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Assessment of the Validity of the 2HELPS2B Score for Inpatient Seizure Risk Prediction

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IMPORTANCE Seizure risk stratification is needed to boost inpatient seizure detection and to improve continuous electroencephalogram (cEEG) cost-effectiveness. 2HELPS2B can address this need but requires validation.

OBJECTIVE To use an independent cohort to validate the 2HELPS2B score and develop a practical guide for its use.

DESIGN, SETTING, AND PARTICIPANTS This multicenter retrospective medical record review analyzed clinical and EEG data from patients 18 years or older with a clinical indication for cEEG and an EEG duration of 12 hours or longer who were receiving consecutive cEEG at 6 centers from January 2012 to January 2019. 2HELPS2B was evaluated with the validation cohort using the mean calibration error (CAL), a measure of the difference between prediction and actual results. A Kaplan-Meier survival analysis was used to determine the duration of EEG monitoring to achieve a seizure risk of less than 5% based on the 2HELPS2B score calculated on first- hour (screening) EEG. Participants undergoing elective epilepsy monitoring and those who had experienced cardiac arrest were excluded. No participants who met the inclusion criteria were excluded.

MAIN OUTCOMES AND MEASURES The main outcome was a CAL error of less than 5% in the validation cohort.

RESULTS The study included 2111 participants (median age, 51 years; 1113 men [52.7%]; median EEG duration, 48 hours) and the primary outcome was met with a validation cohort CAL error of 4.0% compared with a CAL of 2.7% in the foundational cohort (P = .13). For the 2HELPS2B score calculated on only the first hour of EEG in those without seizures during that hour, the CAL error remained at less than 5.0% at 4.2% and allowed for stratifying patients into low- (2HELPS2B = 0; <5% risk of seizures), medium- (2HELPS2B = 1; 12% risk of seizures), and high-risk (2HELPS2B, ≥2; risk of seizures, >25%) groups. Each of the categories had an associated minimum recommended duration of EEG monitoring to achieve at least a less than 5% risk of seizures, a 2HELPS2B score of 0 at 1-hour screening EEG, a 2HELPS2B score of 1 at 12 hours, and a 2HELPS2B score of 2 or greater at 24 hours.

CONCLUSIONS AND RELEVANCE In this study, 2HELPS2B was validated as a clinical tool to aid in seizure detection, clinical communication, and cEEG use in hospitalized patients. In patients without prior clinical seizures, a screening 1-hour EEG that showed no epileptiform findings was an adequate screen. In patients with any highly epileptiform EEG patterns during the first hour of EEG (ie, a 2HELPS2B score of ≥2), at least 24 hours of recording is recommended.

Supplemental content

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The use of continuous electroencephalogram (cEEG) monitoring in hospitalized patients has expanded markedly over the last decade.[1,2] The growth is partially a response to evidence that subclinical or electrographic seizures are relatively common in hospitalized patients,[3-10] including patients without a primary neurological diagnosis (10%-12%).[11,12] Evidence supporting the importance of detecting and treating electrographic seizures comes from the association between electrographic seizures and worse neurological outcomes, including epilepsy.[13-16] Indeed, cEEG has been found to be cost-effective[17] and associated with decreased mortality.[13]

Factors limiting cEEG use include high labor and hardware costs. A tool to guide cEEG use and duration is needed. Clinical criteria based on baseline patient characteristics alone do not accurately predict seizure risk. Incorporating epileptiform EEG findings (eg, sporadic epileptiform discharges [spikes or sharp waves] and periodic discharges) improves seizure prediction.[3,6,10,18,19] The 2HELPS2B[18] scoring system was developed to address this need. It is a point system designed to stratify inpatient seizure risk based on 5 EEG features and a single clinical factor (remote history of seizures or recent suspected acute symptomatic seizure) (**Table 1**). The 2HELPS2B score was developed using the riskSLIM[20,21] machine-learning methods applied to a large data set (5427 studies) from the Critical Care EEG Monitoring Research Consortium database.[22]

However, to determine the optimal clinical use of 2HELPS2B, a validation study is required.[23,24] This investigation first validated 2HELPS2B in an independent cohort from a more diverse multicenter collaboration. Next, we determined if the 2HELPS2B score assessed during a 1-hour screening EEG remains well calibrated to overall seizure risk. Finally, we used a survival analysis to determine the duration of EEG monitoring based on the initial risk assessment.

