Ultrasonographic estimation of ventricular volume in infants born preterm with posthemorrhagic ventricular dilatation: a nested substudy of the randomized controlled Early Versus Late Ventricular Intervention Study (ELVIS) trial

Benavente-Fernández, I.; Steggerda, S.J.; Liem, K.D.; Lubián-López, S.; Vries, L.S. de

Ultrasonographic Estimation of Ventricular Volume in Infants Born Preterm with Posthemorrhagic Ventricular Dilatation: A Nested Substudy of the Randomized Controlled Early Versus Late Ventricular Intervention Study (ELVIS) Trial

Isabel Benavente-Fernández, MD, PhD[1,2,3], Sylke J. Steggerda, MD, PhD[4], Kian D. Liem, MD, PhD[5], Simón Lubián-López, MD, PhD[2,3], and Linda S. de Vries, MD, PhD[4,6]

Objective To study the potential role of ventricular volume (VV) estimation in the management of posthemorrhagic ventricular dilatation related to the need for ventriculoperitoneal (VP)-shunt insertion and 2-year neurodevelopmental outcome in infants born preterm.

Study design We included 59 patients from the Early vs Late Ventricular Intervention Study from 4 participating centers. VV was manually segmented in 209 3-dimensional ultrasound scans and estimated from 2-dimensional ultrasound linear measurements in a total of 1226 ultrasounds. We studied the association of both linear measurements and VV to the need for VP shunt and 2-year neurodevelopmental outcome in the overall cohort and in the 29 infants who needed insertion of a reservoir. We used general estimating equations to account for repeated measures per individual.

Results Maximum pre-reservoir VV (β coefficient = 0.185, P = .0001) and gestational age at birth (β = −0.338; P = .0001) were related to the need for VP shunt. The estimated optimal single VV measurement cut point of 17 cm^3 correctly classified 79.31% with an area under the curve of 0.76 (CI 95% 0.74-0.79). Maximum VV (β = 0.027; P = .012) together with VP shunt insertion (β = 3.773; P = .007) and gestational age (β = −0.273; P = .0001) were related to cognitive outcome at 2 years. Maximum ventricular index and anterior horn width before reservoir insertion were independently associated with the need of VP shunt and the proposed threshold groups in the Early vs Late Ventricular Intervention Study trial were associated with long-term outcome.

Conclusions Pre-reservoir VV measurements were associated with the need for VP-shunt insertion and 2-year cognitive outcome among infants born preterm with posthemorrhagic ventricular dilatation. *(J Pediatr 2023;261:113578)*.

Trial registration ISRCTN43171322.

Posthemorrhagic ventricular dilatation (PHVD) is a complication that can occur in up to one-third of patients with a severe form of germinal matrix-intraventricular hemorrhage (GMH-IVH) and is known to have a negative impact on neurodevelopmental outcome.[1-3] Linear measurements of the lateral ventricles from 2-dimensional (2D) ultrasound (US) scans are the most commonly used parameters to diagnose and monitor PHVD in the infant with a very low birth weight.[4] Advances in neuroimaging methods provide a unique opportunity to study the neonatal brain, and there is an increasing research interest aiming to elucidate which measurements of the lateral ventricles could provide a better approach to PHVD.[5,6] The most frequently used linear measurements in 2D-US are ventricular index (VI), anterior horn width (AHW), and thalamo-occipital distance (TOD). AHW from the second week of birth is the strongest predictor of PHVD onset and severity and, combined with VI, may aid in early PHVD diagnosis and decision-making on need for surgical intervention.[7]

2D	Two-dimensional	MRI	Magnetic resonance imaging
3D	Three-dimensional	PHVD	Posthemorrhagic ventricular dilatation
AHW	Anterior horn width		
BSITD	Bayley Scales of Infant and Toddler Development	PMA	Postmenstrual age
		TOD	Thalamo-occipital distance
ELVIS	Early vs Late Ventricular Intervention Study	US	Ultrasound
		VI	Ventricular index
GM-IVH	Germinal matrix-intraventricular hemorrhage	VP	Ventriculoperitoneal
		VV	Ventricular volume

