A novel magnetic resonance imaging-based scoring system to predict outcome in neonates born preterm with intraventricular haemorrhage

KATHARINA GOERAL[1] | GREGOR KASPRIAN[2] | BRITTA M HÜNING[3] | THOMAS WALDHOER[4] | RENATE FUIKO[1] | VICTOR SCHMIDBAUER[2] | DANIELA PRAYER[2] | URSULA FELDERHOFF-MÜSER[3] | ANGELIKA BERGER[1] | MONIKA OLISCHAR[1] | KATRIN KLEBERMASS-SCHREHOF[1]

1 Division of Neonatology, Intensive Care and Neuropediatrics, Department of Pediatrics and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna; **2** Division of Neuroradiology and Musculoskeletal Radiology, Department of Radiology, Medical University of Vienna, Vienna, Austria. **3** Department of Pediatrics I, Neonatology, University Children's Hospital Essen, University Duisburg-Essen, Essen, Germany. **4** Department of Epidemiology, Center of Public Health, Medical University of Vienna, Vienna, Austria.

Correspondence to Katharina Goeral at Division of Neonatology, Intensive Care and Pediatric Neurology, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Währingergürtel 18-20, 1090 Vienna, Austria. E-mail: katharina.goeral@meduniwien.ac.at

PUBLICATION DATA
Accepted for publication 28th October 2021.
Published online 28th November 2021.

ABBREVIATIONS

CUS	cranial ultrasound
IVH	intraventricular haemorrhage
PVHI	periventricular haemorrhagic infarction

AIM To create a magnetic resonance imaging (MRI)-based scoring system specific to neonates born preterm with intraventricular haemorrhage (IVH), which could serve as a reliable prognostic indicator for later development and might allow for improved outcome prediction, individually-tailored parental counselling, and clinical decision-making.
METHOD This retrospective, two-center observational cohort study included 103 infants born preterm with IVH (61 males, 42 females; median gestational age 26wks 6d), born between 2000 and 2016. Term-equivalent MRI was evaluated using a novel scoring system consisting of 11 items. A total MRI score was calculated and correlated with neurodevelopment between 2 years and 3 years of age. Prediction models for outcome were defined.
RESULTS The proposed MRI scoring system showed high correlation and strong predictive ability with regard to later cognitive and motor outcome. The prediction models were translated into easy-to-use tables, allowing developmental risk assessment.
INTERPRETATION The proposed MRI-based scoring system was created especially for infants born preterm with IVH and enables a comprehensive assessment of important brain areas as well as potential additional abnormalities commonly associated with IVH. Thus, it better represents the severity of brain damage when compared with the conventional IVH classification. Our scoring system should provide clinicians with valuable information, to optimize parental counselling and clinical decision-making.

Despite increased survival rates of neonates born extremely preterm, brain lesions remain a major problem and are associated with high mortality and morbidity.[1] The incidence of periventricular haemorrhagic infarction (PVHI) as a consequence of intraventricular haemorrhage (IVH) has remained high recently. According to the Vermont Oxford Network (https://public.vtoxford.org), 24% of very-low-birthweight infants experienced IVH in the industrialized world during the last decade. IVH is commonly detected in the neonatal intensive care unit using cranial ultrasound (CUS), and though there is a correlation between ultrasound-based IVH grading and neurodevelopmental outcome, large inter-study variations exist.[2–5] In light of the large number of infants born preterm at risk of brain injury in combination with increasing survival rates of infants born extremely preterm, there is an urgent need to develop a robust method to appraise lesions in the neonatal brain.

Although certain CUS variables have been linked to poor subsequent development,[6–11] it remains challenging to accurately predict outcome. CUS-based categorical features include ventricular area, size of intraventricular echodensity, size of PVHI, shape, topography, bilaterality of PVHI, and division according to venous anatomy. In contrast to CUS, which is heavily operator-dependent, magnetic resonance imaging (MRI) allows for a more accurate and less biased assessment of the neonatal brain. During the last decade, MRI-based scores at term-equivalent age have been established as prognostic markers of outcome in neonates born preterm.[12–14] To our knowledge, all published MRI-based scoring systems have been developed for the entire population born preterm, and though

 DOI: 10.1111/dmcn.15116

severity and location of brain damage are thought to play an important role in later development, scoring systems especially designed for infants with IVH have not yet been established.

The aim of the present study was to create an MRI-based score specific to infants born preterm with IVH, assessing important brain areas as well as potential additional abnormalities commonly associated with this type of brain injury, and thereby, going beyond the scoring of the conventional 4-grade IVH classification.

METHOD

This retrospective, two-center, observational cohort study included neonates born preterm less than 34 weeks' gestational age with IVH. The study cohort was further restricted to those patients who underwent MRI during their clinical course and who had standardized neurodevelopmental follow-up. Exclusion criteria were major congenital anomalies, cerebral malformations, metabolic disorders, chromosomal abnormalities, as well as death before follow-up. Patients were treated at either the Department of Pediatrics and Adolescent Medicine of the Medical University of Vienna, Austria or the Department of Pediatrics I of the University Hospital Essen, Germany, between October 2000 and January 2016.

CUS examinations were performed repeatedly from birth until term and IVH grades were classified based on maximum lesion extension, as seen on CUS according to Papile et al.[15] This is refered to as the conventional IVH classification. In addition, the presence of posthaemorrhagic ventricular dilatation and information on whether neurosurgical intervention was required was recorded.

Magnetic resonance imaging

In Vienna, neonatal brain imaging was performed around term-equivalent age using a 1.5 Tesla MRI scanner (Philips Ingenia, Philips Healthcare, Best, the Netherlands) and an adult head or knee coil in combination with a vacuum air extraction device. In Essen, a 1.5 Tesla MRI (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) and standard coil was used until February 2011 and thereafter, a 3 Tesla MRI (Skyra, Siemens Healthcare, Erlangen, Germany) in combination with a magnetic resonance compatible incubator. MRI was reviewed and approved for analysis by a paediatric neuroradiologist (GK) and analysed together by three investigators (GK, KG, KKS) who were blinded to perinatal data, clinical course, previous CUS findings, and outcome data. In cases of disagreement between investigators, a consensus was reached by discussion. For analysis, imaging data of multiplanar T2-weighted turbo spin echo sequences was used to allow a wide use of the proposed scoring system, even if only standard sequences are available. Diffusion-weighted images and T1-weighted spin echo sequences were not used for scoring; however, these were available for the reviewing neuroradiologist in order to differentiate between periventricular infarcted regions (persisting defect) and reversible perihaemorrhagic oedema.