Key Points

Question Is the 2HELPS2B inpatient seizure risk prediction tool valid for predicting electrographic seizures in an independent patient cohort and what duration of electroencephalogram (EEG) is needed to calculate it?

Findings In this study of an independent cohort of continuous patients undergoing EEG, the 2HELPS2B calibration error and area under the curve were not statistically different from the foundational study. One hour of screening EEG is sufficient to stratify continuous EEG (cEEG) seizure risk and recommend cEEG monitoring duration.

Meaning 2HELPS2B may be a useful tool to incorporate into the workflow of a cEEG service to maximize the efficiency of EEG resources and simplify communication regarding the clinical significance of EEG findings.

Table 1. 2HELPS2B

		%					
Risk Factor	Score	0	1	2	3	4	5+
Frequency >2 Hz[a]	1						
Independent sporadic epileptiform discharges	1						
LPD/BIPD/LRDA	1						
Plus features (superimposed rhythmic, fast, sharp)[b]	1						
Prior seizure[c]	1						
BIRD	2						
Total Score							
Predicted risk of seizure,[d] 2HELPS2B score		<5	12	27	50	73	88
Actual risk of seizure							
FS[e]		3	12	34	52	71	84
VAL[f]		4	15	34	55	75	93

Abbreviations: BIPD, bilateral independent periodic discharges; BIRD, brief potentially ictal rhythmic discharge; FS, foundational study; LPDs, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; VAL, validation study cohort.

[a] Frequency of any periodic or rhythmic pattern of more than 2 Hz except generalized rhythmic delta activity.

[b] Plus features include superimposed rhythmic, fast, or sharp activity only on LRDA, LPDs, or BIPDs.

[c] Prior seizure includes a remote history of epilepsy or recent events suspicious for clinical seizures.

[d] Predicted seizure risk is based on the 2HELPS2B model.

[e] Foundational study is the actual risk of seizures from the foundational cohort (N = 5427).

[f] VAL is the actual risk of seizures based on the current validation study cohort (N = 2111).

Methods

Subject Recruitment

After receiving institutional review board approval at the respective institutions, data from consecutive cEEG monitoring sessions were collected at the University of Wisconsin (Madison), Massachusetts General Hospital (Boston), Emory University and affiliated Grady Memorial Hospital (Atlanta, Georgia), Duke University (Durham, North Carolina), Medical University of South Carolina (Charleston), and Université Libre de Bruxelles, Hôpital Erasme (Bruxelles, Belgium). The need for informed consent was waived for reasons of minimal risk by respective institutional review boards. The participating hospitals are members of the Critical Care EEG Monitoring Research Consortium. Inclusion criteria included a cEEG duration of at least 12 hours and being 18 years or older. Exclusion criteria included EEG for post-cardiac arrest prognosis or elective epilepsy monitoring unit admission. Data were collected retrospectively from a review of the medical records and EEG reports from January 2012 to January 2019. Any clinical or EEG variable not documented in the medical record or EEG report was presumed to be absent.

Clinical Variables

Data collected from the medical record review included sex, remote history of seizure, suspected acute symptomatic clinical seizure prior to cEEG, age at time of cEEG (years), etiology/indication (ischemic stroke, subdural hematoma, traumatic brain injury, suspected seizure/spell, central nervous system tumor, central nervous system infection, metabolic encephalopathy, subarachnoid hemorrhage, intracerebral hemorrhage, hydrocephalus, or unexplained altered mental status)

for cEEG, mental status at the start of EEG (alert: Glasgow Coma Scale[25] score [GCS] = 15; encephalopathy: GCS = 9-14; comatose: GCS, <9), number of nonsedating antiseizure drugs at 1 hour, 12 hours, 24 hours, 48 hours, and 72 hours, and use of nonopioid intravenous (IV) sedatives at 1 hour, 12 hours, 24 hours, 48 hours, and 72 hours. Antiseizure drug and IV sedative data were not available from Hôpital Erasme.