From the [1]Area of Paediatrics, Department of Child and Mother Health and Radiology, Medical School, University of Cádiz; [2]Division of Neonatology, Department of Paediatrics, Puerta del Mar University Hospital; [3]Biomedical Research and Innovation Institute of Cádiz (INiBICA) Research Unit, Puerta del Mar University, Cádiz, Spain; [4]Division of Neonatology, Department of pediatrics, Leiden University Medical Center, Willem-Alexander Children's Hospital, Leiden; [5]Division of Neonatology, Department of Paediatrics, Radboud University Medical Centre Nijmegen, Amalia Children's Hospital, Nijmegen; and [6]Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, The Netherlands

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Although a growing body of evidence has demonstrated a strong association of earlier age at initiation of temporizing treatment for PHVD and lower rates of shunting and adverse outcome, the optimal timing of intervention is still not clear.[8,9] Three-dimensional (3D)-US allows detailed bedside brain examination and the possibility of volume measurements of different neonatal brain structures.[6,10-13] Ventricular volume (VV) can be estimated through manual delineation of the ventricular contour, which has been proven to be an accurate and valid method and showed good correlation with VV measured by magnetic resonance imaging.[6,14] Moreover, VV can be estimated from the mentioned 3 linear measurements if no 3D-US is available.[6] However, it is yet to be determined whether VV can play a potential role in the assessment of PHVD in infants born preterm. Our aim is to study the association of VV to the need for ventriculoperitoneal (VP)-shunt insertion and 2-year neurodevelopmental outcome in a subpopulation of patients from the Early vs Late Ventricular Intervention Study (ELVIS) trial (ISRCTN43171322). To enable the potential clinical application of VV estimation in routine 2D-US in the neonatal intensive care unit, we further explored the predicted VV based on linear measurements.

Methods

In this substudy of the ELVIS clinical trial, we included patients recruited in 4 participating centers (1 Spanish center: Hospital Puerta del Mar, and 3 from The Netherlands: Radboud University Nijmegen Medical Centre, Leiden University Medical Center, and Utrecht University Medical Center). The ELVIS trial (ISRCTN43171322) recruited 126 infants between 2006 and 2016 to compare the effects of low-threshold (VI >97th percentile and AHW >6 mm and/or TOD >25 mm) vs high-threshold (VI >97th percentile + 4 mm and AHW of >10 mm) intervention in infants born preterm with progressive PHVD.[15-17] Approval from the research ethics board at each center and informed written parental consent were obtained for all the patients participating in the study.

Three-Dimensional Ultrasound

We manually segmented the VV of the 209 available 3D-US. We used the virtual organ computer-aided analysis method (GE HealthCare) as previously described.[6] This software tool grants volumetric segmentation by rotating the structure of interest around a fixed axis, allowing manual or automatic contour delineation.[6,18] It is considered the gold standard 3D-US method for performing volumetric measurements,[19] as it has been validated and displays both in vitro and in vivo high reliability and good intra- and interobserver agreement.[13,20-24]

Linear Measurements and VV

We studied the association of the 3 linear measurements to VV using multilevel regression analysis to account for repeated measurements. We validated the models and subsequently obtained the equations to enable VV estimation from linear measurements. Each of the participating centers reviewed their US scans and provided the available linear measurements, VI, AHW, and TOD, together with clinical and outcome data. We estimated the VV for each US of all the included patients applying the obtained equations. We studied the association of both linear measurements and VV to the need for VP shunt insertion and 2-year neurodevelopmental outcome.

Neurodevelopmental Outcome

Neurodevelopment was assessed at 2 years' corrected age using the Bayley Scales of Infant and Toddler Development (BSITD), Second Edition, or Third Edition and conversion from the BSITD, Second Edition, mental developmental index was performed to the BSITD, Third Edition,[25] composite scores (standardized with mean of 100; SD 15) for cognitive and motor skills. An adverse cognitive outcome was defined as a Bayley cognitive score >1 SD below the mean.

