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ABSTRACT

BACKGROUND AND PURPOSE: There is a wide range of clinical and radiographic factors affecting individual surgeons' ultimate decision for CSF diversion for pediatric patients following prenatal myelomeningocele repair. Our aim was to construct a composite index (CSF diversion surgery index) that integrates conventional clinical measures and neuroimaging biomarkers to predict CSF diversion surgery in these pediatric patients.

MATERIALS AND METHODS: This was a secondary retrospective analysis of data from 33 patients with prenatal myelomeningocele repair (including 14 who ultimately required CSF diversion surgery). Potential independent variables, including the Management of Myelomeningocele Study Index (a dichotomized variable based on the shunt-placement criteria from the Management of Myelomeningocele Study), postnatal DTI measures (fractional anisotropy and mean diffusivity in the genu of the corpus callosum and the posterior limb of internal capsule), fronto-occipital horn ratio at the time of DTI, gestational ages, and sex, were evaluated using stepwise logistic regression analysis to identify the most important predictors.

RESULTS: The CSF diversion surgery index model showed that the Management of Myelomeningocele Study Index and fractional anisotropy in the genu of the corpus callosum were significant predictors ($P < .05$) of CSF diversion surgery. The predictive value of the CSF diversion surgery index was also affected by fractional anisotropy in the posterior limb of the internal capsule and sex with marginal effect ($.05 < P < .10$), but not by the fronto-occipital horn ratio ($P > .10$). The overall CSF diversion surgery index model fit the data well with statistical significance (eg, likelihood ratio: $P < .001$), with the performance (sensitivity = 78.6%; specificity = 86.5%, overall accuracy = 84.8%) superior to all individual indices in sensitivity and overall accuracy, and most of the individual indices in specificity.

CONCLUSIONS: The CSF diversion surgery index model outperformed all single predictor models and, with additional validation, may potentially be developed and incorporated into a sensitive and robust clinical tool to assist clinicians in hydrocephalus management.

ABBREVIATIONS: CDSI = CSF diversion surgery index; FA = fractional anisotropy; FOHR = fronto-occipital horn ratio; gCC = genu of the corpus callosum; MD = mean diffusivity; MMC = myelomeningocele; MOMS = Management of Myelomeningocele Study; PLIC = posterior limb of the internal capsule

Hydrocephalus is the most common surgical condition encountered in pediatric neurosurgical care. It is a complex, typically life-long disease for which no cure currently exists. Given its incidence of approximately 1 in 500 children, many resources have been dedicated to studying diverse etiologies, management strategies, and, ultimately, outcomes related to this disease. Further complicating the management of this patient population, the diagnosis of progressive hydrocephalus in a child with large ventricles can be difficult to establish and standardized diagnostic criteria are lacking.[1,2] Surgical intervention or the lack of a timely intervention can lead to complications, highlighting the need for improved patient selection for better long-term outcomes.

The scope of the current work is to study hydrocephalus in the context of patients who are born with open neural tube defects, specifically, those with myelomeningocele (MMC) who underwent prenatal repairs. MMC is the most common form of spina bifida. In addition to hydrocephalus, the condition is associated with other anomalies of the CNS such as Chiari II malformation, brainstem deformities, low-lying venous sinuses, and a small posterior fossa. To address the question of whether better functional results could be obtained with earlier MMC repair, the Management of

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Myelomeningocele Study (MOMS) prospectively compared patients undergoing prenatal repair with those who had standard postnatal repair.[3] The initial results were published in 2011, and the primary outcome related to the need for shunt placement demonstrated a statistically significant difference between the 2 groups (40% versus 82%, $P < .001$) in favor of the prenatal repair group.[3] Given the wide variety of clinical and radiographic factors affecting individual surgeons' ultimate decision for CSF diversion, the known propensity for children undergoing prenatal MMC repair to have large ventricles at baseline, and the overall lack of consensus in diagnosing hydrocephalus in the pediatric population at large, the decision to insert a ventriculoperitoneal shunt was based on an independent committee of neurosurgeons who reviewed the clinical and radiographic data for each child to ascertain the need for CSF diversion.

That these criteria are not universally accepted or applied is evidenced by the fact that while 64 of 91 children (70%) in the prenatal cohort of the MOMS trial met the criteria for shunting as recommended by the independent study committee, only 40 of the 91 children (44%) actually received a shunt, with the remainder believed not to truly have progressive hydrocephalus or require CSF diversion by their primary neurosurgical provider.

