congenital anomalies, chromosomal and metabolic disorders, and neonatal meningitis.

2.2. cUS

2.2.1. Image acquisition. Serial cUS scans were performed by a team of experienced sonographers who have worked more than 5 years, using an Mindray M5 scanner (Shenzhen) with a special standardized preset in accordance with the standard protocol: scanning with a transducer frequency of 8 MHz within 48 hours of birth, and scanning weekly during admission until discharge or TEA and again monthly until 6 months or elder. Most scans were done beside bed.

2.2.2. Assessment periventricular echodensities (PVE) cerebral hemorrhages hydrocephaly. PVE were defined and classified in reference to van Wezel–Meijler et al.[4] Cerebral hemorrhages were classified in accordance with the Papile standard.[5] Hydrocephaly grades were classified into 3 degrees on the basis of ventricular index and in accordance with Lara et al mild hydrocephaly- less than 13 mm; moderate hydrocephaly- 13 to 15 mm, and severe hydrocephaly- more than 15 mm.[5] Weekly and monthly ultrasonic reports of the infants were obtained for brain injury classification. Images of the first cUS, TEA-cUS, and last cUS were reviewed blindly by 2 doctors and classified to 3 degrees in accordance with PVE grade, hydrocephaly degree, cystic periventricular leukomalacias (c-PVL) and hemorrhage grade of the Papile standard.

2.2.3. Brain injury classification at first cUS. Normal/mild injury: no PVE or homogeneous PVE-I.

Moderate injury: PVE-II (regardless of appearance and duration), or accompanied by germinal matrix hemorrhage (GMH) degree 1 to 2 or single choroid plexus.

Severe injury: PVE-III or accompanied by GMH degrees 3 to 4.

2.2.4. Brain injury classification at TEA and last cUS. Normal/mild injury: mild hydrocephaly and/or less than 2 local c-PVLs.

Moderate injury: moderate hydrocephaly or more than 2 local c-PVLs.

Severe injury: severe hydrocephaly or extensive c-PVLs.

2.3. MRI

2.3.1. Image acquisition. MRI examinations were performed on living very preterm infants using Skyra 1.5-T Siemenz MR system (Siemenz Medical Systems, Avanto, Germany) in accordance with the standard protocol[6] for the imaging of newborn infant brains. The scans included at least T1-weighted (repetition time/echo time (TR/TE, 1860 ms/8.5 ms), T2-weighted (TR/TE, 4670 ms/99 ms), diffusion-weighted (TR/TE2, 3600 ms/102 ms), and susceptibility-weighted (TR/TE, 49 ms/40 ms) images on the transverse plane. MRI examinations were performed at approximate TEA, preferably between the 40-week and 44-week postmenstrual ages (PMA, i.e, TEA-MRI).

2.3.2. Visual assessment. Special attention was given to the brain WM. Punctate white-matter lesions (PWMLs) were defined as small areas of high signal on T1-weighted images and of mostly low signal on T2-weighted images.[6,7] Diffuse excessive high signal intensity (DEHSI) was defined as areas of excessive high signal intensity diffused within the periventricular and/or subcortical WM on T2-weighted images.[8,9] This definition was based on the most severe changes.[8] Normal/mild injury: normal-appearing WM, homogeneous DEHSI or few ($\leq$6) PWML, and normal/mildly abnormal lateral ventricles (less than 13 mm with a normal shape or mildly abnormal at most). Moderate injury: multiple (>6) PWMLs, small localized cystic lesions, inhomogeneous DEHSI, and/or moderately abnormal lateral ventricles (13–15 mm and/or moderately abnormal in shape). Severe injury: extensive or diffused inhomogeneous SI changes and/or hemorrhagic or cystic lesions involving the periventricular and/or subcortical WM and/or severely abnormal lateral ventricles (over 15 mm and/or severely abnormal in shape).

2.4. Clinical follow-up

With the Bayley test, the Mental Developmental Index (MDI) and PDI of the infants were recorded at TEA and at 6 months, 1 year, 2 years, and so on after discharge. The results of the last follow-up (until January 2017) were recorded, including intelligence (MDI), PDI, and clinical outcome. Exclusive of dead cases, the MDI and PDI were divided into 3 groups: normal (85 points and higher), less than 85 points were CP which subdivided 2 groups, mildly abnormal (70–85 points), and abnormal (less than 70 points).