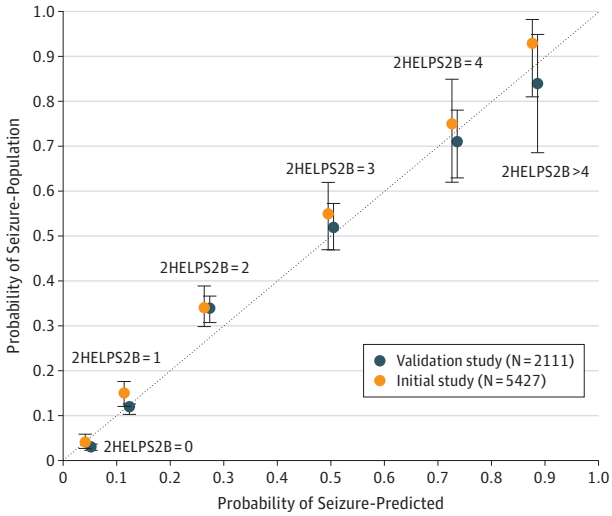
EEG Variables and Univariate Analysis

Electroencephalogram reports were reviewed at 1 hour, 12 hours, 24 hours, 48 hours, and 72 hours using American Clinical Neurophysiology Society critical care EEG monitoring terminology.[26] This terminology has been shown to have high interrater reliability.[27] The overall duration of EEG monitoring was reported. The following factors were assessed: presence or absence of sporadic epileptiform discharges (spikes or sharp waves), lateralized periodic discharges (LPD), lateralized rhythmic delta activity (LRDA), bilateral independent periodic discharges (BIPD), and brief potentially ictal rhythmic discharges (BIRDs) as well as the frequency of any periodic or rhythmic patterns (0.5, 1, 1.5, 2, 2.5, and 3 Hz) and the presence of superimposed rhythmic, fast, or sharp patterns associated with any rhythmic delta or periodic patterns, known collectively as *plus features*, were also recorded. As in the foundational study, the frequency variable was treated as a binary variable with a cutoff at 2 Hz or less and more than 2 Hz and only the frequency of LPDs, LRDA, BIPDs, and generalized periodic discharges (GPDs) were considered, as the frequency of generalized rhythmic delta activity (GRDA) is not associated with seizure risk.[28] Similarly, as in the foundational study, the plus features are treated as a binary variable. Plus features were considered present if there was superimposed rhythmic, fast, or sharp activity associated with LPDs, LRDAs, or BIPDs (plus features on GPD or GRDA were not included as they are not associated with increased seizure risk). The presence of electrographic seizures was also recorded. Additionally, the exact time (to the minute) of the first seizure onset was recorded for all participants from Massachusetts General Hospital (1000 participants [47.4%]) and Hôpital Erasme (404 participants [19.1%]). A univariate analysis for risk factor assessment was performed using the Fisher exact test with estimation of odds ratios (ORs).

Validation of 2HELPS2B

The primary outcome measure for validation was a root mean squared risk-calibration error (CAL) of less than 0.05 in the validation cohort, as it was felt that a less than 5% error was needed for reliable clinical use. For this primary outcome, the 2HELPS2B score was calculated over the entire EEG monitoring to replicate the methods of the original study. The CAL is a measure of the error between the predicted incidence of seizures vs the actual incidence of seizures. It is a mean of the square of the error taken over each risk level (2HELPS2B = 0 and 2HELPS2B = 1). The CAL is a standard method for evaluating a predictive model when the goal is to create stratified risk levels.[29] A CAL of 0.00 characterizes an ideal classifier. An example of the graphical representation of this error is found in **Figure 1**. In this graph, the performance of an ideal classifier is represented by a dashed line at a 45° angle from the origin. Ninety-five percent confidence intervals were generated via bootstrapping. The CAL was statistically compared between the original and validation cohorts using 2-sided permutation testing.

Figure 1. Risk-Calibration Graph of the Error for the 2HELPS2B Model in the Initial Study Cohort and the Validation Cohort



The dashed line is an ideal classifier with a calibration error of 0. Data are presented with 95% confidence intervals. The calibration error on the validation cohort was 4.0% (95% CI, 2.8%-6.2%). In the initial study cohort, the *t* error was 2.7% (95% CI, 2.0%-3.6%); errors between cohorts were not significantly different with a *P* value of .13.

A secondary measure was the area under the curve (AUC) using a receiver operating characteristic curve analysis. This measure is primarily a measure of accuracy for binary classification and not multilevel risk stratification, but it is warranted in this case as a comparison with the foundational study. The AUC is presented with bootstrapped 95% confidence intervals and is statistically compared with bootstrapping in the "pROC" package[30] in R (R Foundation).

