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Combining Transcranial Doppler and EEG Data to Predict Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

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Background and Objectives: Delayed cerebral ischemia (DCI) is the leading complication of subarachnoid hemorrhage (SAH). Because DCI was traditionally thought to be caused by large vessel vasospasm, transcranial Doppler ultrasounds (TCDs) have been the standard of care. Continuous EEG has emerged as a promising complementary monitoring modality and predicts increased DCI risk. Our objective was to determine whether combining EEG and TCD data improves prediction of DCI after SAH. We hypothesize that integrating these diagnostic modalities improves DCI prediction.

Methods: We retrospectively assessed patients with moderate-severe SAH (2011-2015, Fisher=3-4 or Hunt-Hess=4-5) who had both prospective TCD and EEG acquisition during hospitalization. Middle cerebral artery (MCA) peak systolic velocities (PSV) and the presence or absence of epileptiform abnormalities (EA), defined as seizures, epileptiform discharges, and rhythmic/periodic activity, were recorded daily. Logistic regressions were used to identify significant covariates of EA and TCD to predict DCI. Group-Based Trajectory Modeling (GBTM) was used to account for changes over time by identifying distinct group trajectories of MCA PSV and EA associated with DCI risk.

Results: We assessed 107 patients, and DCI developed in 56 (51.9%). Univariate predictors of DCI are presence of high-MCA velocity ($PSV \geq 200\text{cm/s}$, Se=27%, Sp=89%) and EA (Se=66%, Sp=62%) both on or before day 3. Two univariate GBTM trajectories of EA predicted DCI (Se=64%, Sp=62.75%). Logistic regression and GBTM models using both TCD and EEG monitoring performed better. The best logistic regression and GBTM models used both TCD and EEG data, Hunt-Hess score at admission, and aneurysm treatment as predictors of DCI (Logistic Regression: Se=90%, Sp=70%; GBTM: Se=89%, Sp=67%).

Discussion: EEG and TCD biomarkers combined provide the best prediction of DCI. The conjunction of clinical variables with the timing of EA and high-MCA velocities improved

model performance. These results suggest that TCD and cEEG are promising complementary monitoring modalities for DCI prediction. Our model has potential to serve as a decision support tool in SAH management.

Classification of Evidence: This study provides Class II evidence that combined TCD and EEG monitoring can identify delayed cerebral ischemia after subarachnoid hemorrhage.

Introduction

Delayed cerebral ischemia (DCI) is the leading complication of subarachnoid hemorrhage (SAH). Previously, it was believed that DCI is caused solely by large vessel vasospasm, and thus, transcranial doppler ultrasound (TCD) currently serves as the standard of care for DCI monitoring. Although TCD serves as a non-invasive, portable, bedside monitoring exam, it is done infrequently (at best 1-2 times per day), is operator dependent, can be limited by patient anatomy (poor temporal bone window), and can be affected by other physiologic parameters (such as heart rate and blood pressure). Additionally, we now know that vasospasm alone does not fully explain DCI¹⁻³.

Continuous EEG (cEEG) has emerged as a promising supplementary diagnostic tool for DCI prediction and addresses some limitations of TCD monitoring. CEEG is non-invasive and portable, and most importantly can provide several days of continuous data. Studies have demonstrated quantitative cEEG measures such as relative alpha variability and post-stimulation alpha/delta ratio⁴⁻⁶ and epileptiform abnormalities (EA)^{7,8} to be associated with DCI. There is also evidence that patients usually first exhibit cEEG changes prior to developing DCI and that EEG is more strongly associated with DCI than elevated TCD velocities^{8,9}. TCD and cEEG offer

potentially synergistic information about DCI risk. Yet, the *combined* utility of TCD and cEEG data for DCI prediction has not been assessed.

Here, we sought to address whether integrating TCD and cEEG measures can identify DCI after SAH. We hypothesize that combining TCD and cEEG parameters in a single model will improve DCI prediction compared to either modality alone.

Methods

Study Population

We retrospectively evaluated cEEG, TCD, and electronic medical records from 107 moderate- to high-grade SAH patients from the Massachusetts General Hospital between September 2011 and January 2015. The inclusion criteria were: (1) age ≥ 18 years; (2) Moderate- to high-grade SAH (Hunt-Hess grade 4-5 or Fisher group 3-4); (3) non-traumatic SAH; (4) TCD data available; (5) cEEG lasting at least 24 hours and not discontinued more than 24 hours before diagnosed DCI events. We excluded patients who developed non-convulsive or convulsive status epilepticus due to confounding of EEG interpretation. We perform daily TCD monitoring as part of standard clinical care, and record peak systolic velocities (PSV) at the middle (MCA), anterior (ACA), and posterior (PCA) cerebral arteries. We performed cEEG monitoring as part of standard clinical care in all high-grade SAH patients. Monitoring typically began within 48 hours of admission and continued for ten days.

Standard Protocol Approvals, Registrations, and Patient Consents

For this retrospective analysis, we sought approval from the MGH institutional review board to conduct this study (IRB: 2013P001024). The IRB approved waiver of participant consent.

TCD

We only looked at MCA PSV, as the sensitivity and specificity of ACA and PCA TCD values for predicting DCI are limited¹⁰ and were not consistently available in many patients. We defined “high-MCA velocity” as MCA PSV measurement $\geq 200\text{cm/s}$. While this is a classic threshold for vasospasm¹¹⁻¹³, we chose to use the term “high-MCA velocity” in this paper to denote arterial narrowing and avoid confusion, given “vasospasm” and “DCI” have been used interchangeably in the literature¹⁴⁻¹⁶.

EEG recordings

cEEG were recorded using conventional 10-20 scalp electrode placement. We defined epileptiform abnormalities (EAs) as seizures, epileptiform discharges (EDs), lateralized or generalized periodic discharges (LPDs and GPDs), and lateralized rhythmic delta activity (LRDA). The presence or absence of these abnormalities on each day, based on daily cEEG reports generated by fellowship-trained clinical neurophysiologists, was tallied for each patient with “day of bleed” marked as day 0.