Statistical Analysis

We first performed a descriptive analysis to compare the baseline characteristics of the study sample by intervention group. We used the mean (±SD) or the median [IQR], according to the variable's distribution. The Pearson χ^2 test was used to compare 2 dichotomous variables with the Fisher exact test used when the expected frequency was less than 5. Continuous variables were compared using Mann–Whitney *U* test or *t* test, as appropriate.

We first developed and validated a predictive model of VV based on the association between the linear measurements and the manually segmented VV on the 3D-US scans from Puerta del Mar Hospital, Cádiz, Spain. We used multilevel regression analysis to consider repeated measurements as previously performed by our group.[6] Internal validity of the model was tested through cross-validation, and the mean value for all R^2 was estimated, which represents the real predictive ability of the model when performed on external data. There is no universally accepted threshold for determining the adequacy of R^2; however, it is generally considered that values >0.75 indicate a good fit for the model. Moreover, external validity of the model was tested by evaluating its shrinkage after splitting the sample (training group and validation group). External validity is acceptable if the loss of prediction (shrinkage) is ≤10%. Once developed and validated, we applied the obtained equations to the provided linear measurements from other centers.

After estimating VV in our study sample, we used logistic regression and general estimating equations to study the association between linear measurements and VV before reservoir insertion and the need of VP shunt and cognitive scores at 2 years, accounting for repeated measures. When using logistic regression, global performance of the model was studied through receiver operating characteristic analysis and diagnostic accuracy indexes with sensitivity, specificity, and positive and negative predictive values. We estimated the

optimal VV cut point based on the method of Liu, which maximizes the product of the sensitivity and specificity.[26]

Finally, we constructed an easy-to-use table of predicted VV to enable future research and clinical application of VV estimation from 2D-US in PHVD. Statistical analysis was performed using Stata 16.0 (StataCorp).

Results

Study Sample

We included 59 patients recruited in 4 centers participating in the ELVIS trial, 32 (54.2%) randomized to the low- and 27 (45.8%) randomized to high-threshold group. A detailed description of the perinatal characteristics, US measurements, and outcome data of the study sample can be seen in Table I. We analyzed 1226 US from the included 59 patients (Figure 1).

VV Estimation

After we manually segmented the VV of the 209 3DUS scans available, we estimated the VV from the 3 linear measurements using multilevel regression analysis. We validated the models and subsequently applied the obtained equations (Appendix) to the provided linear measurements from 2D-US. The most accurate estimation of VV was found when based on the 3 measurements: VI, AHW, and TOD (R^2_{Mean} = 0.77). Moreover, the intraclass correlation coefficient was 0.86 (CI 95% 0.82-0.89) between manual and estimated VV in the 3D scans.

VV and the Need for VP Shunt

When we adjusted for repeated measures, maximum VV attained ($\beta = 0.185$; $P = .0001$) and gestational age ($\beta = -0.338$; $P = .0001$) were related to the need for VP shunt (generalized estimating equation parameters: number of observations = 1226; number of patients = 59; Wald $\chi^2[2] = 250.77$; Pearson $\chi^2[1226] = 1186.29$; $P = .0001$).

When considering only those who had a reservoir insertion, maximum VV before reservoir insertion ($\beta = 1.484$, $P = .001$) was related to the need for VP shunt ($P = .0001$; Wald $\chi^2[2] = 59.13$) and gestational age ($\beta = -1.007$, $P = .0001$), with those requiring VP shunt insertion reaching a maximum VV of 19.6 (±2.8) cm^3 before reservoir insertion, whereas those who did not require VP shunt reached a maximum single VV of 15.36 (±3.22) cm^3 with an OR of 1.38 (95% CI 1.018-1.868). The estimated optimal cut point was 17 cm^3 for single VV (Figure 2) and 34 cm^3 when considering the volume of both lateral ventricles, which can correctly classify 79.31% with a sensitivity of 81.82%, specificity of 77.78%, positive predictive value of 69.23%, and negative predictive value of 87.50% with an area under the curve of 0.76 (CI 95% 0.74-0.79). As VV is related to postmenstrual age (PMA), we have estimated optimal cut point values for single VV in relation to VP shunt insertion based on PMA (Figure 3). Maximum VI and AHW before reservoir insertion were independently associated with the need for VP shunt whereas TOD and threshold group were not (Table II).

