


ORIGINAL WORK



Predicting Shunt Dependency from the Effect of Cerebrospinal Fluid Drainage on Ventricular Size

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Abstract

Background: Prolonged external ventricular drainage (EVD) in patients with subarachnoid hemorrhage (SAH) leads to morbidity, whereas early removal can have untoward effects related to recurrent hydrocephalus. A metric to help determine the optimal time for EVD removal or ventriculoperitoneal shunt (VPS) placement would be beneficial in preventing the prolonged, unnecessary use of EVD. This study aimed to identify whether dynamics of cerebrospinal fluid (CSF) biometrics can temporally predict VPS dependency after SAH.

Methods: This was a retrospective analysis of a prospective, single-center, observational study of patients with aneurysmal SAH who required EVD placement for hydrocephalus. Patients were divided into VPS-dependent (VPS+) and non-VPS dependent groups. We measured the bicaudate index (BCI) on all available computed tomography scans and calculated the change over time (Δ BCI). We analyzed the relationship of Δ BCI with CSF output by using Pearson's correlation. A k-nearest neighbor model of the relationship between Δ BCI and CSF output was computed to classify VPS.

Results: Fifty-eight patients met inclusion criteria. CSF output was significantly higher in the VPS+ group in the 7 days post EVD placement. There was a negative correlation between delta BCI and CSF output in the VPS+ group (negative delta BCI means ventricles become smaller) and a positive correlation in the VPS- group starting from days four to six after EVD placement ($p < 0.05$). A weighted k-nearest neighbor model for classification had a sensitivity of 0.75, a specificity of 0.70, and an area under the receiver operating characteristic curve of 0.80.

Conclusions: The correlation of Δ BCI and CSF output is a reliable intraindividual biometric for VPS dependency after SAH as early as days four to six after EVD placement. Our machine learning model leverages this relationship between Δ BCI and cumulative CSF output to predict VPS dependency. Early knowledge of VPS dependency could be studied to reduce EVD duration in many centers (intensive care unit length of stay).

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Introduction

Acute hydrocephalus is a known complication of subarachnoid hemorrhage (SAH), with an incidence of 15–87% [1–4]. Acute hydrocephalus requires the placement of an external ventricular drain (EVD), but the disturbance of cerebrospinal fluid (CSF) hydrodynamics persists in almost half (45%) of these patients requiring a ventriculoperitoneal shunt (VPS) [5–7]. The optimal management of EVD in the setting of SAH remains controversial. Prolonged use of EVD is associated with complications and worse functional outcomes, and premature removal of EVD might put the patients at risk of recurrent hydrocephalus with adverse consequences for recovery from SAH [8–12]. There are conflicting recommendations in the literature regarding the optimal timing and method of EVD weaning [4, 13–15]. Early recognition of VPS dependency or EVD liberation may prevent prolonged EVD duration and complications while expediting transfer out of the intensive care unit in many centers.

Several studies have identified risk factors associated with VPS dependency; few have created classifiers to support individual prediction, and none have used time-varying measurements. The examined risk factors include high Hunt and Hess scale, low Glasgow Coma Scale score at presentation, high Graeb and LeRoux score, high Fisher grade, older age (≥ 60 years of age), computed tomography (CT) findings (hemorrhage, third ventricle diameter, bicaudate index), posterior circulation aneurysm, aneurysm treatment modality (surgical clipping vs. endovascular coiling), and CSF output [1, 12, 16–22]. All these risk factors were assessed once at the onset of SAH (CSF output was evaluated immediately after EVD placement). Bicaudate index (BCI), defined as the ratio of the distance encompassing the lateral ventricles and the distance between the inner tables of the skull at the level of the caudate nucleus [23], has been assessed as a risk factor either at the onset of SAH [1, 3, 24] or right before VPS placement [2].

We hypothesized that time-varying features related to CSF hydrodynamics could accurately identify VPS dependence by using a machine learning statistical classification model. Among known risk factors for VPS, the BCI and CSF output offer dynamic or time-varying information, as opposed to static clinical scales and aneurysm characteristics.

Methods

Study Population

We studied consecutive patients with aneurysmal SAH who had an EVD placed and who were admitted to the neurological intensive care unit. They were enrolled in a prospective observational study of SAH outcomes. Consent was obtained from the patient or a surrogate. The medical center's institutional review board approved the study. This was a retrospective analysis of the prospective observational study.