DCI “Alarms”

We defined DCI alarms as the presence of either an EA or high-MCA velocity.

DCI Classification

We defined DCI according to an international consensus definition as either: (1) new focal neurologic deficits and/or decrease in the Glasgow Coma Scale of at least 2 points, persisting for a minimum of one hour, not explained by other causes (e.g. complications of a procedure, sedation, spike in intracranial pressure, re-rupture, hydrocephalus, systemic or metabolic

abnormalities) by means of clinical assessment, imaging or laboratory data, or (2) the presence of cerebral infarction on CT or MRI imaging of the brain, acquired at the discretion of the clinical team, that was not present on any neuroimaging done within the first 48 hours following early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment.¹⁴ Although “delayed neurologic deterioration” is a more general term in the absence of angiographic or radiologic evidence, we consider the two definitions overlapping. The consensus definition more specifically refers to this as “clinical deterioration caused by DCI”, which we will abbreviate to DCI for conciseness.

As previously published⁷, we adjudicated the presence or absence of DCI using a multi-step process of (1) prospective daily structured research coordinator interviews with the clinical team, (2) independent medical record review by three of the authors (ESR, MBW, SFZ) blinded to cEEG and TCD findings, (3) consensus adjudication in any case of uncertainty or disagreement.

Data Analysis

We compared baseline characteristics between DCI and non-DCI groups with two-tailed t-tests and Fisher exact tests. We censored longitudinal data once patients developed DCI. We imputed missing data for the MCA PSV via mean (linear) imputation.

We used swimmer plots to visualize the temporal relationship between EAs, high-MCA velocity, and DCI for individual patients. We calculated cumulative distribution functions (CDF) for the first instance of EA and high-MCA velocity. We used a non-parametric bootstrap with 1000 replications to estimate 95% confidence intervals. Then, we compared differences in the incidence of these events across DCI and non-DCI groups with Kolmogorov-Smirnov tests.

We used logistic regression and forward stepwise selection to select TCD and cEEG predictors of DCI. We treated TCD data in two different ways: (1) as a binary, max carried forward

predictor, whether someone had high-MCA velocity (defined as PSV \geq 200cm/s) on or before each day, and (2) as a continuous, max carried forward predictor using the highest PSV values on or before each day. We also used cEEG data as a binary max carried forward predictor by dichotomizing based on whether a patient had any form of EA present on or before each day. We fit a series of logistic regressions using these TCD and cEEG predictors of DCI and selected the earliest day that was significantly associated with DCI. Then, we explored the utility of combining TCD and cEEG in a multivariate regression model. Finally, we calculated model accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), updated post-test probabilities, and C-statistics. The updated post-test probabilities (denoted as “ Δ PPV” and “ Δ NPV”) are calculated by subtracting PPV from the study’s DCI prevalence, and subtracting NPV from the study’s non-DCI prevalence, respectively. The C-statistic is equal to the area underneath the Receiver Operator Characteristic (ROC) curve. The closer the C-statistic is to 1, the better the model performance. These metrics were calculated through leave-one-out cross-validation (LOO-CV). LOO-CV fits a model on all but one patient at a time, and the model predicts the outcome of the observation left out. This process is done iteratively then pooled to compare the actual outcomes to calculate model performance metrics. We also reported these metrics based on the threshold defined by the Youden index, $\max(\text{sensitivity} + \text{specificity} - 1)$, for DCI prediction. For sensitivity analysis, we compared model prediction for early DCI and late DCI. We defined “early” DCI as any DCI event occurring on or prior to the median DCI date of our cohort.

We used group-based trajectory modeling (GBTM) to describe the evolution of TCD and cEEG over time and test the association of trajectory group membership with DCI. GBTM is a finite mixture model that assumes a population is composed of a specified number of subgroups that follow distinct trajectories of one or more repeated measures over time, in this case, MCA PSV and EA. Rather than assuming individuals’ group membership *a priori*, GBTM probabilistically

gathers individuals into statistically meaningful subgroups. After each sequential observation, individuals' posterior probability of membership in each trajectory group is updated based on full available data. These posterior probabilities can then enter into predictive models such as logistic regression to test the association of trajectory group membership with outcome¹⁷⁻²⁰.

We included data from the first ten days after SAH for each patient in GBTMs. We jointly modeled MCA PSV using a beta distribution and EA using a binomial distribution. To select the optimal number of trajectory groups, we compared the Bayesian Information Criteria (BIC) for each of the models that we fitted. We identified an inflection point that was the best balance between model fit and parsimony. We used LOO-CV to calculate the posterior probability of group membership for each patient on each day. We then entered these posteriors into adjusted outcome models to predict DCI. We assessed model performance by calculating model accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), updated post-test probabilities, and C-statistics, again using the threshold defined by the Youden index. For the best model, we performed sensitivity analysis by reporting model performance for early and late DCI events.

We also modeled time-to-DCI using a survival regression model with binary TCD, EEG, and demographic variables as features. To assess performance for each of these survival regression models, we used LOO-CV and reported the cumulative sensitivity, dynamic specificity, and C-statistics at each time point.

Statistical analysis was done using R (The R Foundation), and GBTM analysis was done using the Traj package in STATA (StataCorp). Significance was determined based on $\alpha=0.05$.

We attempted to address sources of bias via prospective identification of patients and adjudication of DCI classification. There is a risk of selection bias in the inclusion criteria, but it is clinically justified since rates of DCI is higher in high-grade SAH patients.

Data Availability

The data from this study are available from the corresponding author on request.

Results

Cohort Composition

227 patients were screened, and 107 were confirmed eligible and included in the study. No patient was lost to follow-up given the short timeline of DCI development. Of the 107, 56 (52.3%) experienced DCI. The median day of DCI was 6 (Interquartile Range=[5, 9]). DCI most commonly occurred on days 5 (10/56, 17.86%) and 9 (8/56, 14.29%) (Figure 1A). The mean age was 56.5 ($SD \pm 14.17$), and 75 (70.1%) patients were female. EA and high-MCA velocity incidences peaked on day 3 for the DCI group (Figure 1B-C). A table of the variables considered in our analysis can be found in Table 1.