In the present study, we constructed a composite index (the CSF diversion surgery index [CDSI]) that integrates the information from conventional clinical measures and multiple objective noninvasive neuroimaging biomarkers on the basis of DTI parameters that have been applied frequently in previous hydrocephalus-related analysis.[4-16] We will identify the set of the most important predictors for the CDSI model based on stepwise logistic regression, and we hypothesized that the model will minimize the potential for clinical bias and help improve the diagnosis of progressive hydrocephalus, thereby providing guidance to clinicians in determining the need for CSF diversion in patients undergoing prenatal myelomeningocele repair.

MATERIALS AND METHODS

Participants

All participants were selected from a retrospective study approved and conducted under the guidelines of the Cincinnati Children's Hospital institutional review board. In a previous study, we reported the predictive value of DTI measures in a cohort of 35 pediatric patients with prenatal repair for their need for CSF diversion surgery and for the timing of surgery in those who did require surgical treatment. All these patients underwent DTI with a similar MR imaging protocol. Fifteen of the 35 patients later underwent CSF diversion surgery for hydrocephalus. All the prenatal MMC repairs, postnatal imaging, and CSF diversions surgeries (all treated with shunt placement) were performed in the same institution at the Cincinnati Children's Hospital. The details of the demographic and clinical information for these 35 participants can be found elsewhere.[4]

The participants in the present study included 33 of the 35 participants from the previous study. These 33 participants included 14 patients with prenatal MMC repair who underwent DTI and required CSF diversion surgery and 19 patients with prenatal repair who underwent DTI but did not require surgical treatment.

The decisions for shunt placement for all the participants in the present study were made by a single neurosurgeon on the basis of the criteria set forth by the MOMS trial, first using the original protocol[3] and then adopting the revised criteria by Tulipan et al.[17] According to the initial MOMS protocol, a patient with a prenatal MMC repair requires shunt insertion if the patient meets any of the 4 criteria.[3] The first criterion (criterion 1) is that the patient meets at least 2 of the 4 following components: a) increasing occipital frontal cranial circumference, crossing percentiles; b) bulging fontanelle or split sutures; c) increasing ventriculomegaly based on consecutive imaging; and d) head circumference greater that the 95th percentile at gestational age. Criteria 2, 3, and 4 from the MOMS trial for shunt placement are the presence of marked syringomyelia with ventriculomegaly, ventriculomegaly with symptomatic Chiari malformation, and CSF leakage, respectively.[3] In 2015, on the basis of the outcome of the MOMS trial, Tulipan et al suggested revising the original MOMS criterion 1 to require 1b and at least 1 of the other 3 components of criterion 1 (1a, 1c, and 1d), a change reflecting neurosurgeons' inclination to use overt clinical signs of increased intracranial pressure to justify shunt placement.[17]

The description of the clinical variable related to the MOMS criteria for shunt placement was extracted from the notes from patients' visits to the neurosurgery clinic. All these patients had close clinical follow-up after initial visits to the neurosurgery office. The assessment based on the MOMS criteria for shunt insertion was performed multiple times during these visits. For those patients who needed shunt placement, we used the information during the last visit when the patient met the criteria of MOMS protocol before the operation. For those patients in the no-shunt group, we reviewed the notes for all the visits to the neurosurgery office within 1 year after the DTI scan. This timeframe of 12 months as the follow-up time was decided to make sure these nonshunted children included in the present study were not shunted soon after the DTI scan. Two participants from the original study were excluded from the analysis in the present study because we were not able to identify the Neurosurgery Clinic Visit record for the MOMS criteria related to clinical variables for shunt placement. All 33 remaining patients had Chiari II malformation based on prenatal imaging. Three patients in the no-shunt group had grade II or grade II-III Chiari II malformation. The other 30 patients had grade III Chiari II malformation (Online Supplemental Data). Six of the 33 patients underwent both pre- and postrepair MR imaging: Five demonstrated reversal of hind brain herniation (from grade III to grade I), and one remained unchanged (grade II).[4] The detailed demographic and clinical information for these 33 participants are included in the Online Supplemental Data.