Patients were divided into two groups: the VPS-dependent group (VPS+) and the non-VPS dependent group (VPS–). They were the patients who required or did not require a VPS placement prior to hospital discharge, respectively. We collected data on demographics, neuroimaging, Hunt and Hess grades, Fisher scale [3, 17, 25], CSF output, EVD, and VPS placement date. Exclusion criteria were patients who died in the hospital, as VPS planning would not be relevant. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

EVD Management and Weaning Practices

In our institution, EVDs are placed for the treatment of symptomatic hydrocephalus and kept open at 20 cm H₂O until the aneurysm is secured. After aneurysm securement, the EVD is set open to drain continuously at 10 cm H₂O during the vasospasm window. EVD weaning trials are started after the vasospasm window and whether the patient has a good neurological examination to follow. Weaning trials include raising the EVD by increments of 5 cm H₂O daily, and then clamping after reaching 20 cm H₂O for 24 hours. The clamp trial is aborted if there are adverse clinical changes (headache, vomiting, or deterioration of consciousness level), intracranial pressure elevations exceeding 20 mm Hg for more than 20 minutes, or CSF leakage. At the end of the clamp trial, if there is radiographic evidence of hydrocephalus, this is also considered a failed clamp trial. Patients are considered candidates for VPS placement after failing two clamp trials. Ventriculitis can delay VPS placement until CSF profiles are adequately normalized with antibiotic treatment.

Neuroimaging and CSF Data

We measured BCIs in all available CT studies during the patient's hospital stay. Readers were blinded to demographic data, clinical baseline, CSF output, and VPS

outcome. The BCI was calculated by using a linear measure of the width of the frontal horns where the heads of the caudate nuclei produced the maximum indentation of the lateral ventricle, divided by the corresponding distance between the inner tables of the skull at this level [23]. The measurement was obtained at the CT section that included the foramen of Monro. When the foramen of Monro was not clearly seen, the measure was made in two adjacent CT sections, and the mean value of the BCI was used. All readers (CR, KT, BW, LC, JE, RR, HK, and AA) participated in group and individual training sessions for BCI measurements. The training materials contained radiological neuroanatomy imaging and examples of BCI measurements. Adequate time was allocated to each reader to understand the interpretative and measurement process fully. Readers had the training materials available later in the active phase of the study. To evaluate the reader's agreement, readers were paired. Two authors measured the BCI in ten CT scans together; afterward, they separately measured BCI in an additional 20 CT scans and crosschecked their results.

Delta BCI were calculated by subtracting the BCI value of the first CT scan (after EVD placement) from the BCI value of subsequent candidate CTs. CSF output data was available from nursing flowsheets in 2 hour intervals. Cumulative CSF volumes (in mL) were calculated to correspond to the timing of each CT scan (starting from and accumulating since the time of the first post-EVD scan). Delta BCIs and corresponding cumulative CSF outputs were calculated for seven consecutive days after EVD placement. For example, on day 4 after EVD placement, delta BCI would equal day 4 BCI (if CT available) minus BCI of the first post-EVD CT, and the corresponding CSF

output would be cumulative between the times of those two scans.

Statistical Analysis

Pearson correlation coefficients were calculated between BCI and cumulative CSF output and between Δ BCI and cumulative CSF output for each day. A p value <0.05 was considered statistically significant. Figures 1 and 2 demonstrate Fisher's Z-transformation that was performed between the correlation values of VPS+ group and VPS- group for each day from days one to seven after EVD placement.

Weighted k-nearest neighbor (KNN) [26] was applied to compute a classification model for VPS dependency. KNN is an algorithm that classifies an object by a majority vote on the basis of the k number of neighbors from the feature map, in which k is an integer. KNN is a Lazy Learner (meaning that it does not require training) and works well with smaller data sets. Weighted KNN is a type of KNN, but it gives a different weight on each neighbor according to its distance. A neighbor with a closer distance has a higher weight compared with a neighbor with more space away from the data point.