High-MCA velocity and presence of EAs precede DCI

We visualized the time relationship between the first occurrence of high-MCA velocity, EA, and DCI using swimmer plots (Figure 2A-B). The plot shows that 53/56 (94.64%) DCI patients experienced at least one DCI alarm before their DCI event, compared with 42/51 (82.35%) of non-DCI patients ($p=0.08$).

We created cumulative plots to visualize and compare the first instances of EA and high-MCA velocity in the DCI and non-DCI groups. The timing at which the first instance of EA occurs differed in the DCI vs. non-DCI groups (Kolmogorov-Smirnov test, $p<0.01$), with the separation

in the 95% confidence interval occurring on day 5. There was no significant difference in the first instance of high-MCA velocities between the DCI and non-DCI groups (Figure 2C-D).

For DCI patients who had both DCI alarms (19/56, 33.93%), EA often preceded high-MCA velocity (14/19, by a mean of 2.5 days), and both preceded DCI (Figure 2E). When we tested each DCI alarm independently and in combination during a patients' monitoring period to predict DCI, we found that using the occurrence of *either* EA or high-MCA velocity resulted in much higher sensitivity (94.64%), but lower specificity (17.65%) and using *both* EA and high-MCA velocity resulted in a much higher specificity (82.35%) but lower sensitivity (33.93%) compared to using a single alarm type to predict DCI (Figure 1D). Still, these analyses had limited performance.

Logistic Regressions with Single Day EEG and TCD parameters

To evaluate the time dependence of the DCI alarms, we fit max carried forward logistic regressions using continuous TCD velocities. Then, we fit logistic regressions using binary max carried forward predictors of cEEG and TCD. These models thus account for data on or before that day. Continuous MCA PSV values were not significantly associated with DCI on any day, but high-MCA velocity occurrence on or before day three ($p=0.042$) was a significant predictor of DCI. For cEEG, EA occurrence on or before day three ($p<0.01$), day five ($p=0.028$), and day six ($p=0.028$) were significant predictors of DCI. Day four was not significant ($p=0.059$).

We combined EA ($p=0.007$) and high-MCA velocity ($p=0.024$) occurrence on or before day three as independent predictors of DCI in a multivariate regression model. The model using both high-MCA velocity and EA presence on or before day 3 (Se=76.09%, Sp=56.82%) outperformed the MCA-only (Se=27.45%, Sp=89.36%) and EA-only (Se=66.00%, Sp=61.70%) models in terms of sensitivity, but C-statistics remain limited (C=0.5405, 95%CI=0.4141-0.6670).

GBTM Outcome Modeling based on final group trajectory membership

To capture trajectory information over time, we implemented GBTM modeling as detailed in the Methods. We first modeled continuous MCA velocities over time and found that a four-subgroup GBTM model best fits the data (Figure 3A-B). Although all four subgroups have distinctive trajectories from one another ($p<0.05$), only one group (yellow, high and rapidly increasing PSV, 17/26 (65.38% DCI)) was significantly associated with DCI (Odds Ratio (OR)=4.84, $p=0.02$, Figure 3B).

We then modeled EA incidences using GBTM and found that two distinct subgroups best fit the data (Figure 3C-D). Patients in group 2 (dark gray, consistently high EA, 37/53 (69.81% DCI)) had a higher risk of DCI (OR=5.09, $p<0.01$) compared to those in group 1 (light gray, decreasing EA, 18/53 (33.96% DCI)). Patients assigned to group 1 experienced either no occurrences of EA or only early during monitoring.

We modeled trajectories of EA and MCA PSV jointly through a multivariate-trajectory model. This type of GBTM model *simultaneously* accounts for MCA PSV and EA trajectories when determining subgroups, and is thus a distinct model from the ones described previously. The best fit multivariate-trajectory GBTM identified four distinct groups when MCA PSV and EA were modeled jointly (Figures 4A-C). Using Group 1 (purple, low/stable PSV and EA, 1/13 (7.69% DCI)) as a reference group, Group 4 (navy blue, moderate/increasing PSV and high/increasing EA, 23/32 (71.87% DCI)) had an increased risk of DCI (OR=23.30, $p<0.01$). Group 3 (orange, high/rapidly increasing PSV, moderate/stable EA, 22/33(66.67% DCI)) also had an increased risk of DCI (OR=18.04, $p<0.01$) compared to Group 1. Group 2 (light green, high/increasing PSV and moderate/stable EA, 6/23 (26.09% DCI)) did not have a significantly different risk of DCI compared to Group 1, but the incidence of DCI remained low in both groups.

GBTM Outcome Modeling based on single-day trajectory membership

Regressing the final group trajectory membership probabilities with DCI identified the group trajectory memberships that were significantly associated with DCI. While this was useful to describe a patient's overall risk for DCI, to *predict* DCI using these group trajectory memberships, we used *daily* group membership probabilities predicted with LOO-CV and regressed them with DCI outcome.

Daily univariate MCA PSV group trajectory memberships were not significantly associated with DCI. Univariate EA trajectory group membership served as a significant predictor of DCI as early as day 3 (Se=64%, Sp=62.75%) and peaked on day 5 (Se=73.53%, Sp=52.94%).

In the multivariate GBTM, group membership served as a significant predictor on days 3 to 7 ($p<0.05$). The day 3 multi-trajectory group membership model (Se=85.11%, Sp=48.98%, Figure 4D) had better sensitivity than the day 3 EA-only trajectory membership model. Model performance using group membership on day 5 performed comparably (Se=81.82%, Sp=42.86%), but may be more limited in its clinical utility given 12/56 (21.42%) DCI patients experienced their DCI event before day 5.