Potential Predictive Model for the CSF Diversion Surgery

In the present study, we aimed to construct a predictive model, the CDSI, for the need for CSF diversion surgery. This composite index model would include both clinically related variables and neuroimaging (DTI) based variables. In this study, a clinical measure related to the MOMS criteria for shunt placement, the "MOMS Index," was defined as a dichotomous variable in which 1 represents a patient who met ≥ 2 of the 4 components in criterion 1 of the MOMS protocol for shunt placement and zero means that

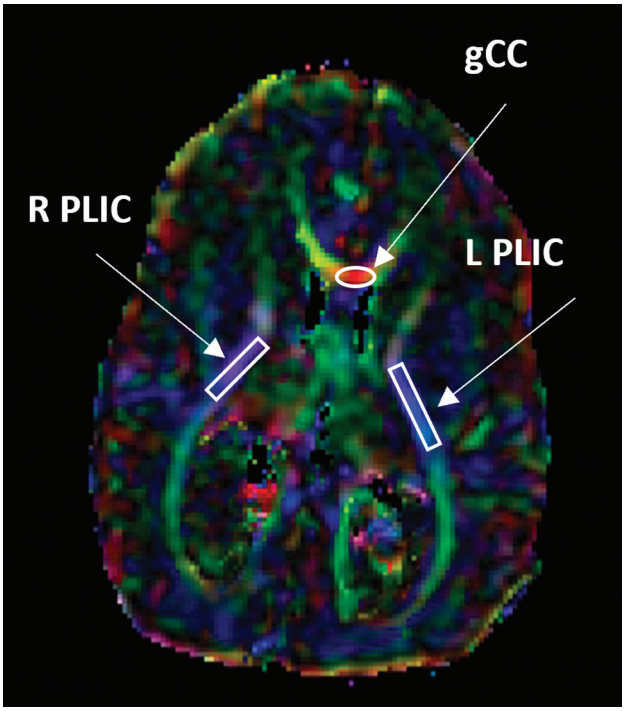

FIG 1. Illustration of ROI delineation in WM in children with prenatal MMC repair on a color-coded FA map. *Arrows* denote areas of the gCC, L PLIC, and R PLIC. L PLIC indicates left posterior limb of the internal capsule; R PLIC, right posterior limb of the internal capsule.

a patient met ≤1 of the 4 components. Patients meeting criterion 2, 3, or 4 from the MOMS protocol was rare in our study cohort: Six of 33 patients had syringomyelia (all small, between 2.5 and 4 mm); no patient had symptomatic Chiari malformation; and 1/33 had CSF leakage. Therefore, these 3 criteria were not included in the model.

DTI data were acquired with a 15-direction spin-echo EPI sequence on a 1.5T Optima MR430s scanner (GE Healthcare) customized for infant scanning.[18-20] Additional sequence specifications included the following: TR/TE = 10,000/93–98.1 ms; FOV = 200 × 200 mm; acquisition matrix = 128 × 28; in-plane resolution (resampled) = 0.78 × 0.78 mm; section thickness = 3 mm; 30 or 32 slices; b-value = all 800 with 1 exception of 1000 s/mm^2; 1 B_0; 1 average. All DTI data underwent preprocessing and analysis using the DTIStudio software (Johns Hopkins University). Additional details of the infant MR imaging scanner and the imaging sequence specifications have been reported elsewhere.[4,18-20] The neuroimaging variables derived from DTI measures included fractional anisotropy (FA) and mean diffusivity (MD) in 2 WM regions (Fig 1): the genu of the corpus callosum (gCC) and the posterior limb of the internal capsule (PLIC). On the basis of our previous data as well as reports in the literature, DTI values in these 2 ROIs were often found to be abnormal in pediatric patients with hydrocephalus or myelomeningocele.[5,13,21-25] The fronto-occipital horn ratio (FOHR),[26] based on MR imaging acquired at the time of DTI scan, was also included in the model to account for the potential effect of the severity of ventriculomegaly. Sex was tested for its significance in affecting the predictive value of the composite index. Two timing variables, including the gestational age at which the postnatal DTI data were acquired and the gestational age at which the MOMS criteria for shunt placement were assessed, were included as potential confounders in the model.