What this paper adds

- Cognitive and motor outcomes in neonates born preterm with intraventricular haemorhage (IVH) can be predicted using the scoring system.
- Gestational age is an important factor in prognostication after IVH.
- Easy-to-use tables facilitate clinical application of the system, which is based on term-equivalent magnetic resonance imaging.

The MRI-based scoring system developed within this study was partly based on previously published scores,[12–14] but adjusted to include lesions that particularly occur after IVH. It consists of 11 items (Fig. 1) that take into account eight brain areas (four within the grey matter: gyrus precentralis, gyrus postcentralis, hippocampus, and basal ganglia; and four within the white matter: pyramidal tract/posterior limb of the internal capsule, corpus callosum, radiatio optica, and crossroad[16]) and three potential additional abnormalities (periventricular leukomalacia and/or white matter volume loss, hydrocephalus, cerebellar tissue loss). Figure 1 gives a general overview of the created score while specifics on functional topography of chosen areas and a detailed MRI score description (step-by-step instruction) are shown in Appendix S1 (online supporting information). Exemplary MRI showing scoring of neonates born preterm included in this study is shown in Figures 2 and 3. As described, graded scores were used for each studied area (0–3, increasing score with increasing pathology). After appraisal, a grey matter score, white matter score, and total MRI score (composed of grey matter score, white matter score, and additional points) were calculated.

Neurodevelopmental outcome

Outcome assessment was performed at the respective follow-up clinic by pediatricians and developmental psychologists using the Bayley Scales of Infant Development (Second or Third Edition) between 2 years and 3 years of age. Published German Bayley norms were used. Outcomes were dichotomized into two groups using conventional standard deviation (SD) banded cut-off points: favourable outcome (no–mild impairment, ≥70) and unfavourable outcome (moderate–severe impairment, <70, equivalent to >2SDs below the norm).[17] Furthermore, functional assessment of visual and hearing ability were included. In the presence of cerebral palsy (CP), a Gross Motor Function Classification System (GMFCS) level was assigned. CP was dichotomized into two groups: no CP+ambulant CP (GMFCS level I–II) and non-ambulant CP (GMFCS level III–V).

Data analysis and ethics

Statistical analysis was performed using SPSS, version 20.0 (IBM Corp., Armonk, NY, USA) and SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). Data are summarized with medians and interquartile ranges (IQRs), means and SDs, and counts and percentages, as appropriate. Univariate associations between IVH grade based on CUS and MRI scores were summarized with Pearson's correlation coefficient.

GREY MATTER SCORE *maximum 12 points*				
Gyrus precentralis	**0** normal	**1.5** mild defect		**3** pronounced defect
Gyrus postcentralis	**0** normal	**1.5** mild defect		**3** pronounced defect
Hippocampus	**0** normal	**1.5** sagittalized without volume loss		**3** volume loss or defect
Basal ganglia	**0** normal	**1** small defect in germinal eminence/ caudothalamic groove	**2** partially affected	**3** pronounced defect

WHITE MATTER SCORE *maximum 12 points*				
Pyramidal tract/PLIC	**0** normal	**1** partially affected - not directly by bleeding	**2** partially affected - directly by bleeding	**3** pronounced defect
Corpus callosum	**0** normal	**1.5** thinning of the corpus callosum plus bowed/elevated appearance		**3** defect by bleeding or EVD/shunt
Radiatio optica	**0** normal	**1** minimal peri-ventricular lesion	**2** partially affected	**3** pronounced defect
Crossroad [a]	**0** normal	**1** minimal peri-ventricular lesion	**2** partially affected	**3** pronounced defect

ADDITIONAL POINTS *maximum 9 points*				
Periventricular leukomalacia/WM volume loss	**0** normal	**1** periventricular signal ↑/mild reduction of WM volume; no cysts	**2** single focal cyst <2mm	**3** larger cyst ≥2mm/ multiple cysts/severe reduction of WM volume
Hydrocephalus	**0** normal	**1** PHVD without narrowing of external CSF spaces	**2** PHVD with narrowing of external CSF spaces	**3** hydrocephalus with intervention
Cerebellum	**0** normal	**1.5** cerebellar tissue loss		**3** severe disruption with tissue loss

TOTAL MRI SCORE *maximum 33 points*

Figure 1: Score description. [a]Crossroad: the assessed area is corresponding to the C4 crossroad described in the paper by Judas et al.[16] PLIC, posterior limb of the internal capsule; EVD, external ventricular drainage; WM, white matter; PHVD, posthaemorrhagic ventricular dilatation; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Outcome variables were analysed as continuous as well as binary variables in two separate regression models. In the first model, both scores were treated as left censored variables and analysed in a linear model adapted for left truncation using the procedure 'nlmixed' in SAS. A random intercept term was added for each patient because of repeated measurements. R^2 values were calculated to evaluate the prognostic relevance of independent variables. In the second model, both scores were treated as binary variables with a threshold value of ≤70 points and >70 points and analysed via a logistic regression model including a random intercept term using the 'genmod' procedure in SAS. Finally, receiver operating curves and area under the curve were calculated for total MRI score as well as conventional IVH classification.[15] *P*-values of <0.05 were considered statistically significant. No adjustment of *p*-values for multiple testing was applied.

Scoring duration was evaluated in 25% of patients. Intra- and interobserver reliability were assessed in 10% of all included neonates. Therefore, scoring was repeatedly performed after several months by a single observer (GK). The interobserver reliability was evaluated by repeating scoring in every infant by a second observer (VS) unaware of the first observers' data. Intraclass correlation coefficients were calculated using the two-way random model for absolute agreement and interpreted according to the Brennan and Silman strength of agreement scale.

The respective local research ethics committee (ethics committee of the Medical University of Vienna: EK 1968/2017; ethics committee of the medical faculty of the University Essen: 17-7877 BO) approved this study.