2.5. Data analysis

Statistical analyses were performed using SPSS version 20.0 (International Business Machines, Armonk, NY). A cross-table was used to assess the consistency between the results of TEA-cUS and TEA-MRI. The consistency ratio between TEA-cUS and TEA-MRI would be calculated by crossing table. The influence factors (including ultrasonic grades of the first time, serious diseases, weight etc) of MDI/PDI scores and death were analyzed through ordinal regression analysis. The sensitivity, specificity, and correlation between the classification of different US and PDI/MDI scores were analyzed using the receiver operating characteristic (ROC) curve.

3. Results

3.1. Basic data

Twelve infants were excluded from this study. The reasons for exclusion included death less than 24 hours. A total of 129 very preterm infants (83 male, 46 female) were included in this group; however, 6 lacked MRI results and 1 lacked MDI and PDI scores. The median GA and birth weight of the included infants were 27.2 weeks (range: 22.5–28 weeks) and 1102 g (range: 500–1650 g). The mean hospital stay were 66 ± 45 days (range: 2 days–220 days), 42 were twins or multiplets while 87 were single. The clinical follow-up deadline was January 2017. The maximum and minimum age of the infants was 59 months and 24 months, respectively, at the final follow-up. Among the 129 very premature babies, 38 died before TEA and 4 died after TEA, 87 survived at finally. The results for 86 survival infants of the MDI/PDI are summarized in Table 1. The mortality and survival rates of the infants were 32.8% and 67.3%, respectively. Among the infants who survived, 72% (62/86) of MDI were normal and 73% (63/86) of PDI were normal. 20.9% (18/86) of MDI/PDI were mildly normal, 5.8% (5/86) of MDI were abnormal, 6.9% (6/86) of PDI were abnormal.

3.2. The serious diseases

The frequency and the percent of the serious diseases in very premature infants was showed in Table 2. In this group, chronic pulmonary dysplasia (CPD) is the most popular diseases (70.5%, 91/129) but congenital heart disease (CHD) is fewest (5.4%, 7/129).

3.3. Ultrasound classification

The first cUS were classified as grades 1 to 3 in accordance with hemorrhage grade of the Papile standard (Fig. 1) and periventricular echodensities (PVE) grade (Fig. 2). The TEA-cUS and TEA-MRI were classified byhydrocephaly degree, c-PVL. The classification of the first cUS (Figs. 1 and 2), TEA-cUS, and last cUS and their relationship are summarized in Table 3. The classification were changed over time. The first ultrasound classification included 6 cases of grade1, 98 cases of grade 2 and 25 cases of grade 3. By the time of TEA, 38 cases died and 91 cases were alive, including 62 cases of grade 1, 25 cases of grade 3 and 4 cases of grade 3. By the time of the last ultrasound examination, 4 cases died and 87 cases were alive, including 75 cases of grade 1, 21 cases of grade 3 and 4 cases of grade 3.

Table 1

The results for the frequency of the MDI/PDI.

	Normal	Mild abnormal	Abnormal
MDI	62 (48.4%)	18 (14%)	6 (4.7%)
PDI	63 (49.3%)	18 (14%)	5 (3.1%)

MDI = Mental Developmental Index, PDI = Psychomotor Developmental Index.

Table 2

The frequency and the percent of the serious diseases in very premature infants.

Diseases	Frequency	Percent (%)
Acute respiratory distress syndrome (ARDS)	91	70.5
Chronic pulmonary dysplasia (CPD)	111	86.0
Sepsis	43	33.3
Congenital heart disease (CHD)	7	5.4
Anemia (severe)	43	33.3
Disseminated intravascular coagulation (DIC)	20	15.5
Neonatal necrotizing enterocolitis (NEC)	11	8.5
Severe metabolic acidosise(sMA)	35	27.1

3.4. Consistency of US and MRI

The consistency ratio between TEA-cUS and TEA-MRI is 88%. There was overall good agreement between the classification of TEA-cUS and TEA-MRI (Spearman $r = 0.73$, $P = .000$). The classification of TEA-cUS and MRI are shown in Table 4. In this group, 6 infants had PWMLs. One case was diagnosed with multiple (>6) PWML and 1 case was diagnosed with small localized cystic lesions via MRI. The subtle white lesions were originally unrecognizable but showed sustained, inhomogeneous periventricular WM echogenicity through cUS.