Two models were generated on the basis of Δ BCI or daily BCI. Other features that were used as inputs were cumulative CSF output, age, Hunt and Hess score, Fisher Score, and sex. A tenfold cross-validation method was used to evaluate the models. The whole data set was divided randomly into ten different subsamples; nine subsamples were used to train the model, and the remaining subsample was used for validation. This process was repeated ten times, using a different subsample for validation each time. The models were further examined by

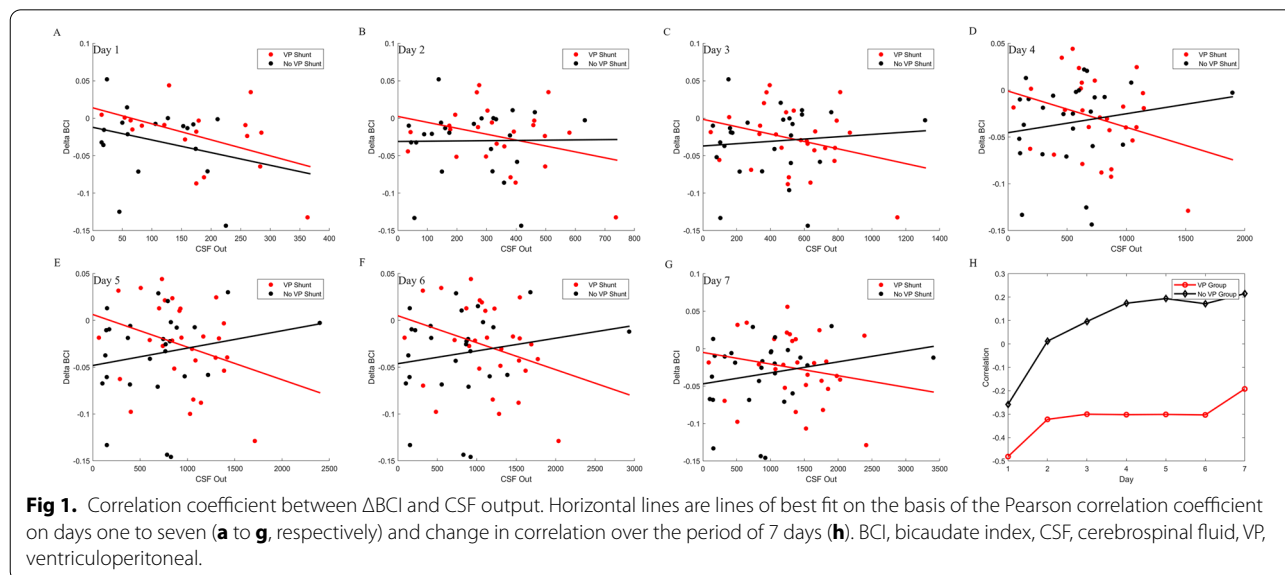
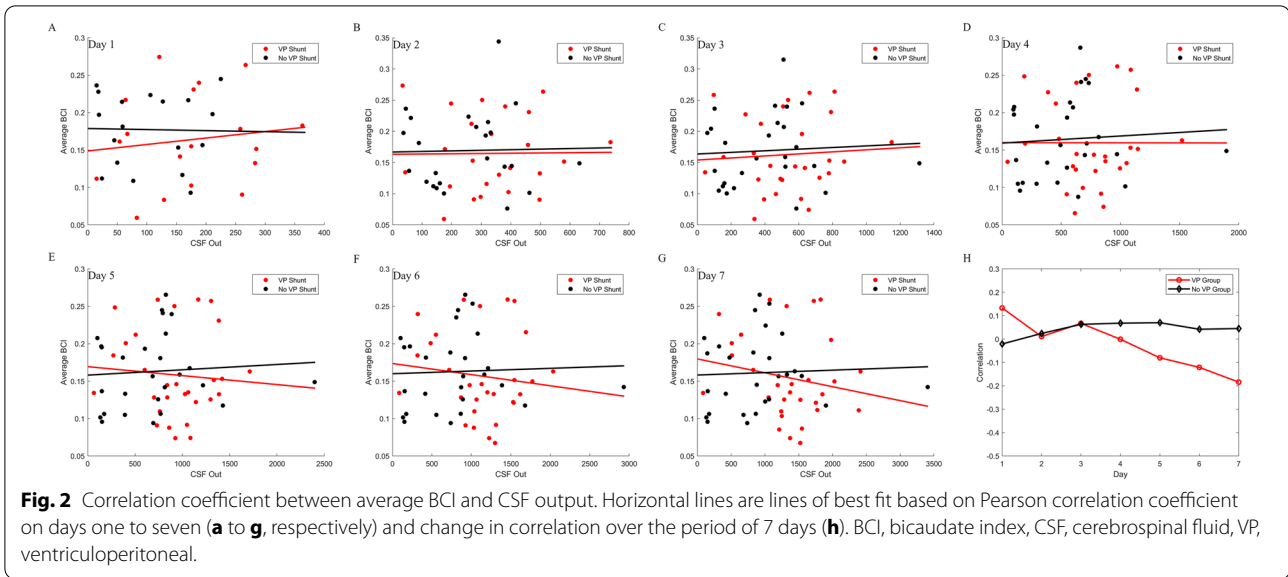