RESULTS

The study cohort consisted of 103 neonates born preterm with IVH (61 males, 42 females; median gestational age 26wks 6d [IQR 25^{+1}–29^{+1}], median birthweight 856g [IQR 675–1200]) diagnosed using CUS. Detailed descriptive data are summarized in Table 1. Forty-five (44%) neonates with posthaemorrhagic ventricular dilatation were treated by insertion of subcutaneously tunneled external ventricular drainage or Rickham/Ommaya reservoir once the ventricular index crossed the 97th centile plus 4mm. Subsequently,

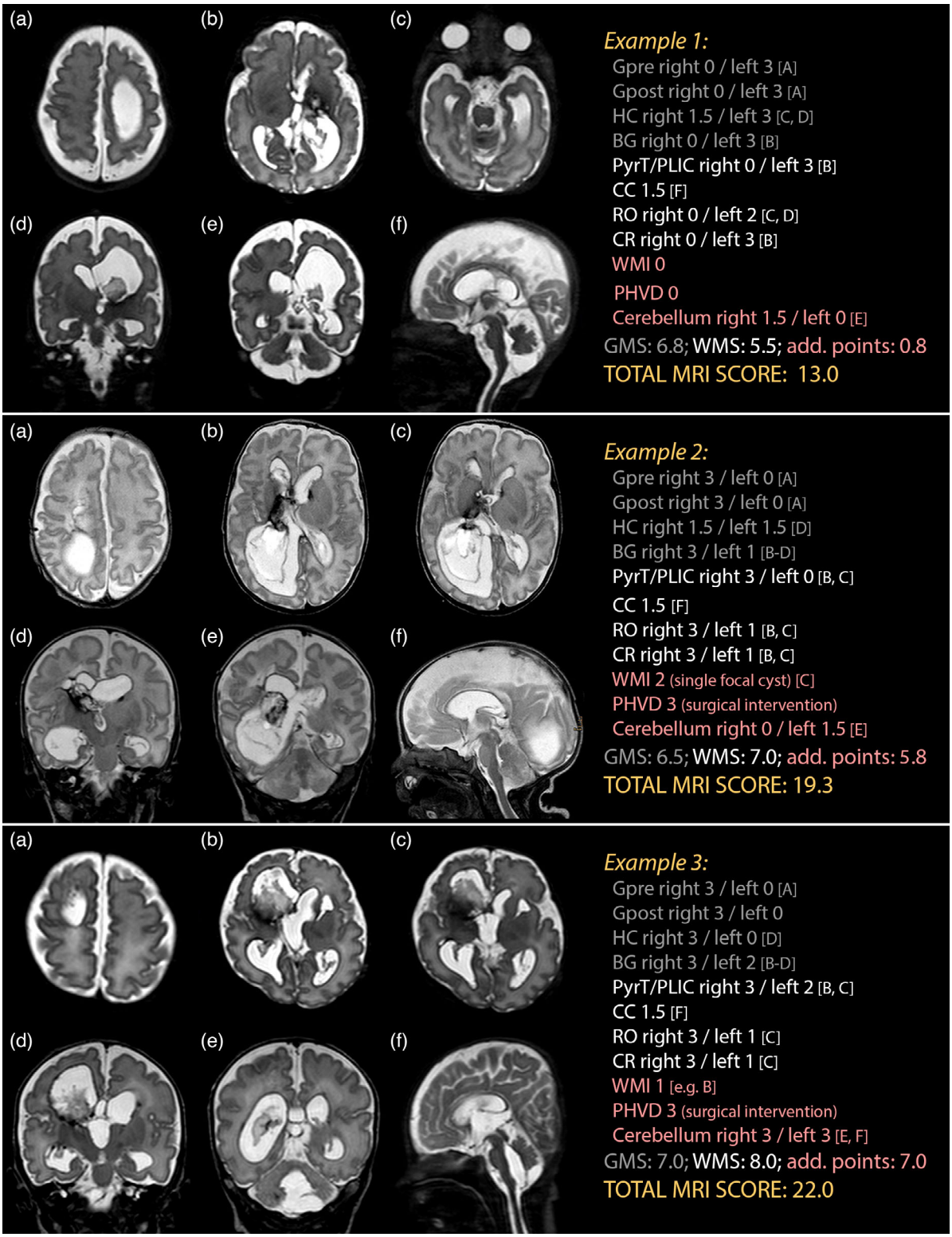

Figure 2: Exemplary scoring 1 (all items and magnetic resonance imaging [MRI] scores). All three patients showed a developmental quotient of >3 standard deviations below the norm for age, cerebral palsy (example [E] 1: Gross Motor Function Classification System [GMFCS] level I; E2 and E3: GMFCS level IV) and had functionally impaired vision improved by aids (E1 and E3: strabismus and myopia; E2: severe amblyopia and optic nerve atrophy). Furthermore, E1 and E2 underwent surgery for epilepsy at 12 to 19 months of age as they had epilepsy refractory to antiseizure medication. Gpre, gyrus precentralis; Gpost, gyrus postcentralis; HC, hippocampus; BG, basal ganglia; PyrT, pyramidal tract; PLIC, posterior limb of the internal capsule; CC, corpus callosum; RO, radiatio optica; CR, crossroad; WMI, white matter injury; PHVD, posthaemorrhagic ventricular dilatation; GMS, grey matter score; WMS, white matter score.

