

Original Article

Residual Seizure Rate of Intermittent Inpatient EEG Compared to a Continuous EEG Model

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ABSTRACT: Background: Subclinical seizures are common in hospitalized patients and require electroencephalography (EEG) for detection and intervention. At our institution, continuous EEG (cEEG) is not available, but intermittent EEGs are subject to constant live interpretation. As part of quality improvement (QI), we sought to estimate the residual missed seizure rate at a typical quaternary Canadian health care center without cEEG. **Methods:** We calculated residual risk percentages using the clinically validated 2HELPS2B score to risk-stratify EEGs before deriving a risk percentage using a MATLAB calculator which modeled the risk decay curve for each recording. We generated a range of estimated residual seizure rates depending on whether a pre-cEEG screening EEG was simulated, EEGs showing seizures were included, or repeat EEGs on the same patient were excluded. **Results:** Over a 4-month QI period, 499 inpatient EEGs were scored as low ($n = 125$), medium ($n = 123$), and high ($n = 251$) seizure risk according to 2HELPS2B criteria. Median recording duration was 1:00:06 (interquartile range, IQR 30:40–2:21:10). The model with highest residual seizure rate included recordings with confirmed electrographic seizures (median 20.83%, IQR 20.6–26.6%), while the model with lowest residual seizure rate was in seizure-free recordings (median 10.59%, IQR 4%–20.6%). These rates were significantly higher than the benchmark 5% miss-rate threshold set by 2HELPS2B ($p < 0.0001$). **Conclusions:** We estimate that intermittent inpatient EEG misses 2–4 times more subclinical seizures than the 2HELPS2B-determined acceptable 5% seizure miss-rate threshold for cEEG. Future research is needed to determine the impact of potentially missed seizures on clinical care.

RÉSUMÉ : Taux de crises convulsives résiduelles détectées au moyen d'examens d'EEG intermittents en milieu hospitalier comparés à un modèle d'examens d'EEG continus. **Contexte :** Les crises convulsives subcliniques sont fréquentes chez les patients hospitalisés et nécessitent des examens d'électroencéphalographie (EEG) pour être détectées et traitées. Dans notre établissement de santé, les examens d'EEG continus (EEGc) ne sont pas disponibles alors que les examens d'EEG intermittents (EEGi) font l'objet d'une interprétation constante en direct. Dans une perspective d'amélioration de la qualité de nos soins, nous avons cherché à estimer le taux de crises convulsives résiduelles non-détectées dans un établissement typique de soins de santé quaternaires du Canada n'offrant pas d'EEGc. **Méthodes :** Nous avons calculé les pourcentages de risque résiduel en utilisant un score validé cliniquement (le « 2HELPS2B ») pour stratifier les examens d'EEG en fonction du risque avant de dériver un pourcentage de risque à l'aide de la plateforme de calcul MATLAB, laquelle nous a permis de modéliser la courbe de décroissance du risque pour chaque enregistrement. Nous avons ainsi généré une gamme de taux de crises convulsives résiduelles estimés selon qu'un examen d'EEG de dépistage pré-EEGc a été simulé, que les examens d'EEG montrant des crises convulsives ont été inclus ou que les examens d'EEG répétés sur le même patient ont été exclus. **Résultats :** Au cours de cette période d'amélioration de la qualité de nos soins s'échelonnant sur 4 mois, 499 patients hospitalisés ayant bénéficié d'un examen d'EEG ont été classés comme présentant un risque faible de crise convulsive ($n = 125$), un risque moyen ($n = 123$) ou un risque élevé ($n = 251$) selon les critères du score « 2HELPS2B ». La durée médiane des enregistrements était de 1:00:06 (EI 30:40 - 2:21:10). Le modèle présentant le taux de crises convulsives résiduelles le plus élevé incluait des enregistrements avec des crises convulsives électro-graphiques confirmées (médiane 20,83 % ; EI 20,6 - 26,6 %) tandis que le modèle présentant le taux de crises convulsives résiduelles le plus faible concernait des enregistrements sans crise (médiane 10,59 % ; EI 4 - 20,6 %). Ces taux étaient significativement plus élevés que le seuil de référence de 5 % (taux de non-détection) fixé en fonction du score « 2HELPS2B » ($p < 0,0001$). **Conclusions :** Nous estimons que les examens d'EEGi en milieu hospitalier omettent de détecter 2 à 4 fois plus de crises convulsives subcliniques que le seuil acceptable de 5 % de crises non-détectées déterminé par le score « 2HELPS2B » pour les examens d'EEGc. Des recherches futures sont donc nécessaires pour déterminer l'impact des crises convulsives potentiellement non-détectées sur les soins cliniques.