ROI placement was performed manually by a single operator. The FOHR measurement was performed by 2 operators. To evaluate the consistency of the manual performance, we assessed intrarater repeatability on the basis of the intraclass correlation coefficient,[27] using DTI values from 2 repeat trials of the same data sets. Interrater compatibility (interrater reliability) for the FOHR was assessed on the basis of the intraclass correlation coefficient using the results from the same data sets generated by the 2 operators. By means of the standard of Koo and Li[28] (poor: <0.5; moderate: 0.5–0.75; good: 0.75–0.9; excellent: >0.9), our evaluation showed that the study presented good-to-excellent repeatability and reliability with all intraclass correlation coefficient values between 0.85 and 0.95.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS; IBM). A logistic regression analysis was performed to assess the effects of the MOMS Index, DTI measures, the FOHR, and sex in predicting the likelihood that patients with prenatal MMC repair required shunting surgery. These independent variables, which included the MOMS Index, gCC_FA, gCC_MD, PLIC_FA, PLIC_MD, gestational age at postnatal DTI, gestational age at MOMS criteria assessment for shunt placement, sex, and the FOHR, were first assessed individually for their association with CSF diversion surgery. The continuous variables, including the 4 DTI measures, 2 age variables, and the FOHR, were *z* score–normalized before being used in the analysis, and subsequently, all these variables were evaluated in a stepwise logistic regression analysis to identify the set of most important predictors.

In the present study, the entry and remove probability was set at 0.2 and 0.25, respectively, in the stepwise logistic regression analysis. These liberal thresholds were selected to be more inclusive and allow quantitative evaluation of variables that were at a marginal level of statistical significance in the log(*P*) model. The variable selection was performed through the backward stepwise logistic regression implemented in SPSS. The selection process started with the full model, which included all the p predictors, and at each step, the potential covariate that contributed the least was excluded until all of the covariates satisfied the entry and exit criteria. No additional regularization was used in the process. To assess the risk of overfitting of the logistic regression model, we also performed leave-one-out cross-validation: The stepwise logistic regression model was derived from 32 patients and tested against the single hold-out patient and was subsequently repeated until the entire data set had been tested. The top-performing covariates from these 33 repetitions were identified to ensure model stability and generalizability.

RESULTS

Single-Predictor Logistic Regression Analysis

The results of the single-predictor logistic regression analysis with potential predictors tested individually (all with the intercept included) are summarized in Table 1. Among the 7 potential predictors tested, a significant relation between predictor and the

Table 1: Single-predictor logistic regression analysis for predicting patients who required CSF diversion surgery[a]

Predictor	β	SE	Wald χ^2	*df*	*P*	Exp(β) OR	Sensitivity	Specificity	Overall Accuracy
MOMS Index	2.262	0.841	7.236	1	.007	9.600	0.643	0.842	0.757
gCC_FA	–1.358	0.506	7.193	1	.007	0.257	0.572	0.842	0.727
gCC_MD	0.970	0.444	4.773	1	.029	2.638	0.571	0.737	0.667
PLIC_FA	–0.953	0.482	3.905	1	.048	0.386	0.500	0.842	0.697
PLIC_MD	0.794	0.506	2.464	1	.117	2.212	0.214	0.947	0.636
Sex	–0.773	0.728	1.129	1	.288	0.462	0.500	0.684	0.606
FOHR	0.173	0.362	0.230	1	.631	1.189	0.070	1.000	0.606

Note:—Sensitivity indicates the percentage of patients who were correctly predicted among patients who required surgery; Specificity, the percentage of patients who were correctly predicted among patients who did not require surgery; SE, standard error.
[a] All the predictors were tested individually with the intercept term included (not shown).

Table 2: Stepwise logistic regression analysis for predicting patients who required CSF diversion surgery

Predictor	β	SE	Wald χ^2	*df*	*P*	Exp (β)	95% CI for Exp (β)	
							Lower	Upper
MOMS Index	4.331	2.125	4.154	1	.042	76.026	1.181	4.895E + 3
gCC_FA	–1.976	0.943	4.390	1	.036	0.139	0.022	0.880
PLIC_FA	–1.283	0.747	2.953	1	.086	0.277	0.064	1.198
Sex	3.216	1.727	3.467	1	.063	0.040	0.001	1.184
FOHR	–1.335	1.078	1.508	1	.219	0.263	0.031	2.216
Constant	–0.308	0.816	3.855	1	.706	0.735	NA	NA

Note:—NA indicates not applicable.

need for surgery was found for the MOMS Index (Wald $\chi^2 = 7.236$, $P = .007$), the gCC_FA (Wald $\chi^2 = 7.193$, $P = .007$), the gCC_MD (Wald $\chi^2 = 4.773$, $P = .029$), and the PLIC_FA (Wald $\chi^2 = 3.905$, $P = .048$) based on the Wald χ^2 test. No significant association was found for the PLIC_MD, sex, and the FOHR (Table 1). The assessment of the predicted probability based on single-predictor logistic regression, including sensitivity, specificity, and overall accuracy, is also reported in Table 1.