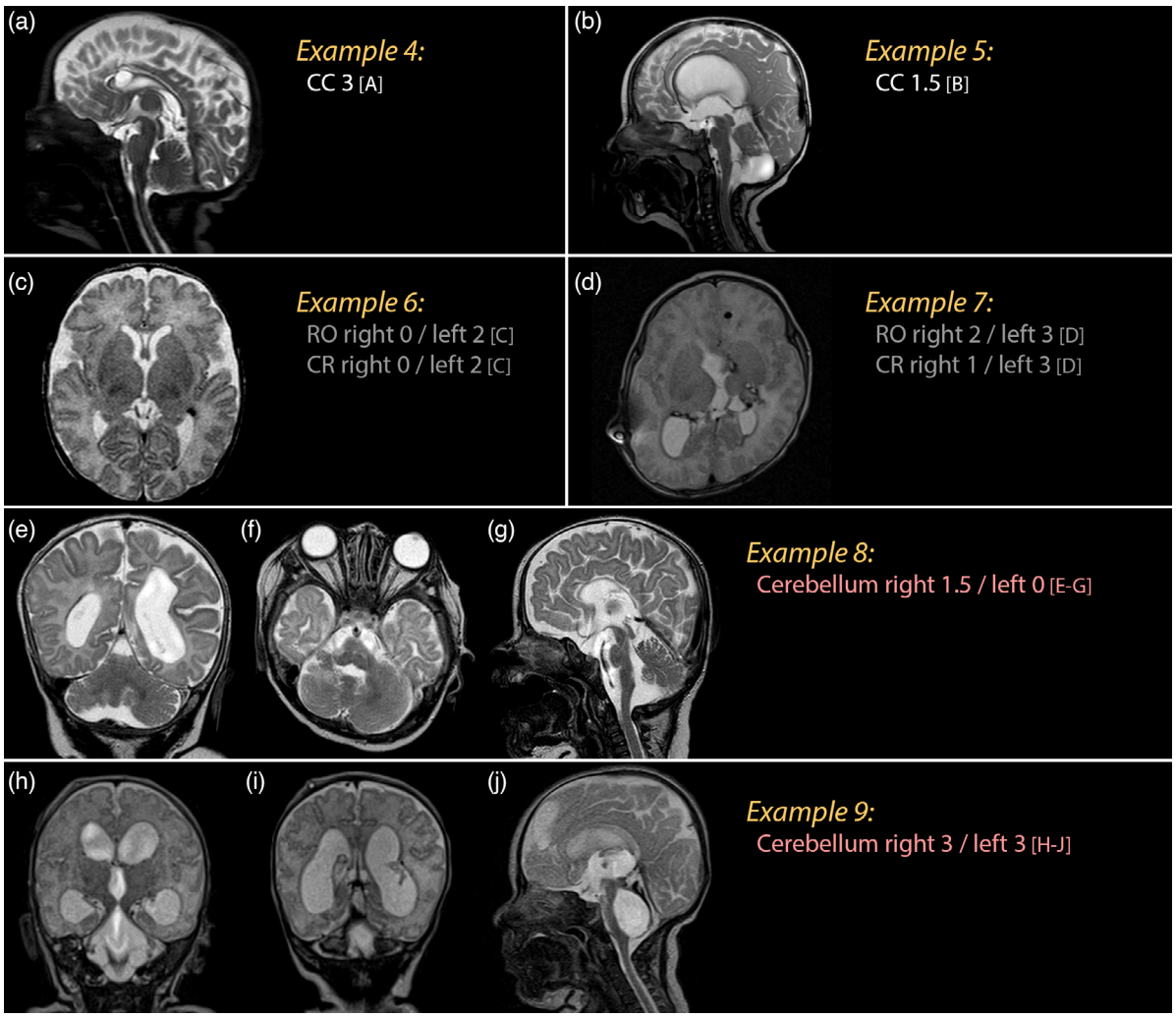

Figure 3: Exemplary scoring 2 (selected items). CC, corpus callosum; RO, radiatio optica; CR, crossroad.

in cases of progressive ventricular enlargement after external ventricular drainage removal, 30 (29%) neonates required the implantation of a permanent ventriculoperitoneal shunt and three (3%) needed a ventriculostomy (requirements for both procedures were weight >2kg and cerebrospinal fluid protein <200mg/dL). Median scoring duration per patient was 1.7 minutes (IQR 1.2–2.5).

MRI scores increase with severity of haemorrhage in neonates with IVH

To determine whether MRI scores reflect standard IVH grading and, if present, the extent of PVHI, 103 previously-obtained term-equivalent MRIs were reviewed and analysed. MRIs were performed at a median gestational age of 39 weeks 2 days (IQR 37^{+3}–40^{+3}) corresponding to a median postnatal age of 12.9 weeks (IQR 9.4–15.6). Fifty-three (51%) neonates did not show parenchymal injury on MRI, while 50 (49%) showed PVHI in either one (n=34, 33%) or both hemispheres (n=16, 16%). The median total MRI score was 6 (IQR 1–10) with a maximum of 30. The median values for all three subscores were 0 (IQR 0–2) for grey matter, 3 (IQR 0–6) for white matter, and 2 (IQR 0–3) for additional points. A significant positive correlation between CUS-based IVH grade and total MRI score as well as all MRI subscores was observed (R^2=0.59/0.54/0.57/0.44 for total MRI score/grey matter score/white matter score/additional points; each p<0.001). Results were divided into no, unilateral, or bilateral PVHI and are shown in Table S1 (online supporting information).

MRI scores predict neurodevelopment

To evaluate the association between individual brain areas and additional abnormalities with later development, detailed analyses were performed. Outcome data were available from 95 patients and are shown in Table 1. As an influencing cofactor, gestational age at birth was significantly correlated with later neurodevelopmental outcome

Table 1: Descriptive data

Characteristic	Median (IQR); *n* [%]
Birth year	2011 (2007–2013)
Gestational age birth, wks	26^{+6} (25^{+1}–29^{+1})
Gestational age MRI, wks	39^{+2} (37^{+3}–40^{+3})
Weight, g	856 (675–1200)
Male/female	61 [59]/42 [41]
Apgar 1′	7 (4–8)
Apgar 5′	8 (7–9)
Apgar 10′	9 (8–9)
IVH grade based on CUS	3 (2–4)
IVH II	34 [33]
IVH III	27 [26]
IVH IV=PVHI[a]	42 [41]
Bihemispheric IVH based on CUS	76 [74]
PHVD	51 [50]
No intervention	6 [12]
Only EVD/Reservoir	12 [24]
EVD/reservoir+shunt	30 [59]
EVD/reservoir+ventriculostomy	3 [6]
MRI scoring	
Grey matter score	0 (0–2)
White matter score	3 (0–6)
Additional points	2 (0–3)
Total MRI score	6 (1–10)
Neurodevelopmental outcome	
Cognitive outcome[b]	69 (50–85)
Motor outcome[b]	65 (49–82)
GMFCS level	
No cerebral palsy	32 [32]
GMFCS level I	47 [47]
GMFCS level II	7 [7]
GMFCS level III	4 [4]
GMFCS level IV	9 [9]
GMFCS level V	1 (1]
Vision	
No impairment or diagnosis[c] not sufficient to require aids	65 [66]
Functionally impaired vision improved by aids	32 [32]
Blindness	2 [2]
Hearing	
No impairment or hearing loss not sufficient to require aids	100 [99]
Hearing loss improved by aids	1 [1]
Hearing loss not improved by aids	0 [0]

CUS, cranial ultrasound; PHVD, posthaemorrhagic ventricular dilatation; EVD, external ventricular drainage; MRI, magnetic resonance imaging; GMFCS, Gross Motor Function Classification System. [a]The diagnoses intraventricular haemorrhage (IVH) grade IV and periventricular haemorrhagic infarction (PVHI) were regarded as synonymous. [b]Median composite scores. [c]Includes strabismus and refractive errors not sufficient to require aids.