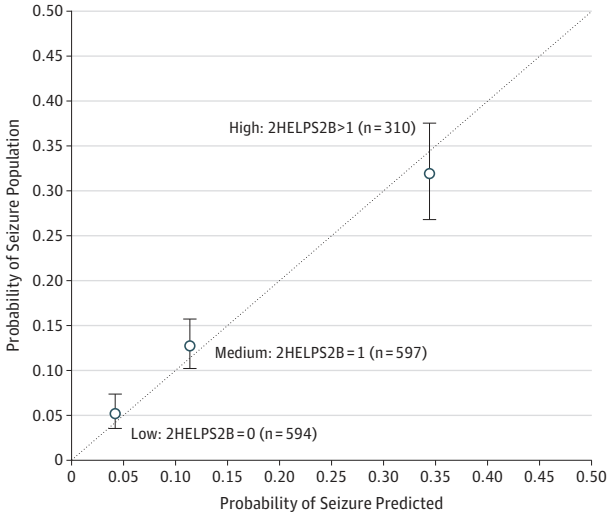
Evaluation of 2HELPS2B With 1-Hour Screening EEG

The 2HELPS2B score was calculated using only the EEG findings from the first hour of recording. Participants who had a seizure during the first hour of EEG were excluded from this analysis, as they had already demonstrated a need for more prolonged EEG monitoring. The CAL was then calculated as in the previous validation procedure with a root mean squared error weighted over all possible risk categories.

Survival Analysis Using 2HELPS2B Risk Stratification

The cohorts from Massachusetts General Hospital and Hôpital Erasme provided the exact time (to the minute) of first seizure onset, allowing for a survival analysis in this subgroup (n = 1407 [66.7%]). Electroencephalogram duration was measured in hours. A Kaplan-Meier survival analysis using the R survival package [31] was applied to 2HELPS2B at 3

Figure 2. Risk-Calibration Graph of the Error for the 2HELPS2B Model Calculated Only During the First Hour of Electroencephalogram (EEG) in the Validation Cohort, Represented With 3 Risk Levels



One-hour screening EEG, seizure risk calibration. The dashed line is an ideal classifier with a calibration error of 0. Data are presented with 95% confidence intervals. The calibration error was 4.2% (95% CI, 2.5%-7.1%). Comparison of the calibration error between 2HELPS2B calculated during the entire study vs only the first hour of EEG was nonsignificantly different with a *P* value of .93. The overall seizure risk for each group is as follows: low, 3.1%; medium, 12.0%; and high, 26.6%.

risk levels—low (2HELPS2B = 0), medium (2HELPS2B = 1), and high (2HELPS2B, ≥2)—between 1 hour (excluding 1-hour screening EEG used to calculate 2HELPS2B) and 72 hours. The risk groups were defined a priori based on the early clinical experience with 2HELPS2B and analysis of the previous cohort. The intention was to define clinically useful groups in which 2HELPS2B could be used to optimize the duration of cEEG monitoring. The lower risk 2HELP2B scores of 0 and 1 were the most common scores and required the shortest duration of monitoring. It is these low- and medium-risk groups for whom 2HELPS2B is most likely to be helpful via shortening the duration of monitoring. The higher-risk scores (2HELPS2B, ≥2) are less common and are more likely to need a patient-specific EEG monitoring duration based on factors like the response to empirical antiseizure drug trials and considerations for ictal-interictal continuum patterns. Rather than trying to determine a specific duration for each of these higher-risk 2HELPS2B scores, these participants were grouped together to ensure an adequate power for survival analysis and provide a recommendation that should be considered the absolute lower limit of monitoring duration for these high-risk patients. All statistical analyses were performed using R, version 3.5.2. For inferential statistical comparisons, all tests are 2-sided with α set to .05.

Results

Demographics

From January 2012 to January 2019, 2111 participants were included from the University of Wisconsin (100 [4.7%]), Duke University (205 [9.7%]), Hôpital Erasme (407 [19.3%]), Medical University of South Carolina (198 [9.4%]), Emory University (201 [9.5%]), and Massachusetts General Hospital (1000 [47.4%]). All participants were independent from the initial study cohort. Emory University provided participants for both studies, with participants for this validation study being enrolled after completing the original study. The median (interquartile range) age of participants was 51 (37-62) years. The median (interquartile range) EEG duration was 48 (47.3) hours. A total of 471 participants (22.3%) had a seizure during cEEG monitoring. Prior risk factors for electrographic seizures on cEEG identified in foundational study were significant on univariate analysis, with $P < .001$ for the following factors: prior seizure (OR, 3.82; 95% CI, 3.00-4.88), presence of LPD, LRDA, or BIPDs (OR, 5.36), sporadic epileptiform discharges (spikes or sharp discharges) (OR, 2.41; 95% CI, 1.92-3.03), frequency of rhythmic/periodic patterns of more than 2 Hz (OR, 4.92), and BIRDs (OR, 11.88; 95% CI, 7.45-19.72). Other risk factors analyzed, including acute structural brain injury, IV sedation, use of antiseizure drugs, and presence of coma at start of EEG, showed no statistically significant associations with subsequent seizures, ORs, and the *P* values found in the eTable in the Supplement.