Fig 1. Correlation coefficient between Δ BCI and CSF output. Horizontal lines are lines of best fit on the basis of the Pearson correlation coefficient on days one to seven (a to g, respectively) and change in correlation over the period of 7 days (h). BCI, bicaudate index, CSF, cerebrospinal fluid, VP, ventriculoperitoneal.



using the area under the receiver operating characteristic curve (AUC).

All data analysis was performed by using MATLAB 2020a (MathWorks, MA) and Microsoft Excel 2010 (Microsoft, Redmond, WA).

Results

A total of 119 consecutive patients with SAH with EVD placement who were admitted between April 2006 and September 2014 were included. Sixty-one patients were removed on the basis of the following criteria: missing CSF output data ($n=41$), patients who died in the hospital ($n=13$), patients without Δ BCI value after EVD placement ($n=7$) (Supplemental Digital Content Fig. 1). The study was undertaken during a transition between electronic medical record systems, and some flowsheets and images were no longer accessible. There was no significant difference in age, sex, clinical SAH presentation severity, and Fisher score between the two groups (Table 1). CSF output was significantly higher in the VPS+ than the VPS- group over the 7 days after EVD placement ($p=0.008$) (Table 1). The average overall EVD duration was 11.8 ± 4.7 days (range 3.5–24.3). The EVD duration in the VPS+ group was 12.8 ± 6 days and 8.6 ± 4.7 days in the VPS- group ($p=0.003$). The rate of ventriculitis in the VPS+ group was 7 (23.3%), and the rate in the VPS- group was 5 (17.9%; $p=0.749$). There was no difference in the mean BCI and Δ BCI between the two groups (Fig. 3).

Delta BCI and CSF output negatively correlated in the VPS(+) groups on days two to seven after EVD placement (Figure 1). (Delta DCI is negative when ventricles become smaller from post-EVD CT to subsequent CT).

In contrast, there was a positive correlation between delta BCI and CSF output in the VPS(-) group. (Figure 1) The correlation of delta BCI and CSF output was statistically significantly different between VPS(+) and VPS(-) from days four to six. (Table 2) There was no significant difference between groups in the correlations between mean daily BCI and CSF output. (Figure 2)

The classification accuracy of predicting VPS dependency with the Δ BCI model was 0.72, with a sensitivity of 0.75, a specificity of 0.70, and an AUC of 0.80 (Fig. 4). The result of mean daily BCI model was 0.64, 0.68, and 0.60, respectively, for accuracy, sensitivity, and specificity, with an AUC of 0.63 (Fig. 4). The specificity and sensitivity are reported at an optimal threshold of 0.53 for the Δ BCI model (and 0.44 for the mean BCI model), corresponding to the maximum Youden index [27].