Keywords: Seizure detection; residual risk; cEEG; intermittent; 2HELPS2B

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Introduction

Subclinical seizures are common in hospitalized patients regardless of neurological status.¹ Since patients are by definition unable to clinically express their symptoms, these seizures require electroencephalography (EEG) for detection. It is widely accepted that extending discrete short-term EEG into continuous EEG (cEEG) increases detection of nonconvulsive seizures and status epilepticus; for instance, a recent meta-analysis reported 2.57 times greater detection with cEEG.² Greater detection affords greater opportunity for intervention.^{3,4} On the other hand, cEEG entails higher hardware and labor costs.⁵ For example, labor is required for ongoing generation of cEEG reports, as cEEG recording alone does not equal timely cEEG intervention. As part of a cEEG report, data description and interpretation are necessary critical steps in the translation of passively acquired data into active intervention(s) for patients as part of an integrated three-fold separation approach to reporting cEEG.⁶ Moreover, the rate of seizure detection decays with time; for example, a study of cEEG with median duration of 7.5 hours found that 64.8% of seizures were detected within the first hour,⁷ while the median time to first seizure in another sample of 665 cEEGs was 44 minutes.⁸ Due to these factors, medical centers with limited and dwindling resources may limit EEG duration to 1 hour or less such that EEG testing may be offered to as many patients as possible for a duration perceived to maximally yield subclinical seizure detection and interpretation. However, this approach entails considerable false-negative risk analogous to the “satisfaction of search” error in diagnostic radiology, wherein a radiologist fails to continue searching for additional abnormalities after identifying the initial one.⁹ In this EEG context, error occurs when EEG is arbitrarily limited to an insufficient duration, which then fails to detect subclinical seizures and thereby generates a false sense of security.

Nevertheless, even at centers with cEEG capability, not all cEEG monitoring requests can be fulfilled, with frequent defaulting to some form of discrete non-cEEG protocol. Consequently, much progress has been made into best determining for whom and how long cEEG is indicated. In particular, the 2HELPS2B model has been developed to stratify initial 1-hour screening EEGs into low-, medium-, and high-risk categories using a battery of clinically validated clinical and EEG characteristics.¹⁰ For medium- and high-risk recordings, the 2HELPS2B model recommends at least 12 and 24 respective hours of cEEG after screening to ensure a residual seizure risk of less than 5% within 72 hours.¹⁰ This percentage is equivalent to a false-negative rate of less than 5%, which also provides 95% confidence that an EEG which does not detect seizures within this time frame can reliably forecast seizure freedom over the next 72 hours assuming a steady clinical state.¹¹ The 2HELPS2B model also provides stratified decay curves of time-dependent seizure risk that can be calibrated to different false-negative thresholds.¹¹ Conversely, the threshold may remain the same (i.e. at 5%), while EEG duration varies along a decay curve in order to yield an estimated residual seizure risk percentage for that EEG.

At our institution, there is no cEEG infrastructure, but EEGs at the Health Sciences Centre (HSC) Winnipeg are interpreted live for the entire duration of the intermittent noncontinuous recording to allow for real-time seizure detection. Our “intermittent-recording-with-continuous-interpretation” approach differs from a “continuous-recording-with-intermittent-interpretation” model of cEEG where interpretation and subsequent seizure detection can occur even after the EEG recording has long since terminated. Nevertheless, delayed

Table 1: 2HELPS2B scoring criteria. Superscript a: We considered TIRDA as a part of this category. Superscript b: We included BIRDA, MF-RDA, MF-PD, LSW, BISW, and GSW (converted into GPD + R) in this category. Based on: Struck A et al. *JAMA Neurology* 2020; 77(4):500

EEG risk factor	Score	n (%)
Frequency > 2 Hz (any periodic or rhythmic pattern except for generalized rhythmic delta activity)	1	131 (26.3)
Independent sporadic epileptiform discharges ^a	1	156 (31.3)
LPD/BIPD/LRDA ^b	1	240 (48.0)
Plus features (superimposed rhythmic, fast, or sharp activity on only LRDA, LPD, or BIPD)	1	139 (27.9)
Prior seizure	1	277 (55.5)
BIRD	2	7 (1.4)