Validation

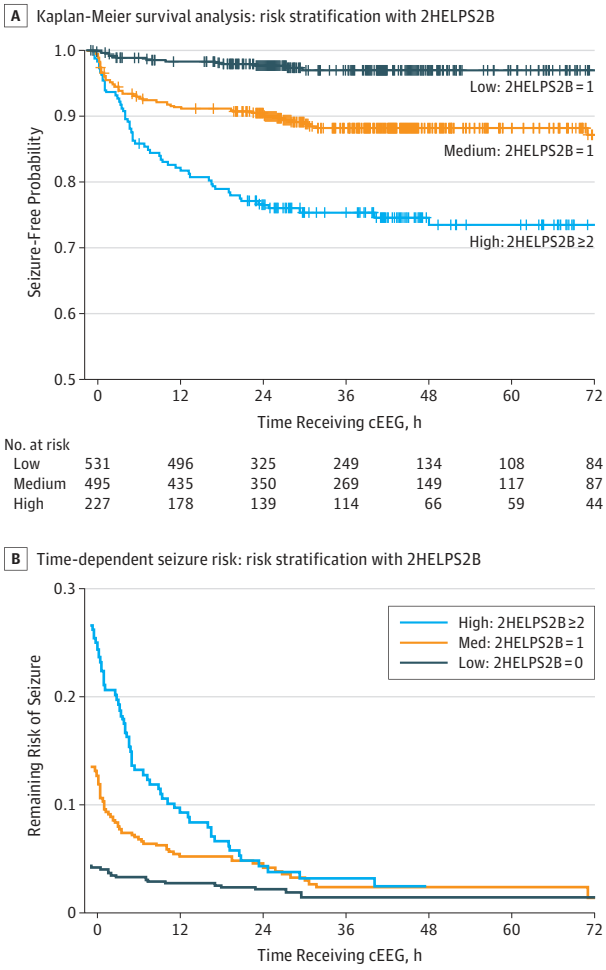
The methods of the initial 2HELPS2B study were recapitulated. The 2HELPS2B score was calculated for the total duration of the EEG and compared with the incidence of seizures for each risk stratification. Figure 1 is a risk calibration graph comparing the error of 2HELPS2B in the initial and validation cohorts. The CAL for the validation cohort was 4.0% (95% CI, 2.8%-6.2%). In the foundational study cohort, CAL was 2.7% (95% CI, 2.0%-3.6%). The CAL had overlapping confidence intervals between cohorts. A statistical comparison of the cohorts using permutation testing resulted in a nonsignificant *P* value of .13. The AUC in the validation cohort was 0.804 (95% CI, 0.781-0.825) compared with the foundational study cohort of 0.819 (95% CI, 0.815-0.868) with overlapping confidence intervals and a nonsignificant *P* value of .29.

One-Hour Screening EEG

The risk-calibration error was evaluated for the 2HELPS2B score calculated based only on findings from the first hour of EEG. The CAL error was 4.2% (95% CI, 2.5%-7.1%) and remains less than 0.05. This CAL error (4.2%) is statistically indistinguishable from the CAL error based on the 2HELPS2B score calculated from the whole EEG (4.0%; $P = .93$).

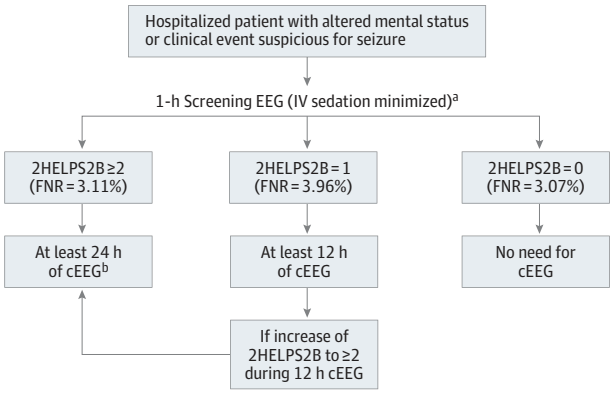
2HELPS2B has 8 potential risk categories, with some categories being rare within the clinical cEEG population. To make the risk stratification more clinically useful, the risk categories were divided into 3 groups to be more reflective of levels of risk that would be associated with EEG monitoring duration, as described in Methods. This divides the cEEG patient population into 3 groups: low risk (2HELPS2B = 0; seizure risk, <5%), medium risk (2HELPS2B = 1; seizure risk, 12%), and high risk (2HELPS2B, ≥2; seizure risk, >25%). **Figure 2** is a risk-calibration graph with the 2HELPS2B stratified into these 3 groups.