CDSI Based on Stepwise Logistic Regression Analysis

The results from the stepwise logistic regression analysis showed the following model:

$$\begin{aligned}\text{CDSI} &= \text{logit}\,(\text{probability of CSF diversion surgery})\\ &= 4.33 \times \text{MOMS\_Index} + (-1.98) \times \text{gCC\_FA}\\ &\quad + (-1.28) \times \text{PLIC\_FA} + (3.22) \times \text{Sex} + (-1.34)\\ &\quad \times \text{FOHR} - 0.31\end{aligned}$$

According to the model, the CDSI, which is the log of the odds of a patient with prenatal MMC repair undergoing CSF diversion surgery later, was positively associated with the MOMS Index with statistical significance based on the Wald χ^2 test (Table 2, $P = .042$). As expected, the model shows that given the values in other predictors holding constant, children who met the MOMS criteria for shunt placement were more likely (>76 times) to require CSF diversion surgery than those who did not meet these MOMS criteria (Table 2).

Among the 4 DTI measures that were entered in the stepwise logistic regression analysis, the CDSI was found to be negatively impacted by gCC_FA with statistical significance (Table 2, $P = .036$) and by the PLIC_FA with marginal significance in the association (Table 2, $P = .086$). This finding suggests that as the FA in the gCC becomes lower in value, the more likely it is that a child would require CSF diversion surgery. The gCC_MD and PLIC_MD were not significantly related to the CDSI and were excluded during the stepwise procedure in the construction of CDSI (see the Online Supplemental Data for variables not included in the equation).

The model also showed that CDSI was negatively related to the patient's sex. While the significance of the impact was marginal ($P = .063$), the data showed that the odds of a female patient who later underwent CSF diversion surgery were 24 time greater than that of a male patient (Table 2, $\text{Exp}(\beta_{\text{sex}}) = 0.04$).

Evaluation of the CDSI as Determined by the Stepwise Logistic Regression Analysis

On the basis of the likelihood ratio test, the overall model provided a better fit to the data as it improved significantly over the null model (Table 3, $P < .001$). As presented in the previous section, the statistical test of predictors included in the regression analysis showed that the regression coefficients were statistically significant for the MOMS Index and the gCC_FA and were marginally significant in the PLIC_FA and in sex based on Wald χ^2 test (Table 2). The Hosmer-Lemeshow test yielded a $\chi^2(8)$ of 7.412 and was insignificant ($P = .493$, Table 3), suggesting that the CDSI fit the data well when the null hypothesis defines a good fit between the model and the data. The variance based on the Cox-Snell test and Nagelkelke test was 54.3% and 73.0%, respectively (Table 3).

The assessment of the predicted probability based on the CDSI is summarized in Table 4. In the 33 patients assessed, the CDSI correctly predicted 11 of 14 for the CSF diversion surgery (78.6%) and 17 of 19 who did not require surgery (89.5%). The sensitivity, specificity, and false-positive and false-negative values of the CDSI are all included in Table 4.

Table 3: Overall model evaluation and goodness-of-fit for the stepwise logistic regression model

	χ^2	*df*	*P*
Overall model evaluation (likelihood ratio)	25.834	5	< .001
Goodness-of-fit test (Hosmer-Lemeshow)	7.412	8	.493
Cox-Snell test (R^2)		0.543	
Nagelkelke test (R^2)		0.730	

Table 4: The frequency of CSF diversion surgery and the predicted frequency by stepwise logistic regression[a]

	Predicted		
Observed	Yes	No	% Correct
Yes	11	3	78.6
No	2	17	89.5
Overall % correct			84.8

[a] Cutoff = 0.5; sensitivity = 11/(11 + 3) = 78.6%; specificity = 17/(2 + 17) = 89.5%; false-positive = 2/(2 + 17) = 10.5%; false-negative = 3/(11 + 3) = 21.4%.