3.5. cUS classification and mortality

All death cases were from grade 2 and grade 3 of the first cUS. Among these, 28 patients died cases were grade 2 of the first ultrasonic classification, accounting for 21.7% (28/129) of the total number and 28.5% (28/96) of grade 2 in first cUS.14 patients died of grade 3, accounting for 10.8% (14/129) of the total number and 56% (14/25) of all children with grade 3. This indicates that the mortality rate of grade 3 severe brain injury is high.

3.6. Correlation between cUS and MDI/PDI

3.6.1. Ordinal regression. The relationship between ultrasound classification of the first time, serious diseases, weight etc and MDI and death. (Table 5): OR <1 (from low to high):Weight, Hospitalization days and Ga. OR >1 (from high to low): grade-3 (first cUS), grade-2 (first cUS), disseminated intravascular coagulation (DIC), twins or multiplets, acute respiratory distress syndrome (ARDS), anemia (Severe), neonatal necrotizing enterocolitis (NEC), severe metabolic acidosise (sMA), sepsis, CHD, and CPD.

The weight of born (OR = 0.36) is the most important protection factors and grades 2 and 3 at first ultrasound (OR = 3.2, OR = 3.78, respectively) are the most harmful factors of mental development and death.

The relationship between ultrasound classification of the first time, severity of diseases, weight etc and PDI and death (Table 6):

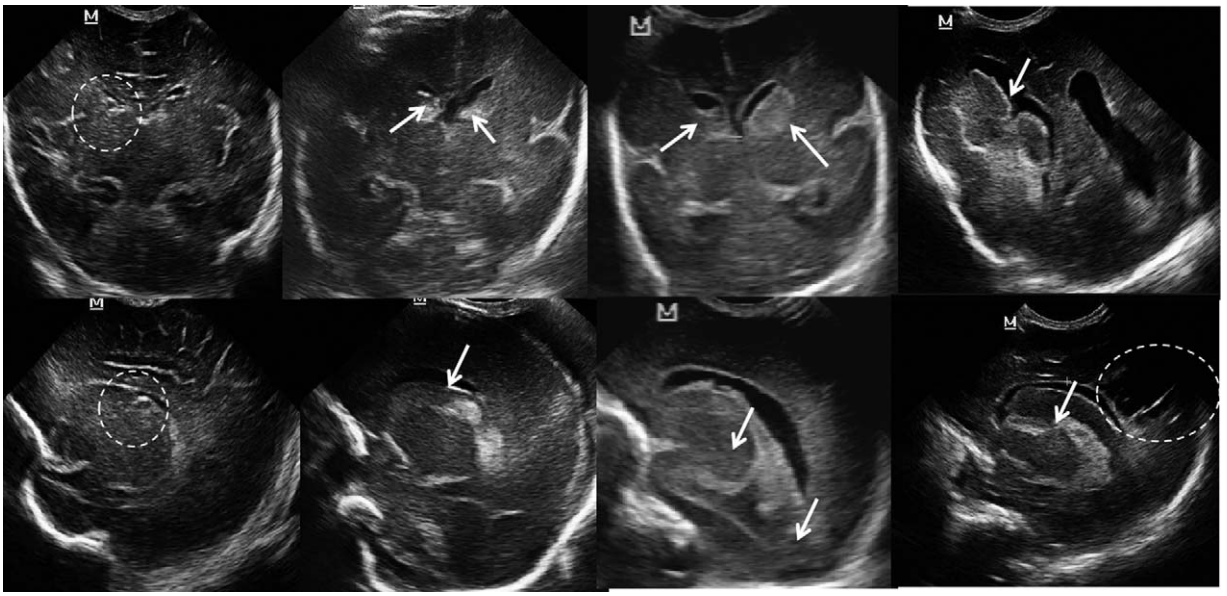


Figure 1. GMH-IVH grade 1-4.

protective factors (OR <1 from low to high): weight, gestational age and hospitalization days. Harmful factors (OR >1 from high to low): grade-3 (first cUS), grade-2 (first cUS), DIC, NEC, ARDS, anemia (severe), sMA, twins or multiplets, sepsis, CHD.