Figure 3. Survival Analysis and Time-Dependent Seizure Risk



A, Survival analysis for 72 hours after 1-hour screening electroencephalogram (EEG). Risk is stratified by 2HELPS2B calculated during the preceding 1-hour screening EEG. Dashes in survival lines represent censoring events (low-risk, n = 531; medium-risk, n = 495; high-risk, n = 227). B, Time-dependent risk of seizures stratified by 2HELPS2B score calculated from the first hour of EEG monitoring, The 72-hour risk of seizures decays rapidly as the duration of continuous EEG (cEEG) monitoring increases. The dashed line represents when the false negative rate drops below 5%.

Figure 4. 2HELPS2B Clinical Algorithm



If a seizure is detected at any time (including in the 1-hour screening electroencephalogram [EEG]), there is a recommendation for at least 24 hours of EEG monitoring after the last seizure.[33] cEEG indicates continuous EEG monitoring; D/, discontinue; FNR, false negative rate.

[a] For patients with coma, a screening EEG of up to 90 minutes may be considered.

[b] In cases of ictal-interictal continuum patterns, which are common in those with a 2HELPS2B score of 2 or greater, a longer duration of monitoring may be required for empirical treatment trials.

Survival Analysis

A survival analysis was applied to 1407 participants (66.7%) from the Massachusetts General and Hôpital Erasme cohort for which the exact time of first seizure onset was available. One hundred fifty-four patients (10.9%) had a seizure within the first hour of screening EEG. Patients with a seizure within the first hour of screening EEG were excluded, as these patients already have an indication for longer duration monitoring (leaving 1253 participants for further analysis). Survival analysis was performed independently for the low- (2HELPS2B = 0; n = 531 [42.2%]), medium- (2HELPS2B = 1; n = 495 [39.5%]), and high-risk (2HELPS2B≥2; n = 227 [18.1%]) groups (**Figure 3**).

The time to reach a less than 5% risk of a seizure within the 72-hour interval was calculated at each level of seizure risk. For the low-risk participants, no additional time after the 1-hour screening EEG was required to obtain a false negative rate (FNR) of 3.11% (95% CI, 1.43%-4.76%); that is, the risk of seizure within 72 hours is 3.11% if the 2HELPS2B score is 0 in the first hour. If the clinician has a lower tolerance for seizure risk, a less than 2.0% threshold could be considered, in which case 3.3 hours of monitoring (including the 1-hour screening EEG) is required. Other thresholds can be estimated from Figure 3.

For the medium-risk group, 10 hours was required to reach an FNR of less than 5%. A more commonly used clinical monitoring duration of 12 hours yielded an FNR of 3.96% (95% CI, 0.4%-5.77%). The overall 72-hour risk of seizure was 12.9% for the medium-risk group. To achieve a risk of seizure of less than 2.0%, 29 hours of EEG monitoring is required (including the 1-hour screening EEG).

The high-risk group required 19 hours to reach an FNR of less than 5%. Using a more commonly used duration of monitoring, 24 hours, the FNR was 3.07% (95% CI, 0.3%-8.6%). The overall 72-hour risk of seizure for the high-risk group was 26.6%. To achieve a seizure risk of less than 2.0%, 30.3 hours of EEG monitoring is needed (including the 1-hour screening EEG). The caveat with the high-risk group is that most of these patient have ictal-interictal continuum patterns that may warrant treatment trials/observation, hence EEG monitoring duration is driven by these considerations in addition to monitoring for discrete electrographic seizures. Based on these results, we proposed the following clinical algorithm for the application of 2HELPS2B (**Figure 4**), with a brief summary table with examples in **Table 2**.