The leave-one-out cross-validation analysis correctly predicted the CSF diversion surgery for 28 of 33 patients. The 5 variables in the model derived from all 33 patients remained consistent in the model from the 33 repetitions of the leave-one-out cross-validation (32/33 for the MOMS Index, gCC_FA, and sex; 31/33 for the PLIC_FA and FOHR). Among these 5 variables, the MOMS Index and gCC_FA remained the top performing covariates for all the repetitions.

The Composite Index CDSI Benchmarked with Individual Indices

When we compared the CDSI on the basis of stepwise logistic regression and individual indices based on single-predictor logistic regression, the performance of the CDSI (Table 4: sensitivity = 78.6%; specificity = 89.5%, overall accuracy = 84.8%) was better than the performance of all of the individual indices in sensitivity and overall accuracy and better than most of the individual indices in specificity (Table 1). The only exceptions were the PLIC_MD and FOHR, which yielded higher specificity (94.7%, 100%, respectively) compared with CDSI. However, these 2 indices both had poorer sensitivity (21.4%, 7%, respectively) and lower overall accuracy (63.6%, 60.6%, respectively) compared with the performance of the composite index (Tables 1 and 4).

As shown in Fig 2*A*, the CDSI based on stepwise logistic regression is plotted in the order of the level of predicted probability for individual patients (solid circle). Among these, 3 patients who needed shunting and 2 patients who did not need shunting were misclassified (in the red solid circle and the blue solid circles, respectively) on the basis of the predictive model (cutoff = 0.5). By contrast, the predictive probability based on single-predictor logistic regression using the MOMS criteria for shunt placement (empty circle) yielded more cases of misclassification: 5 false-negatives and 3 false-positives (in red and blue empty circle, respectively). Figure 2*B* shows the receiver operating characteristic curve for the CDSI model performance with an area under the curve of 0.96.

DISCUSSION

In the present study, our objective was to create a composite index that could be used as a predictive model to objectively improve the capability to manage patients with ventriculomegaly and progressive hydrocephalus. Specifically, we chose a population of patients who had undergone prenatal myelomeningocele repair because these children very frequently have large ventricles at baseline, often in the absence of any detectable symptoms of increased intracranial pressure. This population is suitable for such a study in that it is homogeneous in its etiology of hydrocephalus. Additionally, surgical decision-making is not typically urgent because these patients seldom require CSF diversion shortly after birth, in contradistinction to infants undergoing standard postnatal MMC repair. Thus, the study of the fetal surgery group allows longer clinical and imaging observation for potential signs and symptoms of progressive hydrocephalus as well as radiographic markers of the condition.[29-31]

The present study was a secondary retrospective analysis using data from 33 patients with a history of prenatal MMC repair. In our previous work that used a 35-patient cohort (including the 33 patients in the present study), DTI measures were found to help differentiate patients who required shunt placement from those who did not require the surgery. More important, it was found that using DTI measures yielded higher performance in predicting future shunt placement compared with using ventricle size (FOHR), a common variable in the hydrocephalus diagnosis. In the present study, while still aiming to generate a predictive tool for shunt placement instead of testing a certain predetermined combination of 1 or 2 potential variables, we used stepwise logistic regression, a data-driven approach, to select the optimal combination of variables from 9 potential variables. In its current form, the CDSI comprises the initial MOMS trial and the subsequent MOMS Tulipan revised criteria for shunt surgery, with additional conventional clinical measures and objectives, noninvasive neuroimaging biomarkers based on well-established DTI parameters.[3,4,17] Specifically, we evaluated increasing occipital-frontal cranial circumference, bulging fontanelle or split sutures, progressively increasing ventriculomegaly based on consecutive imaging studies, head circumference greater than the 95th percentile at gestational age, and postnatal DTI measures of the FA and MD of the WM regions of the gCC and PLIC. Finally, we also included the FOHR and tested sex and age for significance.