Discussion

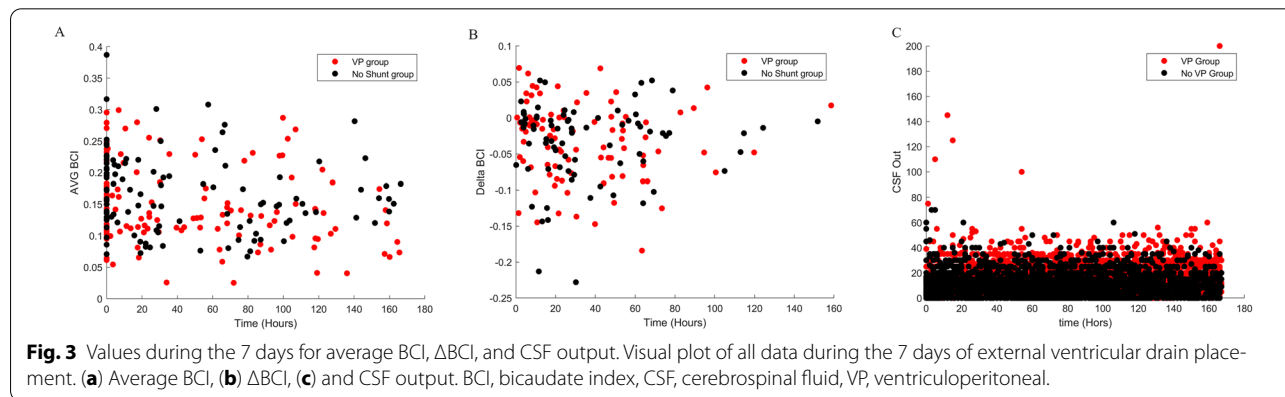
Our study showed that the intra-individual correlation between decreasing BCI and increasing CSF output on days four to six after EVD placement is associated with VPS dependency in patients with SAH. Our model showed that we can leverage this correlation as a feature to classify or predict patients who will need VPS with moderately good accuracy (AUC 0.8). The negative correlation of delta BCI and CSF output in the VPS dependent group suggests a ventricular system which, unaided, can not independently accommodate for either high resistance to CSF outflow or CSF overproduction requiring a drain or shunt to release the pressure. The positive correlation of delta BCI and CSF output in the VPS- group suggests an appropriately accommodating ventricular system.

Table 1 Baseline characteristics

Characteristics	VPS+ (n = 28)	VPS- (n = 30)	p value
BCI, mean (SD)	0.175 (±0.05)	0.161 (±0.113)	0.55
ΔBCI in all available CT scans, mean (SD)	-0.002 (±0.047)	-0.034 (±0.136)	0.242
Cumulative CSF output at 7 days, mean (SD) (mL)	1354.47 (±687.63)	897.79 (±565.92)	0.008
Age, mean (SD) (yr)	56.66 (±14.44)	54.97 (±12.23)	0.633
Hunt & Hess scale			0.665
1	1	1	
2	2	1	
3	12	8	
4	7	12	
5	8	6	
Fisher score			0.096
1	0	0	
2	1	4	
3	26	23	
4	3	1	
Female sex, n (%)	20 (71.4)	22 (73.3)	1
EVD duration, mean (SD) (d)	12.8 (±6)	8.6 (±4.7)	0.003
Ventriculitis, n (%)	7 (23.3)	5 (17.9)	0.749