seizure detection may be preferable to no detection because seizure detection is impossible if recording duration is inadequate, or if there is no recording altogether. Furthermore, lack of not just cEEG infrastructure – but also deficits in general EEG infrastructure – often resulted in transporting inpatients to our hospital EEG laboratory instead of using portable machines for bedside recording. However, our inpatient hospital EEG laboratory is officially designated as an outpatient clinic space such that detected seizures could not be treated short of calling a Code Blue. At the same time, despite being resourced and equipped for an outpatient clinic, the hospital EEG laboratory could still accept critically ill inpatients from outside hospitals for EEG recording, even after working hours when the outpatient clinic had closed, and all its regular staff had departed. Altogether, these factors motivated us to conduct a quality improvement (QI) project to determine an estimated overall “seizure miss rate” (or residual seizure risk rate once EEG is turned off) at our institution and to compare this rate against the quoted benchmark “seizure miss rate” of 5%.

Materials and Methods

2HELPS2B Score Calculation

504 EEG recordings using Natus hardware and software (Neuroworks 7.1 on Microsoft Windows 7) from 297 hospitalized patients were previously acquired from a 4-month internal QI audit of the HSC Winnipeg EEG laboratory from October 2019 to January 2020. Research Ethics Board approval was waived due to the QI nature of this project. We calculated a 2HELPS2B score for each recording (Table 1), with the risk factor of “independent sporadic epileptiform discharges” determined from reviewing recording reports by four neurologists as part of standard clinical care, “prior seizure” determined from reviewing electronic medical records, and all other risk factors directly reconfirmed on visual review of EEG by a board-certified epileptologist (M.C.N.) fluent in American Clinical Neurophysiology Society (ACNS) Standardized Critical Care EEG Terminology.¹² We deviated from this protocol for one EEG recording due to a missing neurologist report, which necessitated confirming “independent sporadic epileptiform discharges” through visual EEG review instead. We considered temporal intermittent rhythmic delta activity (TIRDA) equivalent to an independent sporadic epileptiform discharge due to evidence that it represents epileptogenic abnormalities as well.¹³ We also included bilateral independent rhythmic delta activity (BIRDA), multifocal rhythmic delta activity (MF-RDA), and multifocal periodic discharges (MF-PD) into the same 2HELPS2B risk factor