VV and Outcome

When studying the association of VV to 2-year neurodevelopmental outcome in the 51 patients who survived and were assessed, accounting for repeated measures, maximum VV ($\beta = 0.027$; $P = .012$) together with VP shunt insertion ($\beta = 3.773$; $P = .007$) and gestational age ($\beta = -0.273$; $P = .0001$) were related to cognitive outcome, with VP shunt insertion and maximum VV interaction term being significant ($P = .002$). The GEE parameters were as follows: number of observations = 985; number of patients = 51; Wald χ^2 (4) = 65.25; $P = .0001$.

Table I. Clinical and ultrasonographic characteristics of the study population

Characteristics	Threshold		Total (n = 59)	*P* value
	High (n = 27)	Low (n = 32)		
Gestational age, wk	28.4 (2.4)	28.7 (2.4)	28.5 (2.4)	.658
Birth weight, g	1371.2 (450.4)	1292.9 (321.9)	1326.8 (379.0)	.756
Sex (female)	11 (40.7)	17 (53.1)	28 (47.46)	.435
Death	1 (3.7)	1 (3.1)	2 (3.4)	.710
Periventricular hemorrhagic infarction	6 (22.2)	8 (25)	14 (23.7)	.803
Lumbar puncture (LP)	18 (66.7)	31 (96.9)	49 (83.1)	**.004**
Number of LPs	2 [0-3]	3 [2-3]	2 [1-3]	**.009**
Reservoir	12 (44.4%)	17 (53.1%)	29 (49.2%)	.506
PMA at reservoir, wk	30.6 (2.3)	30.6 (2.5)	30.6 (2.4)	.905
Maximum VI before reservoir insertion	15.38 [14-16.85]	13.4 [12.8-14.02]	14 [13.3-16.45]	**.008**
Maximum AHW before reservoir insertion	12 [10.2-13.3]	9.35 [8.75-10.7]	10.2 [9-12]	**.0056**
Maximum TOD before reservoir insertion	28.8 [28.2-30.25]	26.58 [25.5-31.08]	28.26 [25.6-30.4]	.356
Maximum VV before reservoir insertion (R + L)	35.88 (5.63)	31.21 (8.51)	32.59 (8.05)	**.0001**
VP-shunt insertion	4 (14.8%)	7 (21.9%)	11 (18.6%)	.488
Cerebral palsy	7 (26.9%)	6 (18.8 %)	13 (22.4)	.535
Cognitive score	93.4 (15.8)	96.3 (15.6)	95.0 (15.6)	.255
Motor score	94.6 (17.8)	97.1 (19.4)	95.9 (18.5)	.317

L, left; *R*, right.
Qualitative data are presented as frequency (percentage) and quantitative data as mean (SD) or median [IQR] according to their distribution. analysis was by original assigned groups. Bold values indicate statistically significant results.