The stepwise logistic regression analysis demonstrated the significance of the MOMS trial–related index and the DTI values in the gCC (and the marginal significance in FA in the PLIC) in the assessment of the need for hydrocephalus surgery. These findings corroborate our hypothesis and expectations on the basis of findings from other reports in the literature.[4,5,8,10,13,32,33] The potential influence of sex on the predicted probability (P = .06, Table 2) remains to be further examined for its generalizability. Currently, there is no support in the literature for the sex difference in the need for shunt placement in this patient population. It is unclear why the ventricle size variable (FOHR) was not a significant covariate in the final model from the stepwise logistic regression analysis. It may be attributed to the FOHR being an index of static measurement of ventricle size, while by contrast, the MOMS Index derived from the 4 components of the first criterion of the MOMS criteria for shunt insertion focused mainly on the trend of

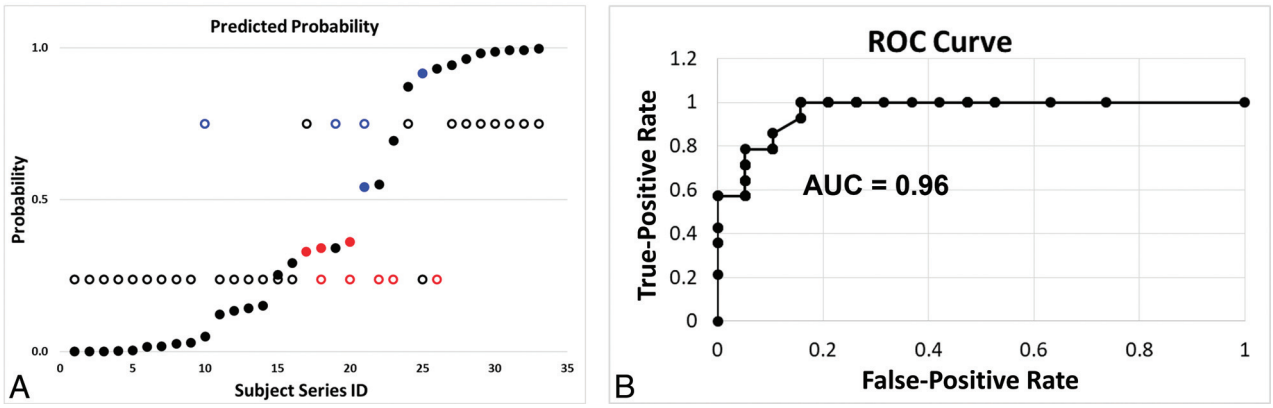

FIG 2. *A*, Comparison of the predicted probability using the CDSI model based on stepwise logistic regression (*solid circles*) and using a logistic regression model with a single predictor (the MOMS Index, in *empty circles*). The data are plotted in ascending order of the predicted probability using the CDSI model, which had 3 false-negative (*red solid circles*) and 2 false-positive cases (*blue solid circles*). The single-predictor logistic regression model using the MOMS Index yielded 5 false-negative (*red empty circles*) and 3 false-positive cases (*blue empty circles*). *B*, The receiver operating characteristic (ROC) curve demonstrating sensitivity and specificity based on the CDSI approach for predicting the need for CSF diversion surgery. AUC indicates area under the curve; ID, identification.

change of the ventricle size, which can be a more accurate reflection of the progression of the underlying disease. Potential confounding factors for the analyses in our study may involve the wide range of timing for different events, including MMC repair, imaging, and MOMS assessment (eg, the FOHR used in the model was assessed using data acquired at the time of postnatal DTI, before the assessment of the MOMS criteria for shunt placement) as well as a series of other factors such as gestational age at birth and socioeconomic status. However, these potential variables would be difficult to test in the scope of the present study due to the insufficient sample size.

As shown in Fig 2, in the 33 cases (14 needing shunt placement, 19 not needing shunt placement), there were 3 false-negative and 2 false-positive cases based on the CDSI model approach. While there is no conclusive evidence with statistical significance, there are some commonalities in the 3 false-negative cases that could help to explain the misclassification. Due to the retrospective nature, the DTI scans were all acquired before patient assessment using the MOMS criteria (and shunt placement for those who needed it). In all of these 3 false-negative cases, there were large increases in ventricle size from the time when DTI was acquired (and the FOHR calculated) to the time when these patients were assessed for their need for shunt insertion. Of note, one patient's ventricle size increased very rapidly and almost doubled in volume within 3 months after DTI scan. One patient, in whom the ventricle size increase was not as severe as in the other 2, presented with a pseudomeningocele (but no true CSF leakage), which would not resolve at the lumbar repair site. These 2 factors together were evidence of progressive hydrocephalus. In the 2 false-positive cases, 1 patient had colpocephaly with small frontal horns. Both patients presented with ventricular size increases and required continued close imaging and clinical follow-up, but the progressions were mild and did not warrant surgical intervention.