Inclusion of Clinical Predictors in Logistic Regressions and GBTMs

We performed logistic regressions with clinical variables as predictors of DCI and found that higher Hunt-Hess score at admission ($p=0.004$; Se=53.57%, Sp=70.59%) and clipping of aneurysm ($p=0.024$; Se=61.11%, Sp=61.7%) were significantly associated with increased risk of DCI. A model with only these two clinical variables performed with sensitivity of 79.63% and specificity of 57.45%.

We included these clinical variables in the best performing logistic regression model. A final adjusted logistic regression model with the addition of Hunt-Hess score at admission ($p=0.016$) and aneurysm treatment ($p=0.013$) as independent clinical covariates of DCI along with EA

($p=0.006$) and high-MCA velocity ($p=0.072$) on or before day 3 resulted in a model with 88.64% sensitivity and 70.73% specificity.

For GBTM models, the addition of the Hunt-Hess score improved the univariate EA day 3 model ($Se=72.92\%$, $Sp=72.34\%$). The addition of data on aneurysm treatment also improved the EA day 3 trajectory model in terms of specificity ($Se=60.42\%$, $Sp=78.72\%$), but most notably improved model sensitivity in day 6 ($Se=92\%$, $Sp=44.68\%$). The model with all three variables (EA day 3 trajectory membership, Hunt-Hess, and aneurysm treatment) had the best performance ($Se=83.33\%$, $Sp=68.09\%$). Models using trajectory group information on subsequent days had similar performances ($Se=80.95\%-84.38\%$, $Sp=65.95$ from days 4 to 6).

Inclusion of aneurysm treatment and Hunt-Hess score as clinical variables also improve the day 3 multivariate-trajectory group membership model ($Se=86.67\%$, $Sp=65.22\%$). This adjusted multivariate trajectory model has the best sensitivity on day 6 ($Se=87.5\%$, $Sp=60.87\%$).

The best logistic regression and GBTM models include both significant clinical variables and both monitoring modalities. A summary of these model performances can be found in Table 2, and an overview of models in our study can be found in Figure 5.

Survival Regression Models

The best survival model used only EA, Hunt-Hess, and aneurysm treatment modality. However, model performance prior to day 5 was limited. The best performance (C-statistic) did not occur until after 8 days post-SAH (eFigure 1, <http://links.lww.com/WNL/B676>).

Sensitivity Analysis

When we assess our best logistic regression (Day 3 with TCD, cEEG, and clinical variables) in early vs. late DCI events, our model is better at predicting DCI events occurring \leq day 6 ($Se=91.30\%$, $Sp=73.17\%$, $C=0.8155$ (0.7126-0.9183)) compared to $>$ day 6 ($Se=85.71\%$,

Sp=70.73%, C=0.7271 (0.5905-0.8636)). A similar pattern can be found with our best GBTM model (Day 3 multivariate trajectory membership and clinical variables) (\leq day 6 (Se=95.24%, Sp=67.39%, C=0.7857 (0.6787-0.8928) vs $>$ day 6 (Se= 91.67%, Sp=56.52%, C=0.7219 (0.5979-0.8459)).

Discussion

In our study, we show that combining EEG and TCD data improves prediction of DCI over either modality alone. Most DCI patients (94.64%) have at least one DCI alarm prior to the DCI event. For DCI patients who had both alarms, EA often preceded high-MCA velocity, and both preceded DCI. The addition of two clinical variables (Hunt-Hess score at admission and aneurysm treatment modality (i.e. surgical clipping or endovascular coiling) further improved model performance.

High-MCA velocity alone at any time during monitoring (up to the day of DCI or discontinuation) weakly predicts DCI. Although we tried to analyze TCD velocities as a continuous variable, binary max carried forward variable, or with GBTMs, none of these approaches improved the univariate model performance. Our best TCD-only model (Se=27.45%, Sp=89.36%) had worse sensitivity than what was described in a recent meta-analysis, where TCD vasospasm (defined by mean flow velocity \geq 120cm/s) had an 89% (76-95%) sensitivity and 71% (56-81%) specificity for DCI²¹. This is possibly due to variable definitions of DCI, since most studies included in the meta-analysis were published prior to the consensus guideline¹⁴ or our use of peak rather than mean flow velocities secondary to data availability. It is also increasingly recognized that DCI can occur without angiographic or radiologic vasospasm, and vice versa^{3,22}. This may be another potential cause for the TCD models' limited performance in our study.

Based on our previously published work that EA occurrence is higher in patients with DCI⁷, we more closely investigated the timing of EA as a predictive marker of DCI in this study. In EA-only logistic regression models, EA was a significant predictor of DCI as early as day 3 (Se=66%, Sp=61.70%), and model performance peaked at day 6 (Se=67.65%, Sp=57.14%). EA-only logistic regression models could detect impending DCI with a higher sensitivity than TCD-only models, a finding also reported in a previous study by our group⁸. For many DCI patients, EA alarms also preceded TCD velocities crossing the 200cm/s threshold (Figure 2E). Other studies have shown similar findings where cEEG changes such as decreasing relative alpha variability⁶ and decreasing alpha and theta power²³ preceded detection of vasospasm on TCD.

The univariate GBTM model for EA identified two trajectory membership groups associated with DCI risk. The group with consistent EA occurrence over time is associated with a 5-fold increase in odds of DCI (69.81% DCI) compared to the group where EAs occur in the beginning but disappear over time (28.30% DCI). This result suggests that individuals who have persistent EAs tend to be at an increased risk of DCI compared to individuals with transient early EAs.

The multivariate GBTM model identified four distinct groups. Groups 1 (purple; low/stable MCA PSVs and EA) and 2 (green; high/increasing MCA PSVs and low/decreasing EAs) can be considered “benign” trajectories, where most individuals belonging to these groups did not experience DCI. This contrasts with group 4 (navy blue; moderate/increasing PSV and high/increasing EA), where most individuals assigned to this final group trajectory did experience DCI. It seems that EA, rather than MCA PSV, drives the trajectory groups’ association with DCI risk. If patients consistently have EAs, as is the case in group 4 (navy blue), DCI risk increases. If EAs are decreasing over time, DCI risk does not increase, even in the presence of increasing MCA PSV (groups 2, 3, 4).