The weight of born (OR = 0.36) is the most important protection factors and grade 2 and 3 in first cUS (OR = 2.25, OR = 2.59, respectively) are the most important harmful factors for motor development and death.

3.6.2. ROC curve. In the ROC figures, the classification of the first cUS was not significantly correlated with MDI/PDI scores were showed in Figure 3 (A and B) ($P > .05$). However, the classification of TEA-cUS and last cUS was significantly correlated with MDI/PDI were showed in Figure 3 (C, D, E, and F) ($P < .05$). The classification of all cUS had high sensitivity (more than 79%) for the prediction of MDI/PDI scores. The specificity of the TEA-cUS was highest for MDI (48%)/PDI (57%) scores (Table 7).

The specificity of the first cUS was lowest (Table 7).

4. Discussion

This study analyzed the clinical data of 129 cases of very premature infants. Among the 129 very premature infants, 38 died before TEA and 4 died after TEA. The mortality and survival rates of the infants were 32.8% and 67.3%, respectively. These values have been reported in the author's previous study.[10] Analyzing the relationship between clinical characteristics and developmental prognosis revealed that low survival rates and poor brain development were associated with low GA; low birth weight; twins or mutiplets; and serious diseases, such as DIC, NEC, ARDS, severe anemia, sMA, and sepsis. This results were similar to the findings reported by Yang Duan[11]

MRI g and cUS are the 2 most important neuroimaging modalities for newborn infants.[12] The diagnostic value of cUS compared to MRI has also been extensively studied.[13–14] Franckx[15] and Duan et al[11] used early cUS, and Burkitt[16] used TEA cUS to predict brain injury on MRI. Sensitivities of 18% to 96% and specificities of 69% and 99% have been reported for these methods. In the present study, the TEA-cUS classifications