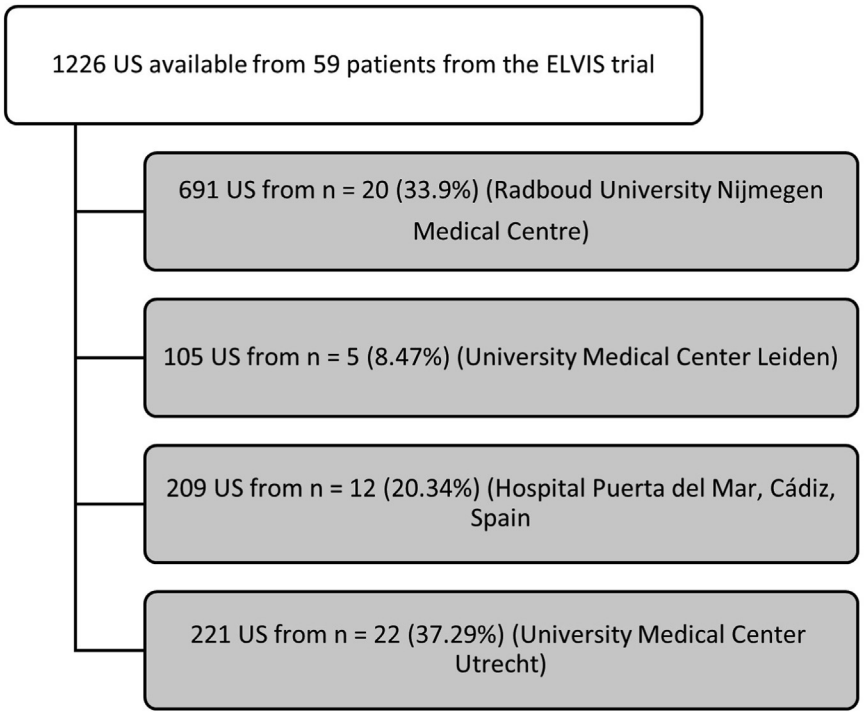


Figure 1. Flowchart of the 1226 ultrasound (US) scans studied in 59 patients from the Early vs Late Ventricular Intervention Study (ELVIS) trial.

We subsequently studied how ventricular size before reservoir insertion was related to cognitive outcome at 2 years. Accounting for repeated measures per individual, VV before reservoir insertion ($\beta = 0.222$; $P = .0001$) and gestational age ($\beta = -1.319$; $P = .0001$) were associated with cognitive outcome at 2 years (generalized estimating equation parameters: number of observations = 253; number of patients = 23; Wald χ^2 [4] = 25.61; $P = .0001$). Regarding the proposed