(cognitive, p=0.039; motor, p<0.001) and, therefore, all analyses were adjusted for gestational age.

Predictive strength of total MRI score and all individual subscores for outcome were high when using the following model: outcome = $b_0 + b_1 \times$ total MRI score + $b_2 \times$ gestational age. The R^2 for total MRI score was 0.65 for cognitive outcome and 0.81 for motor outcome. The R^2 for all subscores was 0.56/0.68/0.74 (grey matter score/white matter score/additional points) for cognitive and 0.75/0.82/0.86 (grey matter score/white matter score/additional points) for motor outcome. Receiver operating curves demonstrated that total MRI score could differentiate between favourable and unfavourable outcomes, with a high area under the curve of 0.78 (95% confidence interval [CI] 0.68–0.88) for cognitive, 0.84 (95% CI 0.75–0.92) for motor outcome, and 0.94 (95% CI 0.88–0.99) for CP. Compared with the conventional IVH grading based on CUS, area under the curve of total MRI score were significantly higher by 0.16 for cognitive, 0.17 for motor outcome, and 0.15 for CP (Fig. S1 [online supporting information]). Based on these findings, our aim was to propose a tool for clinical implementation. This was achieved by translating the results from our model into easy-to-use tables based on gestational age and total MRI score, allowing probability estimation for later development (Tables 2 and 3, Fig. 4).

Intra- and interobserver reliability

The reproducibility of measurements by a single observer, as well as between observers, was classified as very good (≥0.81) according to the Brennan and Silman strength of agreement scale for total MRI score and all MRI subscores (data not shown). The lowest intraobserver reliability was 0.857 for additional abnormalities, the lowest interobserver reliability was 0.902 for white matter score.

DISCUSSION

We developed an MRI-based scoring system to classify IVH in neonates more thoroughly and to provide clinicians with a more accurate tool for predicting subsequent neurodevelopment. By studying 103 neonates born preterm with IVH, we showed that MRI scores increased with extent of haemorrhagic damage to the periventricular region. Moreover, we demonstrated that this MRI score is valuable in routine clinical practice and has strong predictive ability with regard to cognitive and motor outcome, including CP, and significantly higher areas under the curve for subsequent neurodevelopmental outcome compared with the conventional IVH grading.

To date, CUS remains the method of choice for bedside IVH diagnosis.[18] Nevertheless, no established CUS-based grading system[15,19] takes the extent or location of parenchymal involvement, and thereby affected brain areas or bilaterality into consideration.

The scoring system proposed in the present study took precise lesion topography into account by assessing areas of the brain as well as potential additional abnormalities and assigning severity scores using MRI. This imaging modality is not only more precise than CUS, but is also superior at identifying parenchymal injury, more subtle forms of damage (e.g. punctate or diffuse white matter injury), and at detecting additional lesions such as tissue loss or punctate haemorrhages in the cerebellum.[20–23]

Three studies have evaluated the strength of term-equivalent MRI at predicting outcome in infants born preterm.[12–14] First, the association between qualitatively defined white matter as well as grey matter abnormalities and outcome (cognitive delay, motor delay, CP, and neurosensory impairment) at 2 years of age was studied.[12] In 2013, a scoring system evaluating both severity of brain

Table 2: Charts allowing probability estimation of favourable cognitive outcome

	GA (wks)												% Difference between GA of 23wks and 34wks
Total MRI score	23	24	25	26	27	28	29	30	31	32	33	34	
0	60	63	67	70	73	76	78	81	83	85	87	88	29
1	55	58	62	65	69	72	75	78	80	82	84	86	32
2	50	53	57	61	64	68	71	74	77	79	82	84	34
3	45	48	52	56	59	63	66	70	73	76	78	81	36
4	40	43	47	51	54	58	62	65	69	72	75	77	38
5	35	38	42	46	49	53	57	60	64	67	71	74	39
6	30	34	37	41	44	48	52	56	59	63	66	69	39
7	26	29	33	36	39	43	47	50	54	58	62	65	39
8	23	25	28	31	35	38	42	45	49	53	57	60	38
9	19	22	24	27	30	34	37	40	44	48	52	55	36
10	16	18	21	23	26	29	32	36	39	43	47	50	34
11	14	16	18	20	22	25	28	31	34	38	42	45	31
12	11	13	15	17	19	22	24	27	30	33	37	40	29
13	10	11	13	14	16	18	21	23	26	29	32	35	26
14	8	9	10	12	14	15	18	20	22	25	28	31	23
15	7	8	9	10	11	13	15	17	19	21	24	27	20
16	5	6	7	8	9	11	12	14	16	18	20	23	18
17	4	5	6	7	8	9	10	12	13	15	17	20	15
18	4	4	5	6	7	8	9	10	11	13	15	17	13
19	3	4	4	5	5	6	7	8	9	11	12	14	11
20		3	3	4	4	5	6	7	8	9	10	12	10–12
21			3	3	4	4	5	6	6	7	9	10	8–10
22				3	3	3	4	5	5	6	7	8	6–8
23						3	3	4	4	5	6	7	5–7
24							3	3	4	4	5	6	4–6
25								3	3	3	4	5	3–5
26						<3				3	3	4	2–4
28												3	1–3
≥29													0–2

The values show the probability of Bayley score ≥70 (%). Logistic model for cognitive outcome: $\log(P/[1-P]) = -3.0496 + -0.2029 \times$ total MRI score $+ 0.1496 \times$ GA. GA, gestational age; MRI, magnetic resonance imaging.