GBTMs performed comparably to logistic regressions for univariate EA and the multivariate models. GBTM was recently shown to improve upon the accuracy of logistic regressions in models predicting outcomes of patients post-cardiac arrest²⁰. Thus, we expected the trajectory information to enhance prediction compared to logistic regressions, but this was not the case. We believe this may be because our logistic regression variables are max carried forward and not a time-invariant variable, like those used in the 2019 study to compare GBTM and logistic regressions. Of note, both GBTM and logistic regression models performed better than *single-day* logistic regressions (i.e., time-invariant, not max carried forward). It seems that incorporating longitudinal information improves model performance, without a clear benefit of one model over another. Practically, there is some benefit of this, as implementing a logistic regression model may be easier for clinicians to adapt on a large scale. However, the incorporation of trends through GBTM may be important in capturing the changes that occur across the full window of DCI occurrence. There are dynamic processes that occur after SAH, including early injury factors (e.g., blood-brain barrier disruption, seizures, hydrocephalus, inflammation, and edema) that can happen in the first 72 hours post-ictus²⁴⁻²⁶ as well as late injury factors (e.g., delayed cerebral ischemia, delayed hydrocephalus). Looking at trends of both cEEG and TCD may better capture these changes. It is possible that future evaluations of specific EA features, beyond presence or absence of EA, will prove more robust. Incorporating hourly trends, may also make the addition of trends information more valuable.

After evaluating both TCD-only and EA-only models, we found that DCI prediction improves when both modalities are considered together. We believe this is because cEEG and TCD help assess different aspects of DCI physiology, namely the metabolic supply-demand mismatch^{7,24,27}. TCD allows us to directly evaluate reductions in the supply related to large vessel vasospasm. EEG, on the other hand, will enable us to look at markers of excess demand, like EA. By

combining these two modalities, we attempt to capture data reflecting two sides of this delicate balance and end up with a better prediction algorithm.

In our study, higher Hunt-Hess score at admission and clipping of aneurysms were significantly associated with increased DCI risk and improve logistic regression and multivariate GBTM performances. Although the radiographic severity of SAH is also significantly associated with DCI risk based on the literature²⁸⁻³³, our data were limited to cEEG monitoring mainly in patients with high Fisher Scores (FS 3-4). Thus, we were unable to test it as an independent clinical predictor.

These results highlight the importance of clinical variables on the overall prediction of complications like DCI after SAH. Existing literature that uses a combination of clinical and radiographic grading scales to predict DCI has fair discrimination, with C-statistics ranging from 0.63 to 0.79³⁴⁻³⁶.

Our best model, a multivariate logistic regression with binarized, max carried forward EA and TCD values on day 3, Hunt-Hess, and aneurysm treatment achieved a C-statistic of 0.77 (95%CI: 0.67-0.88). We note that the other models, which only include radiographic and clinical scales, may be easier to implement when cEEG monitoring is not available. While our model needs to be externally validated, our results show TCD and cEEG as promising complementary monitoring modalities for DCI prediction and can serve as a decision support tool in SAH management.

Our study has a few limitations. We did not have enough TCD measurements available of other arteries to calculate measures such as the Lindegaard Ratio or to independently assess the utility of ACA and PCA velocities in DCI prediction. The institutional TCD data velocities were preferentially recorded as peak systolic velocities rather than mean flow velocities, and while these values were internally validated to correlate with other modalities for assessing vasospasm,

it remains possible that these measurements contributed to the lower sensitivity in our logistic regression models using only TCD information. Mean flow velocity values are better defined in the literature, with at least 17 TCD studies using mean flow to evaluate DCI from 1992 to 2014²¹. A comparison of PSV to MFV performance in other datasets could help elucidate if this was the case. While our dataset is relatively large for a DCI study, we did not have an independent validation cohort. In the future, larger cohorts across multiple institutions would help externally validate our findings. Our study is limited to EEG text reports and the EEG reports extracted did not comment on the trends of spectral patterns. Thus, we limited our analysis to a daily, binary assessment of cEEG as the presence or absence of EA. There is rich information to be gained from cEEG that can be used to enhance the models. Combining spectral cEEG measures associated with DCI, such as alpha-delta ratio^{4,5,37}, relative alpha variability^{5,6}, and total power³⁷, could improve DCI prediction when used with TCD and should be explored further in the future.

In conclusion, this study provides new evidence that cEEG and TCD *together* provide an improved prediction of DCI. TCD and cEEG provide synergistic information, and models using both TCD and cEEG outperformed models using either modality alone. Models that consider the timing of DCI alarms, using different approaches, performed better than models that did not. Simple clinical variables (Hunt-Hess score and aneurysm treatment modality) further improve multimodal performance with the best model using these clinical variables in addition to the presence of either EA or high-MCA velocity up to day 3 for DCI prediction.

Classification of Evidence: This study provides Class II evidence that combined TCD and EEG monitoring can identify delayed cerebral ischemia after subarachnoid hemorrhage.

Appendix 1: Authors

Name	Location	Contribution
Hsin Yi Chen, BS	Yale University	Analysis and interpretation of data, drafting manuscript
Jonathan Elmer, MD	University of Pittsburgh Medical Center	Analysis of data, revising manuscript for intellectual content
Sahar F. Zafar, MD	Massachusetts General Hospital	DCI Adjudication, revising manuscript for intellectual content
Manohar Ghanta, MS	Massachusetts General Hospital	TCD and EEG data extraction for pre-processing
Valdery Moura Junior, MS	Massachusetts General Hospital	EEG data extraction for pre-processing
Eric S. Rosenthal, MD	Massachusetts General Hospital	DCI Adjudication, revising manuscript for intellectual content
Emily J. Gilmore, MD	Yale University	Interpretation of data, Revising manuscript for intellectual content
Lawrence J. Hirsch, MD	Yale University	Revising manuscript for

		intellectual content
Hitten P. Zaveri, PhD	Yale University	Interpretation of data, Revising manuscript for intellectual content
Kevin N. Sheth, MD	Yale University	Revising manuscript for intellectual content
Nils H. Petersen, MD, PhD	Yale University	Revising manuscript for intellectual content
M. Brandon Westover, MD, PhD	Massachusetts General Hospital	Study design, DCI Adjudication, interpretation of data, revising manuscript for intellectual content
Jennifer A. Kim, MD, PhD	Yale University	Study conceptualization and design, analysis and interpretation of data, revising manuscript for intellectual content