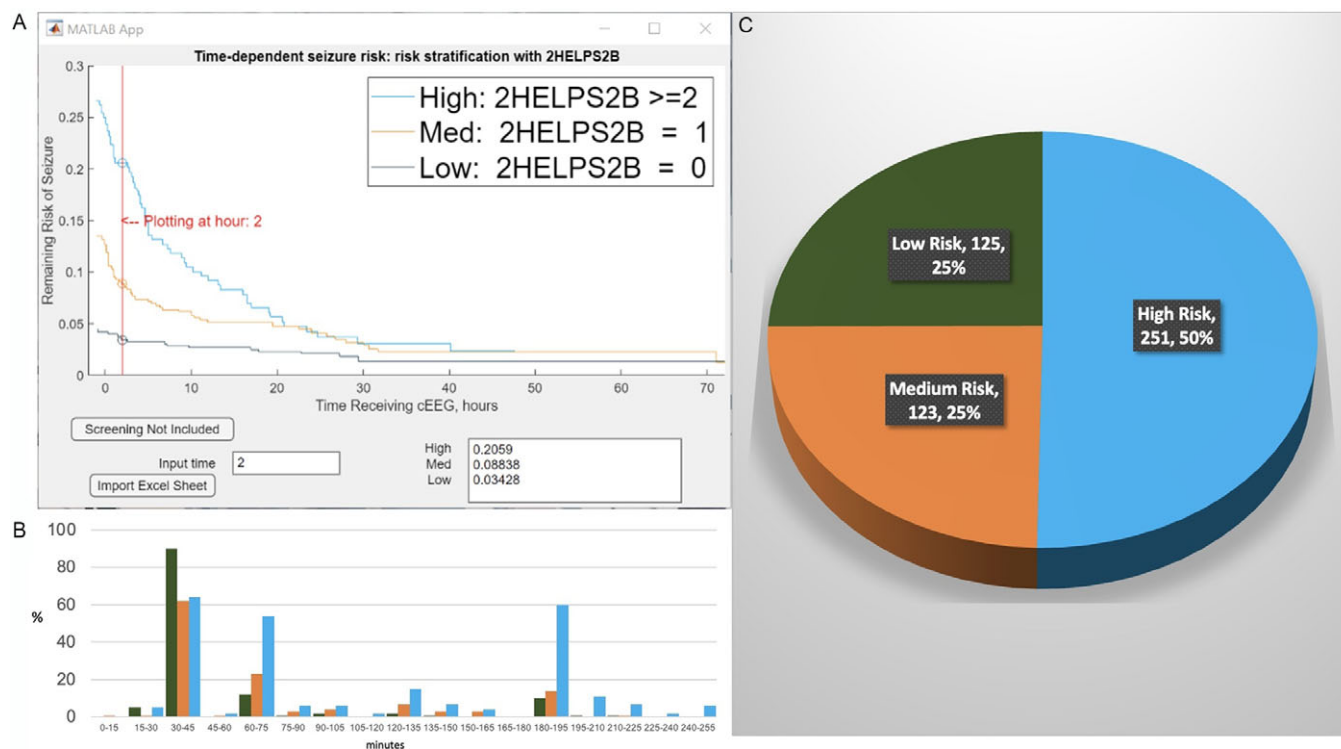


Figure 1: **a** - 2HELPS2B decay curves modeled via a MATLAB calculator program, which returns residual risk percentages for each seizure risk category for a given input EEG duration in hours. Shown in example is an input duration of 2 hours in a scenario where a screening requirement of 1 hour is respected. **b** - Histogram of our EEG sample showing duration spread of low-, medium-, and high-risk recordings. **c** - Percentage and numerical breakdown of our EEG sample by risk stratification. Decay curves modeled from: Struck A et al. JAMA Neurology 2020; 77(4):500.

category of "LPD/BIPD/LRDA" (lateralized periodic discharge/bilateral independent periodic discharge/lateralized rhythmic delta activity) as additional focal, bifocal, or multifocal patterns along the ictal-interictal continuum (IIC). This was due to BIRDA and MF-RDA being lateralized patterns like LRDA, but with their respective bilateral or multifocal nature suggesting increased epileptogenicity relative to the single unilateral lateralization of LRDA. Therefore, we erred on the side of caution to include these patterns into our estimation of residual seizure risk from intermittent EEG. Lastly, we converted the patterns of generalized spike wave (GSW) into generalized periodic discharges plus rhythmic activity (GPD + R). Although scoring was unaffected, we also noted triphasic waves as generalized periodic discharges with triphasic morphology (GPD-TW).

Scoring Serial Intermittent EEG

Unlike initial 2HELPS2B validation studies, EEG recordings could not be converted to cEEG if a seizure were detected. If recording stopped while a seizure remained ongoing, then the residual seizure risk for that EEG was modified to 100% no matter the 2HELPS2B score. If a seizure ended before recording ended, then EEG characteristics of the seizure were incorporated into 2HELPS2B score calculation. Furthermore, some EEGs were repeated on the same individual – typically not more than once per calendar day. To accommodate these variations, we performed separate analyses on (1) all recordings together, (2) subset of seizure-free recordings only, (3) subset of seizure recordings only, and (4) an "ordinal" subset using only the first EEG recording from each patient. Also unlike the validation studies, we calculated the

2HELPS2B score from the entire duration of EEG recording to accommodate many of our recordings being under 1 hour in duration and due to inability to convert to cEEG.

Residual Seizure Risk Calculation and Statistical Analysis

Each EEG was stratified into three 2HELPS2B risk categories: low (score 0), moderate (score 1), and high (score ≥ 2). After stratification, we plotted the exact duration of each EEG into an originally coded program (D.T.) in MATLAB (MathWorks, Natick, USA) that modeled the stratified decay curves from the 2HELPS2B validation study (Fig. 1a) to yield an estimated residual seizure risk percentage for each EEG (except for recordings that ended with ongoing seizure whose residual risk was fixed at 100%). To account for lack of 1-hour screening EEG, and recordings less than 1 hour in duration, we calculated residual seizure risks for two scenarios – (A) one that ignored screening wherein risk immediately started decaying along a given curve from the time EEG started recording, and (B) another that simulated screening wherein risks only started decaying after 1 hour of recording had elapsed. Altogether, this four-group two-scenario approach generated eight total analyses (Fig. 2). Shapiro–Wilk tests evaluated for data normality. For nonnormal data, one-sample Wilcoxon signed-rank tests would be performed for each analysis to assess for a significant difference from a suggested benchmark 5% residual seizure risk.