damage (signal abnormalities) and impaired brain growth (biometrics) was introduced and named the Kidokoro score. In contrast to our scoring system, which is based on visual analysis alone, the Kidokoro score is not only based on visual classification, but also on a total of six quantitative one-dimensional measurements.[13] A subsequent study of 325 neonates born very preterm from three centers applied the Kidokoro score and showed that it can be used to predict neurodevelopmental outcome, as both brain injury and impaired brain growth at term-equivalent age were independently associated with cognitive development.[14] Recently, George et al. validated the Kidokoro score for earlier MRI at 29 to 35 weeks' gestation. Even though the scoring was still valid at this early time point, associations with 12-month outcome were stronger for term-equivalent MRI.[24]

A group from Sweden included more than 100 infants born at less than 27 weeks' gestation and focused on white matter abnormalities, including diffuse excessive high signal intensities, in relation to 30-month outcome. They found a significant association between white matter abnormalities and CP, but not between diffuse excessive high signal intensities and Bayley performance or CP. In contrast to our population, only 10% of included patients showed an IVH grade of III or higher.[25]

In most studies bilateral IVH is considered equivalent to unilateral IVH for data analysis,[4,26] despite the higher prevalence and worse prognosis in bilateral haemorrhage.[7,8,27–29] Differences are particularly valid for infants with PVHI, but not for those with non-parenchymal lesions. We were able to confirm the different outcomes between uni- and bilateral IVH in our patient population. A significant decrease in cognitive and motor outcomes was found in bilateral PVHI when compared to unilateral lesions, accompanied by a significant increase in total MRI score. Hence, it appears valuable to discriminate between uni- and bilateral IVH for outcome prediction.

IVH grades III and IV are partly dealt with as a single entity, categorized as high grade or severe haemorrhage. As described by Whitelaw, this classification may be useful for annual statistics, comparisons over time, or between hospitals.[30] Nevertheless, this unified classification is too general and inadequate for individual neonates. First, because the pathophysiology in grades III and IV differs in that PVHI is not a continuum of grade III but rather a complication due to impaired venous drainage.[11,19] Second, the outcome clearly varies between those grades.[19] This was confirmed by our data, as neonates without PHVI showed significantly better motor development between 2 years and 3 years of age when compared to those with PHVI (data not shown).

Vollmer et al. stated that outcome primarily depends on the presence and type of intracranial lesion and that

Table 3: Charts allowing probability estimation of favourable motor outcome

Total MRI score	GA (wks) 23	24	25	26	27	28	29	30	31	32	33	34	% Difference between GA of 23wks and 34wks
0	49	56	63	69	74	79	83	87	89	92	94	95	46
1	43	49	56	63	69	74	79	83	87	89	92	94	51
2	36	43	49	56	63	69	74	79	83	87	89	92	56
3	30	36	42	49	56	62	69	74	79	83	87	89	59
4	25	30	36	42	49	56	62	69	74	79	83	87	62
5	20	25	30	36	42	49	56	62	69	74	79	83	63
6	16	20	25	30	36	42	49	56	62	68	74	79	63
7	13	16	20	25	30	36	42	49	56	62	68	74	61
8	10	13	16	20	24	30	36	42	49	56	62	68	59
9	8	10	13	16	20	24	30	36	42	49	56	62	55
10	6	8	10	13	16	20	24	30	36	42	49	56	50
11	5	6	8	10	12	16	20	24	30	36	42	49	44
12	4	5	6	8	10	12	16	20	24	30	36	42	38
13	3	4	5	6	8	10	12	16	20	24	30	36	33
14		3	4	5	6	8	10	12	16	20	24	30	28–30
15			3	4	5	6	8	10	12	16	20	24	22–24
16				3	4	5	6	8	10	12	16	20	18–20
17					3	4	5	6	8	10	12	16	14–16
18						3	4	5	6	8	10	12	10–12
19							3	3	5	6	8	10	8–10
20								3	3	5	6	8	6–8
21									3	3	5	6	4–6
22						<3				3	3	5	3–5
23											3	3	1–3
24												3	1–3
≥25													0–2

The values show the probability of Bayley score ≥70 (%). Logistic model for motor outcome: $\log(P/[1-P]) = -6.2628 + -0.2731 \times$ total MRI score $+ 0.2711 \times$ GA. GA, gestational age; MRI, magnetic resonance imaging.

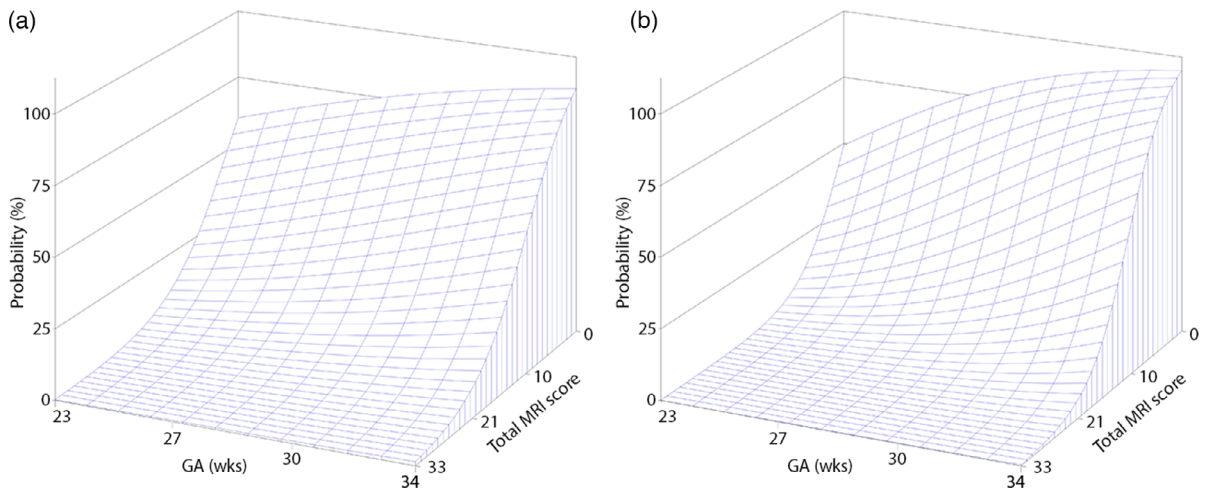

Figure 4: Visual representation of Tables 2 and 3 allowing probability estimation of favourable (a) cognitive and (b) motor outcomes. Probability (%) of Bayley Scales of Infant Development score of ≥70. GA, gestational age; MRI, magnetic resonance imaging.