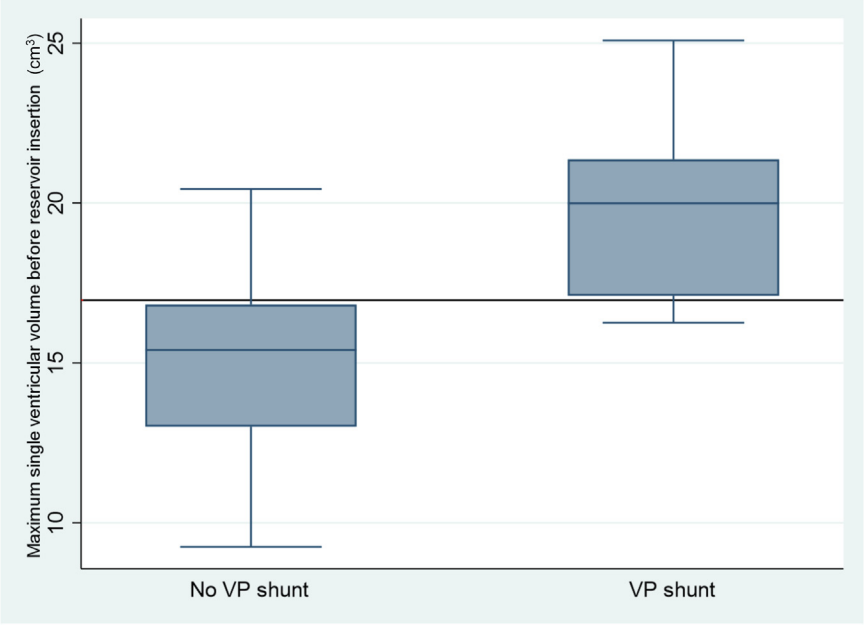
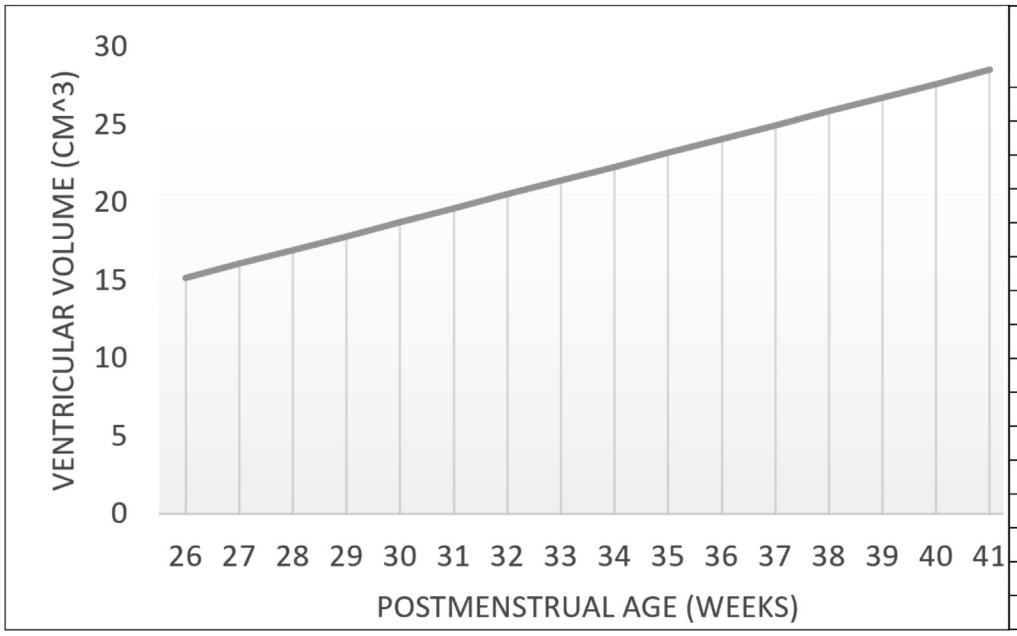


Figure 2. Maximum single ventricular volume before reservoir insertion related to the need of ventriculoperitoneal (VP) shunt. The estimated global optimal cut point is 17 cm^3 for single ventricular volume.



Postmenstrual age (weeks)	Ventricular Volume (cm^3)
26	15.18
27	16.07
28	16.96
29	17.85
30	18.74
31	19.63
32	20.52
33	21.41
34	22.30
35	23.19
36	24.08
37	24.97
38	25.86
39	26.75
40	27.64
41	28.53

Figure 3. Estimated optimal cut-point values for single VV in relation to VP-shunt insertion based on PMA.

Table II. Maximum linear and volumetric measurements before reservoir insertion and threshold group related to the need for a VP shunt

Outcome: VP shunt insertion	Coeff.	*P* value	Generalized estimating equation parameters
Model 1. Maximum linear measurements before reservoir insertion and threshold group			
Max. VI	−0.703	.0001	Number of US scans = 231; patients = 21; Wald $\chi^2(5) = 57.89$; $P = .0001$
Max. AHW	0.715	.0001	
Max. TOD	0.059	.276	
Threshold group	−0.284	.516	
Gestational age	−0.404	.001	
Model 2. Maximum linear measurements before reservoir insertion			
Max. VI	−0.701	.0001	Number of US scans = 230; patients = 21; Wald $\chi^2(4) = 60.05$; $P = .0001$
Max. AHW	0.705	.0001	
Max. TOD	0.072	.147	
Gestational age	−0.394	.001	
Model 3. Threshold group			
Threshold group	−0.092	.719	Number of US scans = 337; patients = 29; Wald $\chi^2(2) = 2.82$; $P = .245$
Gestational age at birth	0.079	.094	
Model 4. Maximum VV before reservoir insertion			
Max. VV	1.484	**.0001**	Number of US scans = 337; patients = 29; Wald $\chi^2(2) = 59.13$; $P = .0001$
Gestational age	−1.007	.0001	

Linear measurements were used in millimeters and VV was measured in cm^3. Bold value indicate statistically significant result.

threshold in the ELVIS trial and the linear measurements we found that threshold ($\beta = 4.40$; $P = .002$) and gestational age ($\beta = -2.002$; $P = .001$) were associated with long-term outcome (number of observations = 146; Patients = 17; Wald χ^2 [5] = 16.85; $P = .005$) (Table III).