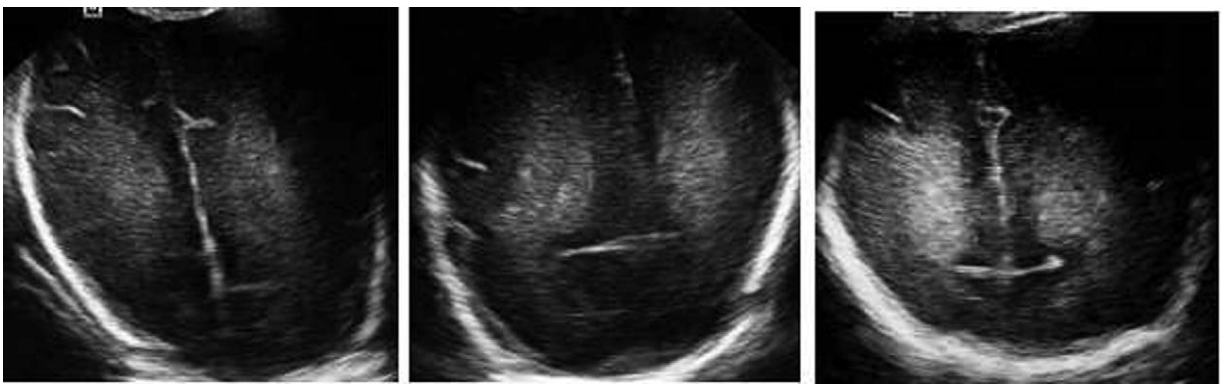
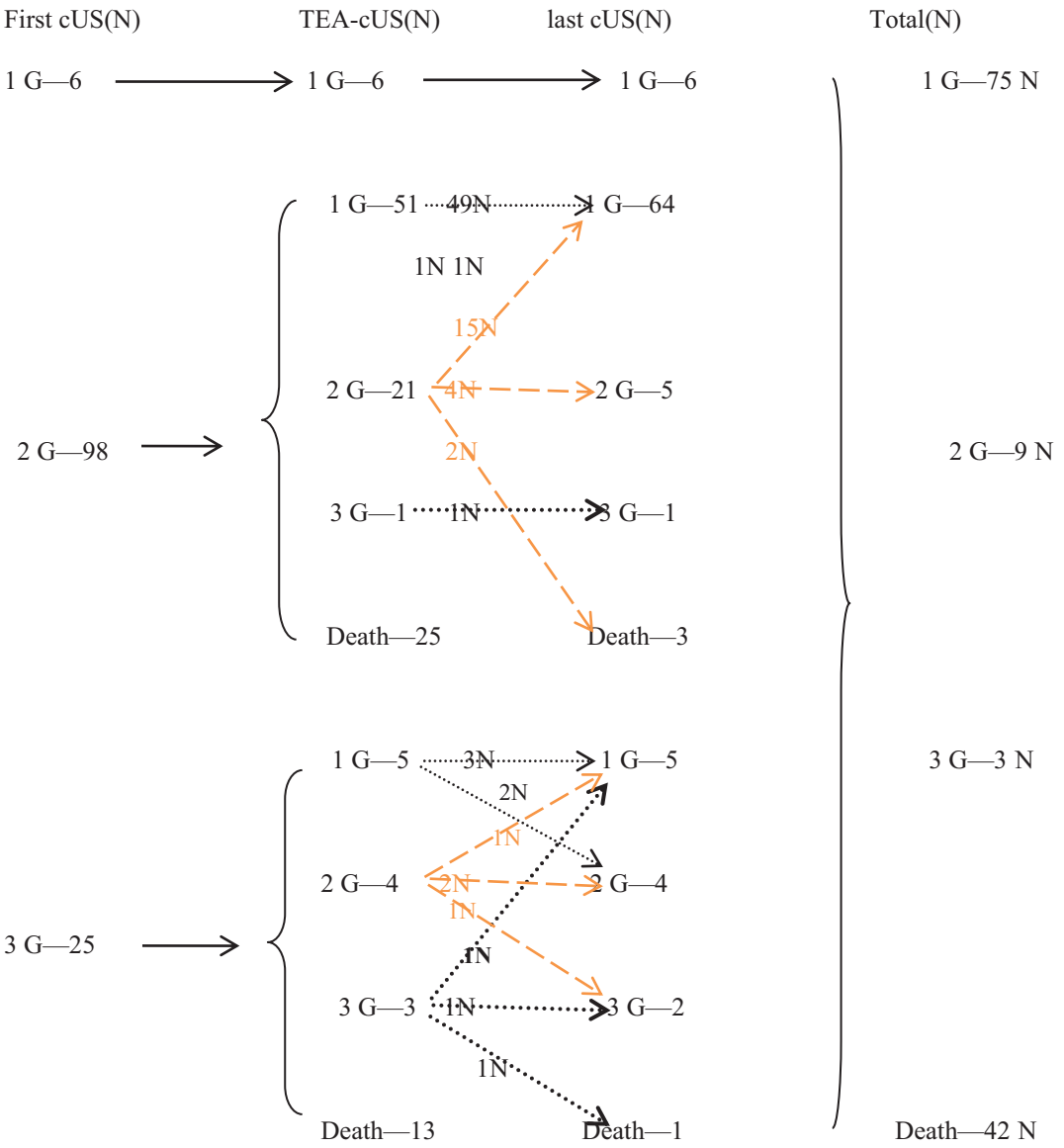


Figure 2. PVE degree I-III.

Table 3

Continuous cranial ultrasound classification and development outcome.



cUS=cranial ultrasound classification, TEA= Term Equivalent Age, N-number, G=grade

Table 4

Crosstabulation of TEA-cUS with TEA-MRI.

	TEA-MRI			
	Normal/ mild injury	Moderate injury	Severely abnormal	Total
TEA-cUS				
Normal/mildly injury	53	3	0	56
Moderately injury	8	12	1	21
Severely injury	0	0	3	3
Total	61	15	4	80

cUS = cranial ultrasound classification, TEA = term equivalent age.

exhibited good agreement with TEA-MRI grading (88%). Serial cUS was used to detect brain injury in very preterm infants to compensate for the inadequacy of ultrasonic frequency that leads to the insufficient evaluation of brain injury. Transient WM changes that may be suggestive of myelin formation, cerebral hemorrhage, and primary lesions were not lost. Thus, the evolution of lesions might be monitored (i.e., hydrocephaly after bleeding), and several forms of brain injury (i.e., focal or diffuse) could be distinguished. However, only end-stage brain injury is readily visualized through MRI. In addition, cerebral hemorrhage may evolve or disappear with time, and focal cysts may have resolved at TEA. Almost all details of the evolution of lesions can be obtained through serial cUS beginning on the first day of cUS to TEA and 6 months. Few lesions are left undetected,

Table 5

Analysis of the relationship between cUS classification, basic data and serious clinical disease and the outcome of MDI and clinical outcomes of children in this group.