gestational age in itself does not have an independent effect on outcome at 8 years of age for a child with a specific lesion. In their group of patients with IVH, outcome was not significantly different when comparing infants born less than 28 weeks' gestational age versus 28 to 32 weeks' gestational age.[31] In contrast, our results confirm gestational age as an influencing cofactor in the presence of IVH and showed a significant correlation to both cognitive and motor outcomes (Tables 2 and 3, Fig. 4). As shown, even with similar MRI scores, the probability of having a Bayley score of 70 or more can be very different depending on gestational age at birth. Differences between 23 weeks and 34 weeks' gestational age for cognitive and motor outcomes were up to 39% and 63% respectively. We postulate that, up to a particular level of brain damage, gestational age represents a major factor for development, beyond that level gestational age becomes less relevant. Herein lies another unique aspect of our work: unlike others who

excluded gestational age as a major determinant in predicting outcome, our calculations clearly attributed gestational age an important role in prognostication.

Strengths and limitations

Since CUS-based grading of IVH and other perinatal data were collected retrospectively, the work presented here had the potential limitations inherent in every retrospective study. The present study included data from two centers, which implies the use of different standard operating procedures and different MRI scanners and protocols. Nevertheless, the scored items can be reliably evaluated on both 1.5 and 3 Tesla MRI scanners. We appreciate that some items require substantial expertise in neonatal MRI interpretation and, thus, may be prone to inconsistent ratings. However, if single items differ, this will only have a limited impact on the overall total score, as it comprises a large number of assessments.

In the early years, neonates with high grade IVH or IVH grade II with additional complications were scanned predominantly. Only after 2011 was the use of routine MRI expanded to a larger population of infants born preterm (e.g. IVH grade II without additional complications). This is reflected in the high rate of PVHI, bihemispheric IVH, posthaemorrhagic ventricular dilatation, as well as high impairment in our population, and will partly affect generalization of our results to other populations born pretertm. We would point out that during the period of this study, a rather late intervention for posthaemorrhagic ventricular dilatation was standard practice at our institution (ventricular index >97th centile plus 4mm).[32–34]

Additional limitations of our study are the long period of inclusion and the fact that IVH was graded during the clinical course and regrading was not possible as CUS studies were only available in a limited number of patients because of archiving. Also, CUS and MRI were not performed at the same point in our study. This is in contrast to the study by Skiöld et al., which showed high agreement between both imaging modalities at term-equivalent age.[35]

Regarding the use of different editions of the Bayley Scale of Infant Development, we were previously able to show that German norms using the Bayley Scale of Infant Development, Third Edition do not overestimate performance and underestimate developmental delay to the same extent as American norms and, therefore, data obtained using the German Bayley Scale of Infant Development, Third Edition are comparable to the German Bayley Scale of Infant Development, Second Edition.[36]

The strengths of the present study included the evaluation of a novel MRI-based scoring system that was created especially for infants with IVH and was evaluated in a large patient cohort of neonates born preterm with IVH. All included patients received MRI during their clinical course, which allowed prospective MRI scoring. Another strength was the evaluation of long-term outcome up to 3 years of age. A comparison of this total MRI score with existing MRI-based scoring systems developed for the entire preterm population will be the subject of future research.

CONCLUSIONS

We propose a new MRI-based scoring system allowing rapid, visual, MRI analysis that does not require volumetrics or other time-consuming measurements and might, therefore, be efficiently implemented in clinical routine. This score was especially designed for predicting subsequent cognitive and motor outcomes in neonates born preterm with IVH and is based on term-equivalent imaging. Our total MRI score allows for a comprehensive assessment of important brain areas as well as potential additional abnormalities commonly associated with IVH. By going beyond the conventional classification of IVH, our scoring system represents the severity of brain damage more accurately.

ACKNOWLEDGEMENTS

We thank Bernd Schweiger, for providing MRIs from patients treated at the University Children's Hospital Essen, Essen, Germany. We also thank other members of the neonatal team dedicated to the care of high-risk neonates, especially Claudia Lindtner, Michael Wagner, and Vito Giordano, as well as all the families for their trust and willingness to share their children's lives with us. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Receiver operating curves of total MRI score and conventional intraventricular haemorrhage grading based on cranial ultrasound.

Table S1: Scoring results divided into no, unilateral, and bilateral IVH based on MRI

Appendix S1: Detailed MRI score description.

REFERENCES

1. Wen SW, Smith G, Yang Q, Walker M. Epidemiology of preterm birth and neonatal outcome. *Semin Fetal Neonatal Med*. 2004;**9**(6):429–35.
2. Sherlock RL, Anderson PJ, Doyle LW, Victorian Infant Collaborative Study Group. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. *Early Hum Dev*. 2005;**81**(11):909–16.
3. Roze E, Van Braeckel KNJA, van der Veere CN, Maathuis CGB, Martijn A, Bos AF. Functional outcome at school age of preterm infants with periventricular hemorrhagic infarction. *Pediatrics*. 2009;**123**(6):1493–500.
4. Brouwer A, Groenendaal F, van Haastert I-L, Rademaker K, Hanlo P, de Vries L. Neurodevelopmental