Statistically significant values are given in bold

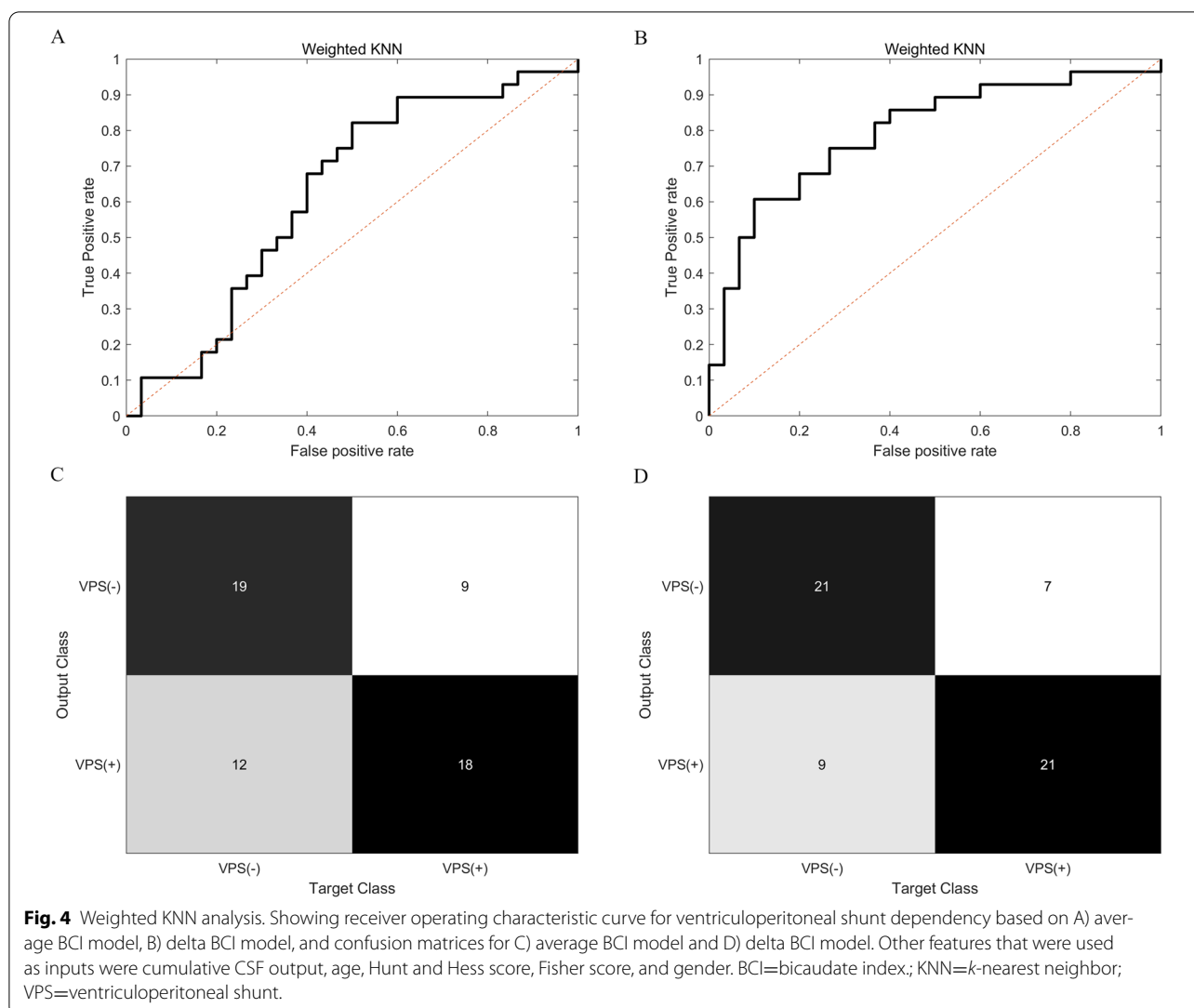
BCI, bicaudate index, CSF, cerebral spinal fluid, CT, computerized tomography, EVD, external ventricular drain, SD, standard deviation, VSP-, non-ventriculoperitoneal shunt dependent, VPS+, ventriculoperitoneal shunt-dependent.

**Table 2 Pearson correlation coefficient between mean BCI and CSF output and between mean delta BCI and CSF output**

Days	Mean ΔBCI			Mean BCI		
	VPS+	VPS-	p value	VPS+	VPS-	p value
1	-0.468	-0.239	0.234	0.133	-0.021	0.336
2	-0.283	0.095	0.195	0.011	0.024	0.484
3	-0.251	0.154	0.077	0.067	0.063	0.494
4	-0.293	0.213	0.0035	-0.001	0.068	0.405
5	-0.268	0.22	0.039	-0.08	0.07	0.298
6	-0.259	0.194	0.051	-0.121	0.042	0.281
7	-0.171	0.229	0.072	-0.184	0.045	0.203

Statistically significant values are given in bold

BCI, bicaudate index, CSF, cerebrospinal fluid, VSP-, non-ventriculoperitoneal shunt dependent, VPS+, ventriculoperitoneal shunt-dependent.



Several risk factors have been used in prior models, such as patient baseline characteristics (age and sex) [7, 17, 25], SAH severity [28, 29], aneurysm location [20, 21], laboratory studies [30], aneurysm treatment modality [25, 31, 32], EVD weaning [33–35], EVD drainage volume [12, 36–40], and course of disease [3, 17, 25], but no time-varying biometrics have yet been used. For example, although BCI has been validated as an objective measurement of hydrocephalus, all studies looking for an association of BCI with VPS dependency have used the BCI at a single point during the hospitalization. Two studies measured BCI in the admission CT scan and showed that VPS was required in patients with a BCI greater than 0.2 [3, 24]. An older study used the measured BCI at the time of shunting. In that study, BCI was stratified by the patients' normal upper age limit and divided the patients into three relative BCI groups. They found that patients

with higher relative BCI values were associated with VPS placement [2]. To our knowledge, our study is the first study to incorporate BCI at multiple time points into a model for VPS dependency, and notably it outperformed a model using single measurements of BCI.