Supplement---<http://links.lww.com/WNL/B676>

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Table 1 Univariate Analysis

	Non-DCI	DCI	p-value
N (%)	51 (47.6)	56 (52.34)	
HH=4-5	26 (51.0)	42 (75.0)	0.017
Aneurysm Treatment (Coil vs. Clip)	29 (56.9)	21 (37.5)	0.037
High MCA on Day 3	5 (9.8)	14 (25.0)	0.043
EA on Day 3	18 (35.3)	33 (62.3)	0.008

Fisher exact tests of EEG, TCD, Hunt-Hess Score at admission, and aneurysm treatment modality (endovascular coiling vs. surgical clipping) show that there is a significant difference between each of these variables between the non-DCI and DCI groups in our study.

Table 2 Model Performance Including Clinical Variables

	Accuracy	Sensitivity	Specificity	PPV (ΔPPV)	NPV (ΔNPV)	C-statistics
Hunt Hess	0.6168 (0.5178- 0.7092)	0.5357	0.7059	0.6667 (+0.1433)	0.5806 (-0.1040)	0.5683 (0.4559- 0.6807)
Aneurysm Treatment	0.6139 (0.5118- 0.7091)	0.6111	0.617	0.6471 (+0.1237)	0.5800 (-0.1034)	--
HH + Aneurysm Treatment	0.6931 (0.5934- 0.781)	0.7963	0.5745	0.6825 (+0.1591)	0.7105 (-0.2339)	0.6738 (0.5656- 0.7819)
High-MCA velocity (Day 3) + HH + Aneurysm Treatment	0.7097 (0.6064- 0.7992)	0.7755	0.6591	0.7170 (+0.1937)	0.7250 (-0.2484)	0.6906 (0.5804- 0.8008)
EA (Day 3) + HH + Aneurysm Treatment	0.7692 (0.6691- 0.8511)	0.8333	0.6977	0.7547 (+0.2314)	0.7895 (-0.3129)	0.7582 (0.6518- 0.8646)
High-MCA velocity (Day 3) + EA (Day 3) + HH	0.7111 (0.606- 0.8018)	0.7826	0.6364	0.6923 (+0.1689)	0.7368 (-0.2602)	0.7105 (0.6009- 0.82)
High-MCA velocity (Day 3) + EA (Day 3) + HH + Aneurysm Treatment	0.8 (0.6992- 0.879)	0.8864	0.7073	0.7647 (+0.2413)	0.8529 (-0.3763)	0.7733 (0.6665- 0.8801)
GBTM EA Trajectory (Day 3) + HH + Aneurysm Treatment	0.7579 (0.6592- 0.8399)	0.8333	0.6809	0.7273 (+0.2039)	0.8000 (-0.3234)	0.7473 (0.6425- 0.8521)
GBTM Multi-trajectory (Day 3) + HH + Aneurysm Treatment	0.7582 (0.6572- 0.8419)	0.8667	0.6522	0.7091 (+0.1857)	0.8333 (-0.3567)	0.7517 (0.6459- 0.8575)

The best model (bolded) was a logistic regression that included TCD, EEG, and clinical variables as covariates. Model performance metrics were calculated via LOO-CV, and C-statistics were

not calculated for models where there is a single binary variable.

ACCEPTED

Figure Legends

Figure 1 High-MCA Velocity and EA Incidences across DCI and non-DCI groups. Patients were monitored with TCD for an average (\pm SD) of 8.98 (\pm 4.30) days with a mean start day 1.75 (\pm 1.18) post-SAH. The mean duration of cEEG recordings was 6.32 (\pm 3.22) days with a mean start date of 1.94 (\pm 1.30) days post-SAH. (A) Histogram of DCI incidence over the first 15 days post-SAH show that peak DCI incidence occurs on day 5 (10/56 DCI patients, 17.86%) and day 9 (8/56 DCI patients, 14.28%). (B) Histogram of TCD “alarms” over the first 15 days post-SAH show that, for DCI patients, peak incidence of TCD alarms occurs on day 3, and peak incidence of TCD alarms for non-DCI patients occurs on day 4. The first instance of any TCD alarm occurrence within the non-DCI group occurred on day 3. (C) Histogram of EEG “alarms” show that a higher proportion of DCI patients get EEG alarms. ETable 1, <http://links.lww.com/WNL/B676> shows counts of DCI and non-DCI patients tabulated against DCI alarms occurring at any time during monitoring (prior to DCI).