VV Estimation from 2D-US: Clinical Application

Based on the previously described VV estimation models, we have developed easy-to-use tables to facilitate VV estimation in the clinical settings from 2D-US linear measurements

Table III. Association between the 2-year adverse cognitive outcome and US measurements before reservoir insertion

Outcome: 2-year adverse cognitive outcome		Coeff.	*P* value	Generalized estimating equation parameters
Model 1. Gestational age, threshold group and linear US measurements prior to reservoir insertion	Gestational age	−2.002	**.001**	Number of US scans = 146; Patients = 17; Wald $\chi^2(5) = 16.85$; $P = .005$
	Threshold group	4.40	**.002**	
	VI	0.995	**.056**	
	AHW	−0.011	.976	
	TOD	−0.030	.824	
		Coeff.	***P* value**	
Model 2. Gestational age and total ventricular volume	Gestational age	−1.319	**.0001**	Number of US scans = 253; Patients = 23; Wald $\chi^2(2) = 25.61$; $P = .0001$
	Total VV (left + right VV)	0.222	**.0001**	

Linear measurements were used in millimeters, and VV was measured in cm^3. Bold values indicate statistically significant results.

(Appendix). These tables allow estimating VV if the 3 measurements are available (which is mostly recommended as the best fitted model, with a greater adjusted R^2: 0.77) than when only VI + AHW or TOD are available.

Discussion

In this nested study of the ELVIS trial, we studied the association of VV in infants born preterm with PHVD to both short- and long-term outcome. We aimed to elucidate whether there is a potential role of VV estimated by US in the management of these patients. We found that maximum VV attained and GA were related to the need for VP shunt insertion and cognitive outcome at 2 years, with VP shunt insertion also related to the latter. Our study demonstrates that the use of the 3 indices, described years ago and with proven good intra- and interobserver agreement,[4,7] provides a good approximation to ventricular complexity, with an accurate estimation of VV. Moreover, VV may contribute to reduce heterogeneity in the monitoring of PHVD between units and has the potential to be included in future prospective studies. Our results should be used with caution due to the small sample size and pending external validation in future research.

The maximum VV attained before reservoir insertion was related to the subsequent need for VP shunt insertion, with an OR of 1.4 for every cm^3 of increment in VV, accounting for gestational age and PMA at reservoir insertion. We suggest different cut-off values related to PMA. Although ventricular size (measured by VV) could accurately predict the need for VP shunt, linear indices and threshold group were not associated with the latter. This result may be considered valuable, as monitoring VV together with linear measurements could be more valuable, as the maximum VV is informative in the diagnostic and therapeutic approach of patients with PHVD. Although maximum VV before reservoir insertion was associated with VP-shunt insertion, it was previously reported that the proposed threshold in the ELVIS trial was not associated with a significant difference in the composite outcome of VP shunt or death, partially explained by the small difference in the linear measurements that this trial considered to randomize to early or late intervention group.[15,16]

The ELVIS trial reported a reduction in death or severe neurodevelopmental outcome in those infants allocated to the low-threshold group after adjusting for gestational age, severity of IVH, and cerebellar hemorrhage.[15] In agreement with this, we found that both the proposed threshold and VI before reservoir insertion were associated independently with adverse long-term outcome, together with gestational age. We also found VV before reservoir insertion and lower gestational age to be related with 2-year neurodevelopmental outcome.