Discussion

2HELPS2B had similar risk calibration and AUC in the validation cohort as in the foundational study. Statistical comparisons of

Table 2. Seizure Risk Based on 1-Hour Screening EEG

Seizure Risk Group	No. (% of Cohort)	Overall Seizure Risk, %	False-Negative Rate,[a] %	Recommend Duration of EEG Monitoring
Low risk:[b] 2HELPS2B score = 0	594 (40)	3.1	3.1	1 h (Length of screening EEG)
Medium risk:[c] 2HELPS2B score = 1	597 (40)	12.0	4.0	12 h
High risk:[d] 2HELPS2B score, ≥2	310 (21)	26.6	3.1	At least 24 h

Abbreviation: EEG, electroencephalogram.

[a] False-negative rate is the probability that a seizure would be missed if the recommended EEG duration was followed. The recommend EEG duration is based on the 2HELPS2B score calculated in the first hour of the EEG, termed the *screening EEG*.

[b] Low risk would be any patient without a recent or remote event concerning for clinical seizure and a screening EEG with no epileptiform abnormalities as defined by the absence of lateralized periodic discharges (LPD)/lateralized rhythmic delta activity (LRDA)/bilateral independent periodic discharges (BIPD), sporadic epileptiform discharges, plus pattern (on LPD/LRDA/BIPD), frequency of LPD/LRDA/BIPD, or GPD more than 2 Hz, or brief potentially ictal rhythmic discharge (BIRD). Of note, generalized periodic discharges or generalized rhythmic delta activity alone would not qualify as epileptiform (unless GPDs are >2 Hz). An example would be a patient with encephalopathy associated with a recent cerebral hemorrhage with no epileptiform EEG abnormalities on screening EEG.

[c] Medium risk would include any patient with a prior event concerning for a clinical seizure or a patient with an epileptiform abnormality on EEG but not both. An example would be a patient with cerebral hemorrhage and a recent event of rhythmic twitching of the right arm and a screening EEG without epileptiform abnormality. Another example would be patient with cerebral hemorrhage and LPDs on screening EEG.

[d] High risk would be any patient that has a combination of these factors that would give a 2HELPS2B score of 2 or greater. An example would be a patient with cerebral hemorrhage and a BIRD on screening EEG. Another example would be LPDs on screening EEG and a recent event of arm twitching.

the fit of 2HELPS2B in foundational study cohort and validation cohort did not show any statistical differences. The 2HELPS2B score calculated during only the first hour of EEG in those without seizures during that hour maintained a mean risk-calibration error of less than 0.05 and allowed for stratifying patients into low (2HELPS2B = 0; < 5% risk of seizures), medium (2HELPS2B = 1; 12% risk of seizures), and high (2HELPS2B≥2; risk of seizures >25%) risk of seizures. Each of the categories has an associated minimum recommended duration of EEG monitoring to achieve at least a less than 5% risk of seizures, a 2HELPS2B score of 0 (1-hour screening EEG), a 2HELPS2Bscore of 1 (12 hours of total cEEG), and a 2HELPS2B score of 2 or greater (24 hours of total cEEG) as outlined in Figure 3 and Table 2. If a more conservative threshold of less than 2% risk is desired, the minimum duration of EEG is as follows: 2HELPS2B score of 0 (3.3 hours of total cEEG), a 2HELPS2B score of 1 (29 hours of total cEEG), and a 2HELPS2B score of 2 or greater (30.3 hours of total cEEG). If any highly epileptiform patterns are seen, the 2HELPS2B score is already 2 or greater; therefore, at least 24 hours of EEG is recommended.

The findings in this study complement and extend previous investigations. Namely, several studies have found a high association between EEG findings of cortical hyperexcitability (sometimes referred to as *cortical irritability*[3,6,10,19]) and seizure risk in hospitalized patients. Conversely, their absence has a high negative predictive value. Similar to prior investigations using survival analyses, the likelihood of seizures quickly attenuates with the duration of cEEG.[3,10,19] In particular, in a previous study, we examined 665 cEEGs from Yale University and Hôpital Erasme with a survival analysis.[19] Reinterpreting this study within the 2HELPS2B framework aligns with the survival analysis in the validation cohort presented in this study. A 2HELPS2B score of 0 requires around 1 hour of EEG in both studies to reach an FNR of less than 5%. For a 2HELPS2B score of 1, around 10 to 17 hours of EEG is required. For a 2HELPS2Bscore of 2 or greater, around 24 hours is required. Additionally, the 2HELPS2B framework allows for a risk stratification of EEG findings that is more fine grained than possible with binary distinctions (present or absent). In our previous survival analysis, coma was an independent risk factor in univariate and multivariate analyses. This was not the case in the foundational 2HELPS2B study nor in the validation study. Coma was also not an independent risk factor for seizures in an earlier study that accounted for epileptiform abnormalities.[3] The reason for this discrepancy is not clear and deserves further investigation. One possible explanation could be that the value of coma for predicting subsequent seizures is largely through the association of coma with epileptiform abnormalities, as LPDs and LRDA have been associated with alteration of consciousness.[32] However, even in our previous survival analysis study in which coma was a significant risk factor, it was not as highly associated as the other predictive variables, and in participant with coma and a 2HELPS2Bscore of 0, only 1.2 hours of EEG were required to reach an FNR of less than 5%. Because of this finding, it may be reasonable to perform slightly longer screening EEG in patients with a coma with 2HELPS2B scores of 0, on the order of 1.2 to 1.5 hours. This is substantially shorter from the common recommendation based on an earlier studies, which recommends 48 hours of cEEG monitoring for all patients with coma[9] and may be partially associated with selection bias from a less prevalent use of cEEG monitoring in the past.