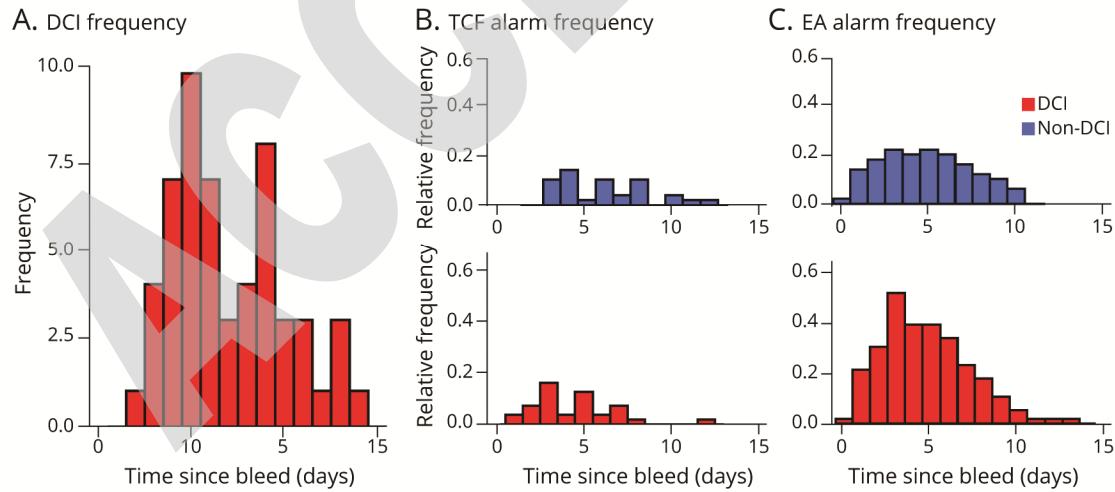


Figure 2 DCI alarms and time of first occurrence in relation to DCI. For DCI patients (A), most receive at least one kind of DCI alarm prior to DCI occurrence. However, many of the non-DCI patients (B) also receive DCI alarms. Cumulative probability plots of the first EEG alarm (C) show that DCI patients receive their first EEG alarm earlier than non-DCI patients, though the difference was not significant until day 5. The cumulative probability plots of the first TCD alarm was not different between non-DCI and DCI groups (D). Finally, (E) shows that in general, EEG alarms precede TCD alarms, and both precede DCI occurrence.

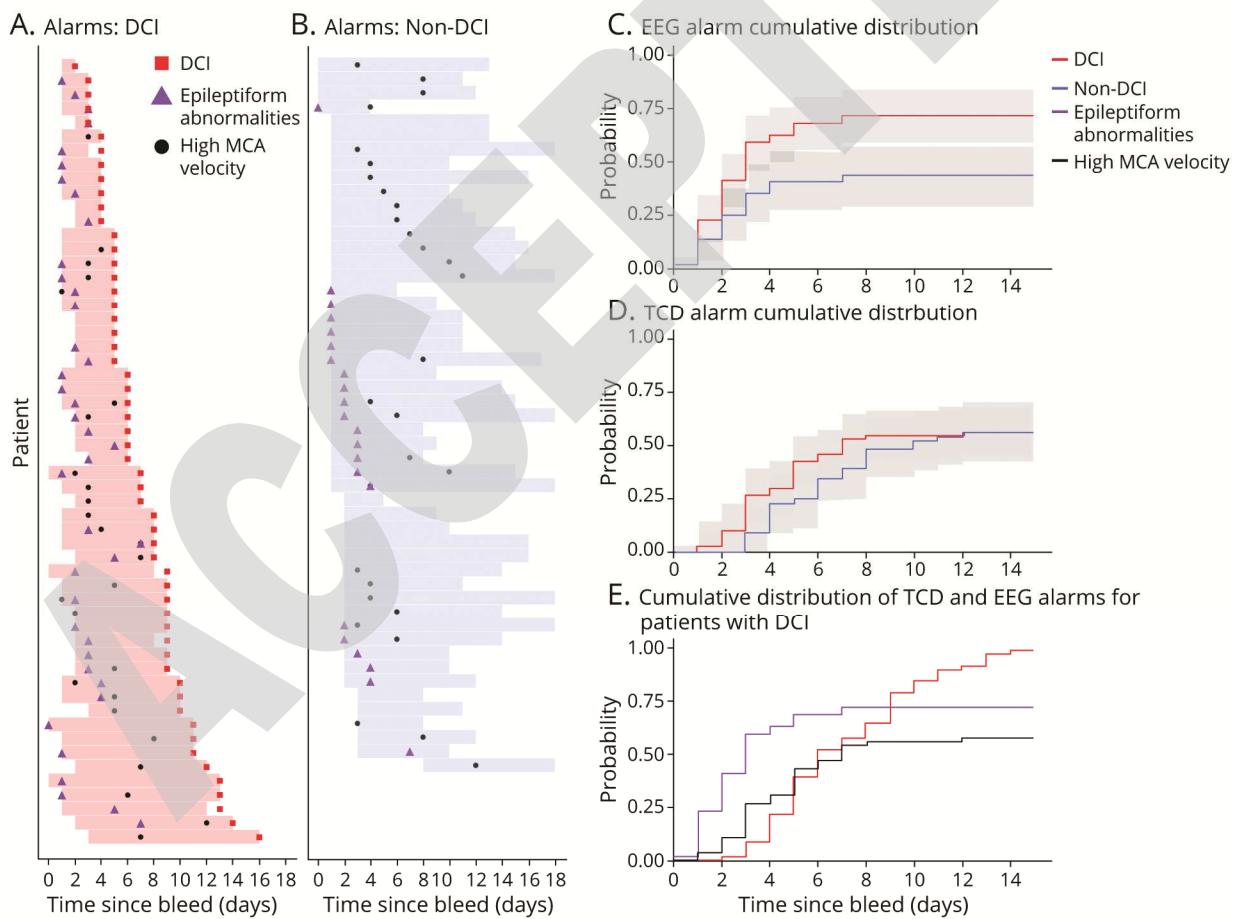


Figure 3 Univariate GBTM. In univariate GBTM of MCA (A), only the group experiencing high, rapidly increasing peak systolic velocities (yellow, group 4) had a significant increase of DCI risk (eTable 2, <http://links.lww.com/WNL/B676>; OR=4.84, p=0.02). Dots represent average MCA value of individuals across the trajectory group, and the solid lines represent the best fit line of each MCA subgroup. Thin lines represent individual MCA trajectories over time.

In univariate GBTM of EA (B), group 2 (dark gray) was associated with a significant increase of DCI risk (eTable 3, <http://links.lww.com/WNL/B676>; OR=5.09, p<0.01) when compared to group 1 (light gray). Opaque dots represent the EA prevalence in the subgroup on each day, and the solid lines represent the best fit line of each EA subgroup. The semi-transparent dots centered around 0 and 1 represent individuals who did (1) and did not (0) have an EA on that specific day.