outcome of preterm infants with severe intraventricular hemorrhage and therapy for post-hemorrhagic ventricular dilatation. *J Pediatr*. 2008;**152**(5):648–54.
5. Patra K, Wilson-Costello D, Taylor HG, Mercuri-Minich N, Hack M. Grades I-II intraventricular hemorrhage in extremely low birth weight infants: effects on neurodevelopment. *J Pediatr*. 2006;**149**(2):169–73.
6. Jary S, Kmita G, Wroblewska J, Whitelaw A. Quantitative cranial ultrasound prediction of severity of disability in premature infants with post-haemorrhagic ventricular dilatation. *Arch Dis Child*. 2012;**97**(11):955–9.
7. Maitre NL, Marshall DD, Price WA, Slaughter JC, O'Shea TM, Maxfield C, et al. Neurodevelopmental outcome of infants with unilateral or bilateral periventricular hemorrhagic infarction. *Pediatrics*. 2009;**124**(6):e1153–60.
8. Bassan H, Limperopoulos C, Visconti K, Mayer DL, Feldman HA, Avery L, et al. Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. *Pediatrics*. 2007;**120**(4):785–92.
9. Vollmer B, Roth S, Riley K, O'Brien F, Baudin J, De Haan M, et al. Long-term neurodevelopmental outcome of preterm children with unilateral cerebral lesions diagnosed by neonatal ultrasound. *Early Hum Dev*. 2006;**82**(10):655–61.
10. Soltirovska Salamon A, Groenendaal F, van Haastert IC, Rademaker KJ, Benders MJNL, Koopman C, et al. Neuroimaging and neurodevelopmental outcome of preterm infants with a periventricular haemorrhagic infarction located in the temporal or frontal lobe. *Dev Med Child Neurol*. 2014;**56**(6):547–55.
11. Dudink J, Lequin M, Weisglas-Kuperus N, Conneman N, van Goudoever JB, Govaert P. Venous subtypes of preterm periventricular haemorrhagic infarction. *Arch Dis Child Fetal Neonatal Ed*. 2008;**93**(3):F201–6.
12. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med*. 2006;**355**(7):685–94.
13. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. *AJNR Am J Neuroradiol*. 2013;**34**(11):2208–14.
14. Kidokoro H, Anderson PJ, Doyle LW, Woodward LJ, Neil JJ, Inder TE. Brain injury and altered brain growth in preterm infants: predictors and prognosis. *Pediatrics*. 2014;**134**(2):e444–53.
15. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978;**92**(4):529–34.
16. Judas M, Rados M, Jovanov-Milosevic N, Hrabac P, Stern-Padovan R, Kostovic I. Structural, immunocytochemical, and mr imaging properties of periventricular crossroads of growing cortical pathways in preterm infants. *AJNR Am J Neuroradiol*. 2005;**26**(10):2671–84.
17. Johnson S, Marlow N. Developmental screen or developmental testing? *Early Hum Dev*. 2006;**82**(3):173–83.
18. de Vries LS, Groenendaal F. Neuroimaging in the preterm infant. *Ment Retard Dev Disabil Res Rev*. 2002;**8**(4):273–80.
19. Volpe JJ. Neurology of the newborn. Amsterdam: Elsevier Health Sciences; 2008. 1109 p.
20. Maalouf EF, Duggan PJ, Counsell SJ, Rutherford MA, Cowan F, Azzopardi D, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. *Pediatrics*. 2001;**107**(4):719–27.
21. Leijser LM, de Bruïne FT, van der Grond J, Steggerda SJ, Walther FJ, van Wezel-Meijler G. Is sequential cranial ultrasound reliable for detection of white matter injury in very preterm infants? *Neuroradiology*. 2010;**52**(5):397–406.
22. Whyte HEA, Blaser S. Limitations of routine neuroimaging in predicting outcomes of preterm infants. *Neuroradiology*. 2013;**55**(Suppl 2):3–11.
23. Rademaker K, Uiterwaal C, Beek F, van Haastert IC, Lieftink A, Groenendaal F, et al. Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. *Arch Dis Child Fetal Neonatal Ed*. 2005;**90**(6):F489–93.
24. George JM, Fiori S, Fripp J, Pannek K, Bursle J, Moldrich RX, et al. Validation of an MRI brain injury and growth scoring system in very preterm infants scanned at 29- to 35-week postmenstrual age. *Am J Neuroradiol*. 2017;**38**(7):1435–42.
25. Skiöld B, Vollmer B, Böhm B, Hallberg B, Horsch S, Mosskin M, et al. Neonatal magnetic resonance imaging and outcome at age 30 months in extremely preterm infants. *J Pediatr*. 2012;**160**(4):559–66.e1.
26. Al-Abdi SY. A severity score for intraventricular hemorrhage in preterm neonates. *Saudi Med J*. 2011;**32**(12):1313–4.
27. Kuban KCK, Allred EN, O'Shea TM, Paneth N, Pagano M, Dammann O, et al. Cranial ultrasound lesions in the NICU predict cerebral palsy at age 2 years in children born at extremely low gestational age. *J Child Neurol*. 2009;**24**(1):63–72.
28. Davis AS, Hintz SR, Goldstein RF, Ambalavanan N, Bann CM, Stoll BJ, et al. Outcomes of extremely preterm infants following severe intracranial hemorrhage. *J Perinatol*. 2014;**34**(3):203–8.
29. Al-Abdi SY, Al-Aamri MA. A systematic review and meta-analysis of the timing of early intraventricular hemorrhage in preterm neonates: clinical and research implications. *J Clin Neonatol*. 2014;**3**(2):76–88.
30. Whitelaw A. A different view: there is value in grading intraventricular hemorrhage. *Acta Paediatr*. 2007;**96**(9):1257–8.
31. Vollmer B, Roth S, Baudin J, Stewart AL, Neville BGR, Wyatt JS. Predictors of long-term outcome in very preterm infants: gestational age versus neonatal cranial ultrasound. *Pediatrics*. 2003;**112**(5):1108–14.
32. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer AJ, Traubici J, van Haastert IC, et al. Posthemorrhagic ventricular dilatation in preterm infants: when best to intervene? *Neurology*. 2018;**90**(8):e698–706.
33. Cizmeci MN, Groenendaal F, Liem KD, van Haastert IC, Benavente-Fernández I, van Straaten HLM, et al. Randomized controlled early versus late ventricular intervention study in posthemorrhagic ventricular dilatation: outcome at 2 years. *J Pediatr*. 2020;**3476**:28–35.e3.
34. Goeral K, Schwarz H, Hammerl M, Brugger J, Wagner M, Klebermass-Schrehof K, et al. Longitudinal reference values for cerebral ventricular size in preterm infants born at 23–27 weeks of gestation. *J Pediatr*. 2021;**3476**:110–7.e2.
35. Skiöld B, Hallberg B, Vollmer B, Ådén U, Blennow M, Horsch S. A novel scoring system for term-equivalent-age cranial ultrasound in extremely preterm infants. *Ultrasound Med Biol*. 2019;**45**(3):786–94.
36. Fuiko R, Oberleitner-Leeb C, Klebermass-Schrehof K, Berger A, Brandstetter S, Giordano V. The impact of norms on the outcome of children born very-preterm when using the Bayley-III: differences between US and German norms. *Neonatology*. 2019;**116**(1):29–36.