One lesson from our previous survival analysis study[19] that remains pertinent is the case of the emergence of cortical irritability/hyperexcitability as an indication to increase the duration of cEEG. Within the 2HELPS2B framework, this would consist of an increase in the 2HELPS2B score over the course of the cEEG, such as going from 1 to more than 1 during the first 12 hours of monitoring, in which case cEEG should be extended to at least 24 hours (Figure 3[33]). The duration of monitoring recommendations are weakest for the high-risk group, as evidenced by the wider FNR confidence interval. This is because these are the rarest patients with the greatest variance in seizure propensity. Often these patients may require monitoring longer than 24 hours even in the absence of seizures. This is the patient cohort that often has periodic or rhythmic patterns considered to be on the ictal-interictal continuum[34] and therefore may require treatment and moni-

toring independent of seizure detection. The guidelines also do not apply when the indication for cEEG is not seizure detection, as in the cases of ischemia monitoring and postcardiac arrest prognosis.

Limitations

Another important limitation of this study is that we consider seizure prediction within a 72-hour window. After 72 hours, participant dropout is high and censorship bias becomes a concern. Accurate predictions beyond this point are not possible with the current data. It follows that it may be reasonable to repeat screening EEGs in patients with prolonged hospitalization with persistent altered mental status and at times when there is a change in clinical status (eg, cerebral hemorrhage expansion, decline in neurological examination results).

The most useful result of this study is that a 1-hour screening EEG with no epileptiform findings in the absence of a clinical history of seizure (either remote or a recent suspected acute symptomatic seizure) may provide sufficient evidence that the patient is at low risk of seizures for at least the next 72 hours (FNR, 3.11%). Another consideration is the effect of IV sedatives. Despite IV sedatives not being a significant modifier of the overall seizure risk, we still believe that to maximize the validity of screening EEG, IV sedation (especially propofol and midazolam) should be minimized as much as clinically possible.

The largest potential limitation of this and similar studies is the inherent selection bias. Not every patient admitted to the hospital who is potentially at risk for seizures receives an EEG, even at centers, such as those in this study, that use EEG often. If centers adopt a protocol such as the one presented in this study and broaden the cross-section of patients receiving at least a screening EEG, we can obtain a less biased and more generalizable assessment of the overall seizure prevalence in hospitalized patients. Another limitation is that this study was designed as a validation study, and as such, we did not collect the many potential clinical variables that were present in the foundational study. Further areas for future study include investigations into real-world cost-effectiveness, efficacy in overall seizure detection within a center or specific ward (eg, neurointensive care unit), correlation with clinical outcomes, and effect on overall health care system resource use, such as reducing unnecessary transfers of patients specifically for cEEG monitoring. A relevant consideration for clinical use of the 2HELPS2B score is the EEG interpreter's familiarity with the American Clinical Neurophysiology Society critical care terminology.[26] We would encourage those wishing to adopt this approach to familiarize themselves with this terminology and review the publicly available training module (https://www.acns.org/research/critical-care-eeg-monitoring-research-consortium-ccemrc/education). The primary benefit of this terminology is to provide a common language to aid in clinical and scientific communication.

Conclusions

The 2HELPS2B score is a promising clinical tool for a systematic and efficient approach to cEEG in hospitalized patients. Additionally, 2HELPS2B may serve as a useful shorthand to improve communication regarding the clinical significance of EEG findings between EEG interpreters and bedside clinicians.

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