CSF output alone has also been studied as a predictor of VPS dependency [12, 36–40], but although some have suggested an important threshold (>214 mL/day in first 72 hours [38], >204 mL/day [12], >201 mL/day [40]), others have found a lower threshold (>130 mL/day) [37] that directly contradicts important thresholds for VPS— prediction (<162 mL/day) [40]. Moreover, some studies did not even find an association between the CSF output and VPS dependency after SAH [36].

Existing scoring systems, such as the CHES [41], SDASH [28], PS3 [29], and CARAS [42], use variables present at the time the patient presents with acute

hydrocephalus requiring EVD placement, but these are unable to give time-varying knowledge of shunt dependency (or ability to wean from EVD) or have an AUC that is comparable with our model. The recent MAGE [12] score also included mean daily CSF output, but the model's AUC was only 0.6. There is wide diversity among these scores' prognostic factors [1, 7, 28, 29, 41–43], their variable accuracy in their predictions [44], and their applicability in modern practice [45].

We relate CSF output with the change in ventricle size over time, which could be considered a biometric informed by intracranial compliance and resistance to CSF outflow. The correlation of decreasing hydrocephalus and CSF output suggests a ventricular system that, unaided, cannot independently accommodate for either high resistance to CSF outflow or CSF overproduction. Our model incorporates dynamism or change over time in ventricular size in relation to CSF drainage and improves upon a model using standalone BCI values. Our model may serve as a tool for early estimation of shunt dependency and recognition of patients requiring relative pressures to drive flow through CSF efflux pathways to decrease EVD placement days and associated complications. Our study is a positive step toward the development of objective and reproducible dynamic parameters that can help identify patients that will become VPS dependent.

There are limitations to our study. First, this study had a small sample size ($n=58$), limiting the complexity of the model that we can derive. Although the classification performance is good, it does not achieve a level of sensitivity and specificity to be clinically useful yet. We seek to increase the sample size for enhanced model development. Further, the model results depend on the BCI, which requires (albeit minimal effort from) skilled individuals. The automatic calculation of BCI would make our methodology even more feasible. Additionally, our model doesn't include an EVD level relative to the tragus, which might be a confounder in our study. Although the practice of keeping the EVD level at 10 cm H₂O above the tragus during the vasospasm window is standard at our institution, we cannot exclude the possibility that the rare instance of an EVD being set unusually low or high could introduce bias by the changes in CSF output in relation to the EVD setting. This should be data that will be included in future validation of this model.

Conclusions

Our study suggests that using validated, objective, and reproducible biometrics of CSF hydrodynamics, CSF output, and Δ BCI can help physicians recognize patients destined for VPS dependency or patients with the ability for EVD to be weaned in a timely way. The

model showed moderate accuracy (comparable performance with other well-known scoring systems). Future studies are needed to validate our findings.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s12028-022-01538-8>.

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Author contributions

The authors contributed to this article as follows: Drs. Park, Rubinos, and Megjhani and Ms. Terilli conceptualized and designed the study, oversaw data acquisition, and intellectually revised the article. Dr. Rubinos drafted the article and intellectually revised it. Drs. Rubinos, Ford, Alkhachroum, Kirsch, and Megjhani, Ms. Wong, Ms. Cespedes, Ms. Terilli, and Mr. Renz were responsible for data acquisition and critically revised the article. Drs. Kwon and Park performed the statistical analysis and critically revised the article. Drs. Velazquez, Roh, Agarwal, Claassen, Connolly, and Park revised the article for intellectual content. The final manuscript was approved by all authors.

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Data availability

Data relating to the findings of this study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval/informed consent

This study adheres to ethical guidelines and has approval from the local institutional review board of Columbia University (AAAL4106), including waiver of consent.

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