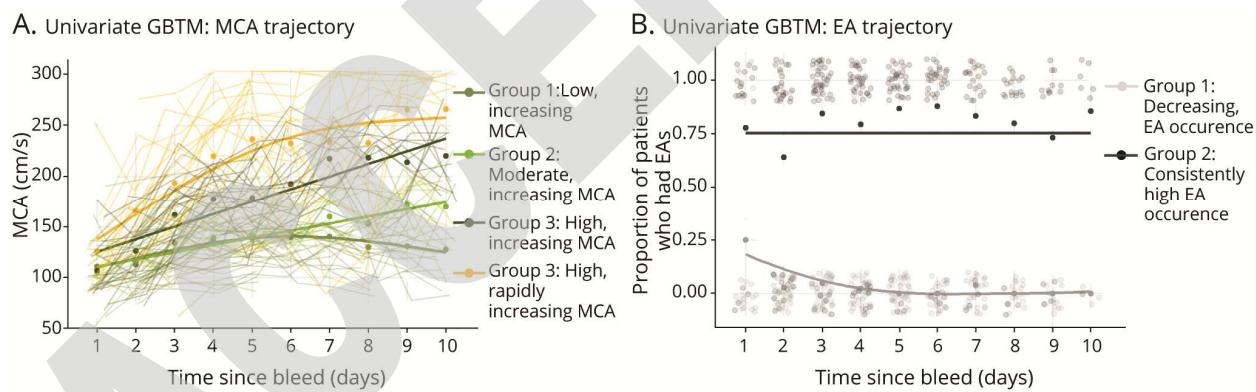


Figure 4 Multivariate GBTM. Multivariate GBTM identified 4 distinct subgroups of MCA (A) and EA (B) when trajectories from both modalities are modelled jointly. Patients in “high risk” groups experience high and rapidly increasing MCA PSVs along with moderate EA (orange; OR=18.04, p<0.01) and moderate and increasing MCA PSVs and increasing EA (navy blue; OR=23.30, p<0.01) (eTable 4, <http://links.lww.com/WNL/B676>). Using trajectory group membership on days 3 and 5 have fair model performance (eTable 5, <http://links.lww.com/WNL/B676>).

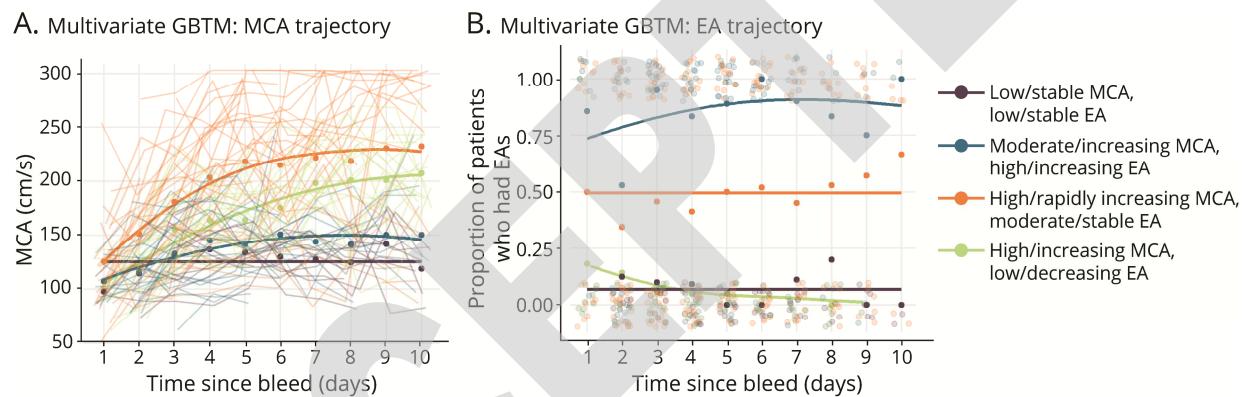
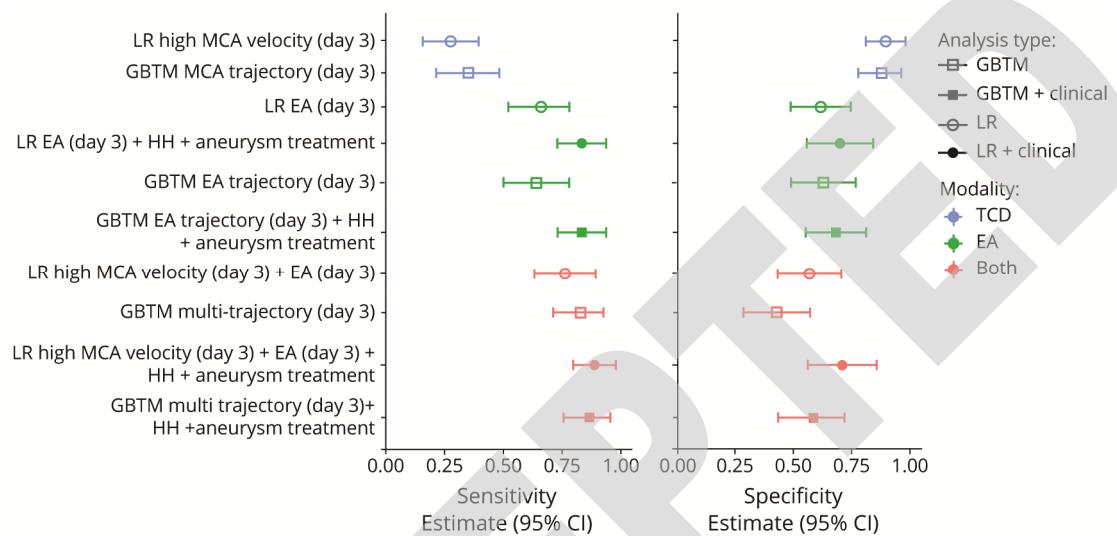


Figure 5 Model Comparison. A comparison of TCD only (blue), EEG only (green) and combined (red) models show that the best models used both modalities and clinical variables. GBTM models performed comparably to logistic regressions.



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