	Items	Estimate	Std. Error	Wald	OR	*P*
Threshold value	Dead	8.057	6.206	1.732	1	.43
	MDI=abnormal	7.272	6.645	1.197	1	.274
	MDI = mildly abnormal	7.633	6.649	1.318	1	.251
	MDI=normal	8.517	6.657	1.637	1	.201
Basic characteristics	Weight	−1.021	0.560	3.321	0.36	.068
	Hospitalization days	−0.006	0.002	5.500	0.99	.019
	Gestational age	−0.007	0.125	.003	0.99	.958
	Twins or multiplets	0.689	0.235	8.565	1.99	.003
First cUS Classification	Grade-3(first cUS)	1.329	0.599	4.912	3.78	.027
	Grade-2(first cUS)	1.164	0.552	4.454	3.20	.035
	Grade 1 (first cUS)	0a	.	.	1	
Serious diseases	DIC	0.863	0.333	6.717	2.37	.010
	ARDS	0.550	0.252	4.758	1.73	.029
	Anemia (severe)	0.364	0.227	2.567	1.44	.109
	NEC	0.227	0.390	0.340	1.25	.560
	sMA	0.207	0.247	0.702	1.23	.402
	Sepsis	0.133	0.233	0.326	1.14	.568
	CHD	0.129	0.472	0.075	1.14	.785
	CPD	0.034	0.304	0.013	1.03	.910

ARDS = acute respiratory distress syndrome, CHD = congenital heart disease, CPD = chronic pulmonary dysplasia, DIC = disseminated intravascular coagulation, NEC = neonatal necrotizing enterocolitis, sMA = severe metabolic acidosise.

and their severity is not underestimated. To our knowledge, few prospective studies have utilized newly designed classification systems to classify the cUS results of very preterm infants with brain injuries. Yang et al[11] summarized the early brain injury of GA $\leq$ 32 week infants on the basis of PIVH and WMD. Skiold[17] used cUS scores to define the severity of the brain injuries of very preterm infants. They included 10 items and categorized brain injuries in accordance with 4 grades:

1. normal = composite score of 10;
2. mild abnormalities = composite score of 11 to 14;
3. moderate abnormalities = composite score of 15 to 20; and
4. severe abnormalities = composite score >20.

Although the scoring system is somehow similar to our classification system, it simply assesses TEA-cUS scoring. This study not only focused on the degree of damage within the WM but also that of cerebral hemorrhage (Papiles). Moreover, it focused not only on early ultrasonic findings but also on late findings, such as hydrocephaly or c-PVL, at TEA-cUS and last-cUS. This classification system provided more information on the grade of brain injury according.

Table 6

Analysis of the relationship between cUS classification, basic data, and serious clinical disease and the outcome of PDI and clinical outcomes of children in this group.

	Items	Estimate	Std. Error	Wald	OR	*P*
Threshold value	Dead	11.926	7.674	2.751	1	.151
	PDI =abnormal	10.451	7.482	1.951	1	.162
	PDI = mildly abnormal	10.768	7.486	2.069	1	.150
	PDI=normal	11.723	7.500	2.443		.118
Basic characteristics	Weight	−1.282	.549	5.454	0.277	.020
	Gestational age	−0.032	0.122	0.068	0.969	.795
	Hospitalization days	−0.007	0.003	7.352	0.993	.007
	Twins or Multiplets	0.648	0.231	7.895	1.912	.005
First cUS Classification	Grade-3(first cUS)	0.951	0.519	3.361	2.588	.067
	Grade-2(first cUS)	0.810	0.469	2.983	2.248	.084
	Grade 1	0a	.	.	1	.
Serious diseases	DIC	0.679	0.324	4.395	1.972	.036
	NEC	0.351	0.390	0.810	1.42	.368
	ARDS	0.346	0.242	2.052	1.413	.152
	Anemia(Severe)	0.290	0.224	1.680	1.336	.195
	sMA	0.218	0.244	0.802	1.244	.371
	CHD	0.197	0.470	0.175	1.218	.676
	CPD	0.075	0.303	0.062	1.078	.804
	Sepsis	0.018	0.231	0.006	1.018	.939

ARDS = acute respiratory distress syndrome, CHD = congenital heart disease, CPD = chronic pulmonary dysplasia, DIC = disseminated intravascular coagulation, NEC = neonatal necrotizing enterocolitis, sMA = severe metabolic acidosise.