It has become clear over the last 20 years that ventricular size, quantified by sequential US, is a critical measurement for PHVD diagnosis, monitoring, and to guide neurosurgical intervention. This approach has been proven to be superior to intervention based on clinical signs when considering neurodevelopmental outcomes.[27] The most frequently used linear measurements are VI, AHW, and TOD. These and some other measurements and ratios have been developed assuming that changes in size of different parts of the lateral ventricle would mirror changes within the entire lateral ventricular system.[28] Frontal occipital horn ratio obtained from US was shown to have good correlation with VV, although VV in that study was estimated using magnetic resonance imaging (MRI).[29] Ventricular cerebrospinal fluid volumes were measured in a previous nested substudy of the ELVIS trial using MRI at term-equivalent age, showing smaller volumes in the low-threshold group.[17] VV estimation was not an option in the clinical setting, as 3D-US is not the standard US tool in most neonatal intensive care units and MRI estimation would not allow the required close monitoring in PHVD. However, 3D-US has been proven to provide accurate and reliable measurements of ventricular volumes in infants born preterm[6,12,14,30] and is routinely used in fetal neurosonography.[13,19,31] Moreover, we show that VV estimation also can be achieved using 2D-US. As VI and AHW are measurements performed anteriorly and TOD is performed at the level of the occipital horn, we had previously explored the association of the 3 measurements to manually segmented VV through 3D-US.[6] When our model was compared with a similar one using MRI, we found that both models were comparable.[14] Some concern was raised regarding the estimation of VV in cm^3, as the linear measurements are taken in millimeters. This is, however, a regression model, not a geometrical estimation of ventricular size. It has been developed as a predictive model and as such allows multivariate and multidimensional analysis in the same manner as we predict the outcome based on different ventricular size, gestational age, and threshold group. This work reinforces our previous hypothesis that although linear measurements are not independently related to the outcome, VV, estimated by at least 2 of these, reflects better the complexity of the ventricular system.[6]

We provide tables to estimate VV based on 2D measurements when 3D-US is not available. This could enable routine estimation of VV when monitoring these patients with US, which can further help elucidating if there is a role for VV in the diagnostic and therapeutic approach of these patients. Based on our findings, we suggest VV measurement as a criterion for neurosurgical intervention in PHVD. When there is no 3D-US available, using the 3 measurements (VI, AHW, and TOD) is a better approach than the use of 1 or 2 of them, as it was more tightly related to the volume of the lateral ventricle ($R^2adj = 0.75$).

There are some other studies that have suggested that VV in infants born preterm with GMH-IVH might have a potential role in the management of these patients.[32] However, the study sample in these studies is heterogeneous with no clear PHVD diagnosis, inclusion criteria, and arbitrary cut-off values for VV. Our study, despite having a small sample size, yields interesting results regarding the association of

VV with short- and long-term outcome in a homogeneous sample of PHVD patients prospectively included in a randomized clinical trial.

Our study has several limitations that need to be addressed. As we wanted to understand whether VV had a role in the clinical settings as a prognostic marker, the proposed cut-off values to predict the need for VP shunt and other analyses related to long-term outcome were based on 29 patients who needed reservoir insertion. Despite the small sample size, we found differences that were statistically significant and clinically relevant. This could be partly explained by the longitudinal study design with serial US as the sample size required in this type of studies is smaller.[33]

In conclusion, VV before reservoir insertion was associated with the need for VP-shunt insertion and 2-year cognitive outcome. VV can be easily estimated form 2D-US measurements. Further research is warranted to confirm the potential role of VV in the diagnostic and therapeutic approach of infants born preterm with PHVD. ■

Declaration of Competing Interest

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Reprint requests: Isabel Benavente-Fernández, MD, PhD, Area of Paediatrics, Department of Child and Mother Health and Radiology, Medical School, Andrés Segovia, C. Dr. Marañón, 3, 11002 Cádiz, Spain. E-mail: isabel.benavente@uca.es

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