Overall, on the basis of our data analysis, the CDSI demonstrated a sensitivity of 78.6% and a specificity of 89.5%, with an overall accuracy of 84.8%, in predicting the need for CSF diversion. This result is better than the performance of all the individual indices based on sensitivity and overall accuracy and also better than most of the individual indices based on the specificity alone (Tables 1 and 4). The objective integration of noninvasive DTI measures with conventional clinical indices provides an evidence-based index that can generate highly accurate data for stratifying patients prospectively into surgical and nonsurgical treatment groups. The overall findings from this study may allow the group-based statistical analysis to be transitioned to individualized decision-making for treatment of this patient population presenting with ventriculomegaly and/or clinical hydrocephalus. As illustrated in Fig 2, the composite index of CDSI helps to integrate information from various aspects, demographic, clinical, and neuroimaging, and provides a quantitative measure of the overall evaluation, which becomes a highly convenient and clinically relevant tool for clinicians to test and apply in decision-making related to treatment in this group following prenatal myelomeningocele repair.

In a similar fashion, the model could be used to study long-term neuropsychological and functional outcomes for infants who have undergone prenatal myelomeningocele repair in comparison with those with postnatal myelomeningocele repair. Outcome studies from the MOMS trial and other post-MOMS trial investigations have reported many data with largely corroborative findings in ambulation, motor functions, and urologic functions at school age or older in these 2 patient populations.[34-39] Identifying significant predictors with the modeling approach for these patients in different subcategories would be highly relevant for the planning of therapeutic intervention and other aspects of the clinical management. In addition, the comprehensive modeling tool could also transform current subjective clinical guidelines for hydrocephalus treatment in other etiologies (eg, congenital hydrocephalus) as well as in patients presenting with hydrocephalus at older ages.

Given the retrospective nature of the current work, certain limitations of the study must be discussed. First, the study should be regarded as exploratory, given its sample-size limitation. We used liberal entry and removed probability thresholds in the stepwise

logistic regression analysis to allow assessing the potential contribution of the factors included in the model. However, the data in the present study need to be replicated with more stringent thresholds with larger-scale data to improve the generalizability of the findings. Second, multicollinearity among the predictors (eg, potential significant correlation between DTI values in the gCC and PLIC or between the MOMS Index and FOHR) may affect the precision of the estimated coefficients and could have led to biased estimates and inflated standard errors. Third, as stated in prior discussion, the timing difference between DTI and clinical evaluation may have contributed to misclassification. Including DTI as part of routine clinical MR imaging protocol and synchronizing it with clinical assessment may help to improve the predictive value of the composite index in future model development and validation studies. Fourth, we selected 2 ROIs, including the gCC and PLIC in the present study. These 2 ROIs are the WM structures that have often been reported to have DTI abnormalities. We also explored other WM regions, eg, the body and splenium of the corpus callosum, the anterior limb of internal capsule, the external capsule, and additional periventricular WM regions. However, due to the presence of ventriculomegaly, small brain size, and other factors, it is not feasible to delineate ROIs for these additional structures in a consistent manner and generate reliable data for all (or at least most) subjects.

In future prospective studies with larger group sizes, additional ROIs as well as biometric measures such as the size of the subarachnoid spaces may be included in the model in which the missing data points may be addressed analytically using imputation or other statistical approaches. Finally, also due to the insufficient power in the present study, not all clinical or radiographic variables were included in the statistical analysis, such as the presence of headache, vomiting, syringomyelia, symptomatic Chiari II malformation, or evidence of CSF leak from the myelomeningocele repair site, to name a few. Some of these factors were not included due to the low frequency of occurrence in our cohort. However, we believe that the data generated in this retrospective review have helped to close a critical knowledge gap and generated important data to support the design of a future clinical trial based on the CDSI with the long-term goal of improving the current standard of care for this patient population.

CONCLUSIONS

In the present study, we constructed a novel composite index that includes clinical, demographic, and neuroimaging measures, with the aim of assisting in the identification of hydrocephalus in patients following prenatal MMC repair. The performance of the CDSI model based on stepwise logistic regression outperformed all single-predictor models, including the models using indices derived from the MOMS trial criteria as well as a series of other variables that were tested separately. By integrating analysis of microstructural WM alterations into a comprehensive model predicting the need for surgical treatment, the CDSI may eventually serve as a robust tool to aid clinicians in their decision-making in hydrocephalus management.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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