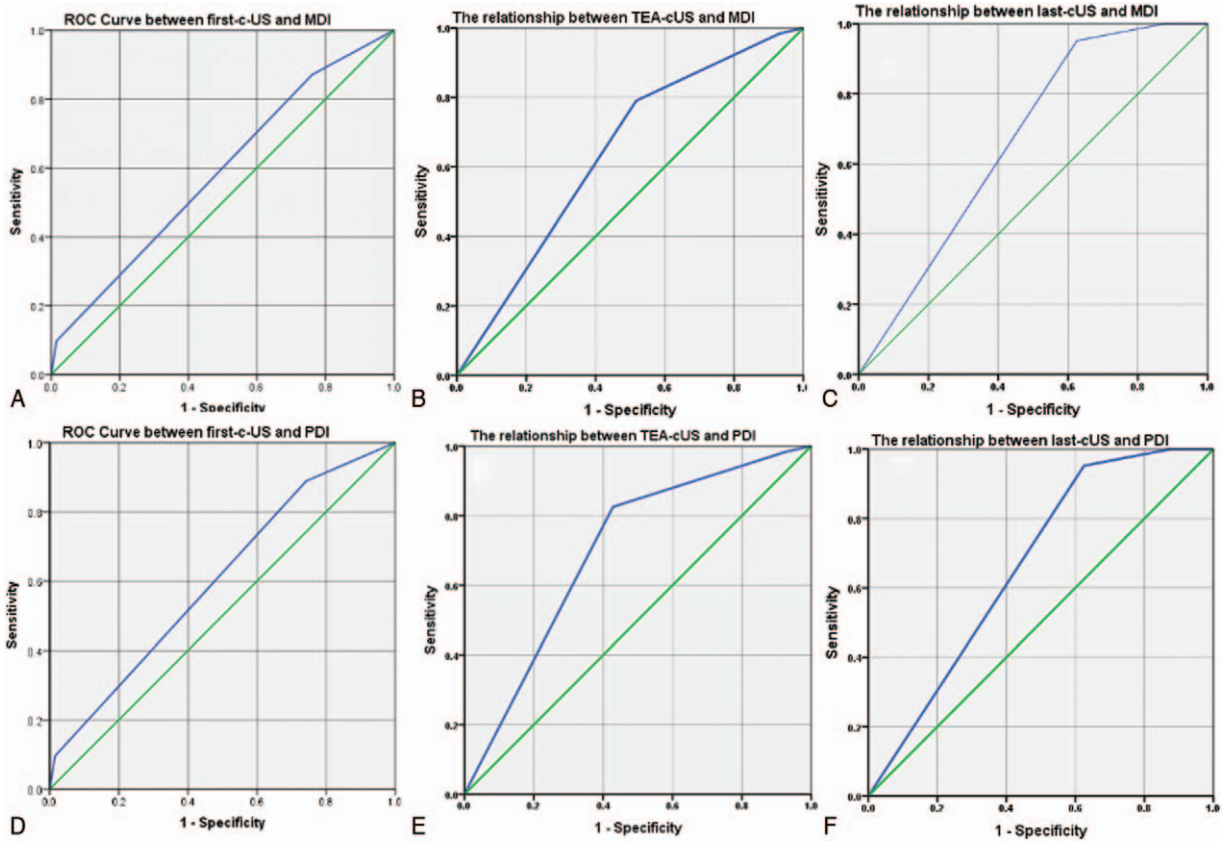


Figure 3. The ROC between classification of cUS and MDI/PDI scores.

All death cases exhibited grades 2 and 3 brain injuries at first cUS. The fatality rate of grade 3 brain injury was (14/25), indicating high mortality rates of severe brain injury. Ordinal regression analysis showed that mental and motor development was affected by multiple factors, among which grades 2 and 3 brain injuries at first cUS were the most important harmful factors. Similarly, a previous report showed that severe (grade 3) injury at term cUS is highly predictive of neurodevelopment at 1 and 3 years.[16]

Yang et al[3] studied the prognosis of psychomotor and mental development in premature infants by using early cUS (less than 3 days). Skiold[17] described a novel scoring system for cUS at TEA, of which the negative predictive values regarding all brain outcomes are high. Franckx[15] used cUS (4 days to 6 weeks) and europhysiological testing to predict the neurological outcomes of very preterm infants. They emphasized that abnormal early CUS is the best predictor of CP presence, motor developmental delay, and cognitive developmental delay. However, these studies analyzed the results of one-time cUS to predict brain development. By contrast, the present study included the classification of the first cUS, TEA-cUS, and last-cUS. The ROC curves showed that the first ultrasonic grading was not significantly correlated with MDI/PDI scores. By contrast, the classification of TEA-cUS and last cUS was significantly correlated with MDI/PDI scores. cUS classifications changed over time. Cerebral hemorrhage and PVE may evolve or disappear over time, and c-PVL or hydrocephalus may have been relieved at TEA or older. The early-stage classification of brain damage may change after treatment. During this period, many cases exhibited improvement, thereby accounting for the grading change that also influenced brain development. These changes might account for the lack of the significant correlation between the first ultrasonic grading and brain development.

Table 7

Area and the coordinates of the curve between classification of cUS and MDI/PDI scores.

	MDI			PDI		
	First cUS	TEA cUS	Last cUS	First cUS	TEA cUS	Last cUS
Area Asymptotic	0.585	0.640	0.667	0.551	0.700	0.704
Sig	0.095	0.032	0.017	0.476	0.002	0.004
Sensitivity	0.871	0.790	0.952	0.889	0.825	0.968
Specificity	0.239	0.483	0.375	0.258	0.571	0.435

cUS = cranial ultrasound classification, MDI = Mental Developmental Index, PDI = Psychomotor Developmental Index, TEA = term equivalent age.

ROC curves showed that TEA-cUS and last classification (all cUS grading) had high sensitivity (79%–96%) for CP prediction, and these results were higher than those reported for the predictive accuracy of CP, which is only 46%.[4] The specificity of the first cUS was the lowest and that of TEA cUS was the highest (57%) among all cUS classifications. Two cases that were originally classified as moderate hydrocephaly at the last US exhibited normal brain development. This finding accounted for the lower specificity of the last cUS than that of TEA cUS. The high sensitivity but low specificity of cUS classification might be attributed to the following factors: First, the early-stage classification of brain damage might change after treatment given that the last ultrasound to the last clinical follow-up of MDI and PDI was separated by a long period. During this period, many cases exhibited improvement, thereby accounting for the low specificity and high false-positive results associated with US. Second, ordinal regression analysis showed that brain development and prognosis were affected by numerous factors. The adverse factors of mental and motor development included grades at first cUS, multiple births, and serious diseases. By contrast, protective factors included GA, birth weight, and hospitalization period. These factors accounted for the low specificity of US. Grades 2 and 3 at first ultrasound were the most adverse factors of mental and motor development. Moreover, these factors indicated that moderate and severe brain injuries are the most influential factors of brain development and prognosis. Third, our sample included 8 infants who exhibited PWMLs on MRI. PWMLs are subtle white lesions that are not easily recognizable but can be characterized by sustained, inhomogeneous periventricular WM echogenicity at TEA or last cUS. Among the infants with PWMLs, 1 (16%) developed CP, and 3 (50%) developed mild CP at follow-up. These results were consistent with those of several recent studies and suggested that the presence of PWML is associated with an increased risk of CP and abnormal MDI and PDI.[1,18]

The low proportion of subjects with severe brain abnormalities and severe impairments in our study is important limitation. Moreover, this study excluded treatment and intervention measures. Another limitation is that cUS images were acquired only via the anterior fontanel. This approach most likely contributed to the low rate of cerebellar injury detection. In future studies, additional acoustic windows, such as the mastoid fontanel, should be used to improve the visualization of areas with low accessibility via the anterior fontanel.

5. Conclusions

The extremely premature infants are at the risk of neurodevelopmental abnormalities that caused neonatal morbidity and mortality. In our study, the classification system for cUS at TEA was described and allowed the quantification of preterm brain injury, and was comparable with established MRI scoring systems. This TEA-cUS is usefulness as a standalone predictor of extremely premature infants' neurodevelopment outcome in further clinical routine examination.

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