Modeling of 2HELPS2B decay curves using MATLAB

The model 2HELPS2B curves were derived from the original authors' publication image.¹¹ The PDF version of their paper was

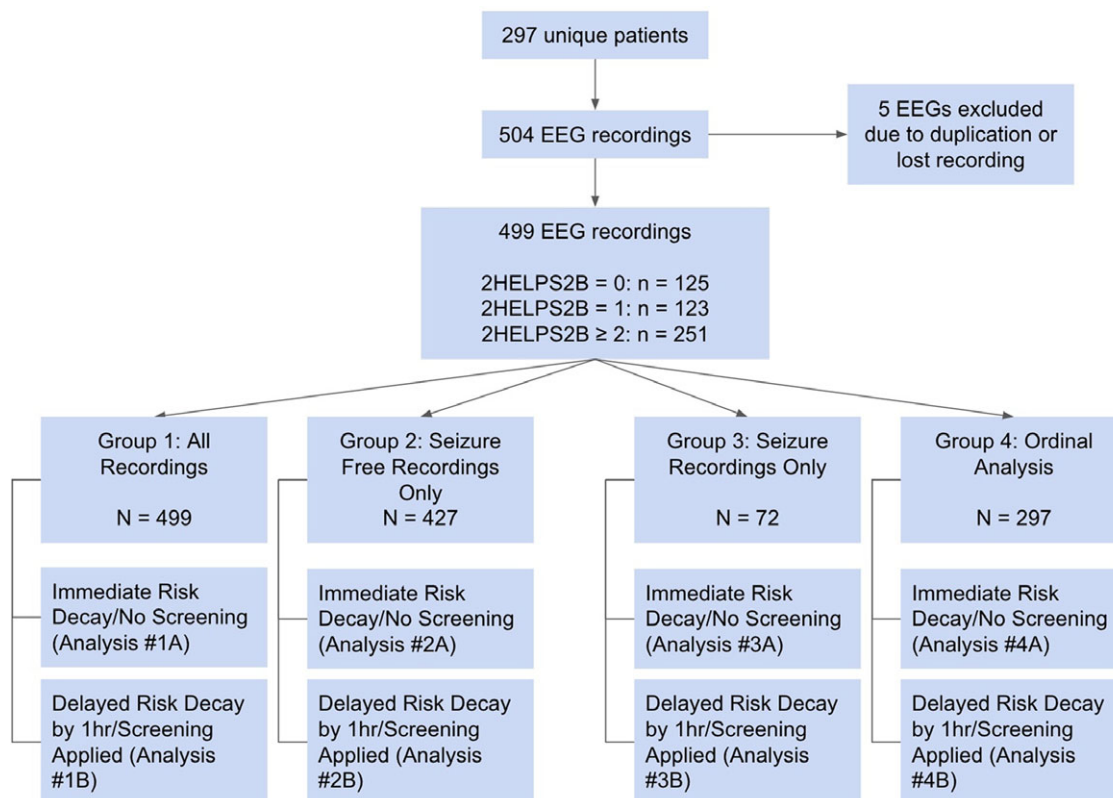


Figure 2: Flowchart illustrating the sorting process of patients and EEG recordings into each of the analyses conducted during our study.

downloaded and evaluated in MATLAB. Due to PDF files supporting vector images, all points on the graph could be determined through their vector art positions embedded in the PDF's metadata. As the point values only represented their respective positions on the current PDF page, a transformation was needed to match the original plot. This required interpolating each line's first y-value, first x-value, and last x-value from the image axis labels. After extracting the required initial values, the positional coordinates were scaled to the fundamental plotted values. The x-values were simply scaled, while the y-values were scaled using the normalized coordinate values, with the initial value replaced due to the plot on the PDF having values that started before the 0 time point. After all values were scaled from the actual coordinate values, we were able to extrapolate all 2HELPS2B values from the estimated scaled data.

Results

All recordings were gathered from 297 inpatients at HSC Winnipeg. Of these patients, 167 (56.2%) were male, and mean age was 58.37 years (standard deviation 18.07). Average male age was 58.22 years (standard deviation 18.31). Average female age was 58.55 years (standard deviation 17.84). These patients produced a total of 504 EEG recordings, of which we included 499 EEG recordings for analysis after excluding 3 recordings which were double-counted and 2 recordings which were lost. Of these remaining 499 recordings, we corrected 6 instances where patients had their name misspelled, corrected 3 instances where the EEG recording was labeled incorrectly, and corrected 1 instance where the neurologist report for the recording was missing by visually

reviewing the EEG for epileptiform discharges. These errors were corrected during the QI process which allowed for their inclusion into our pooled residual risk calculations. Four neurologist electroencephalographers (EEGers) each interpreted 210 (42.1%), 138 (27.7%), 141 (28.3%), and 10 (2%) of the 499 recordings.

Of 499 EEGs, 301 (60.3%) were from males. One hundred and seventy-four (34.9%) recordings were performed from patients on an HSC ward, 92 (18.4%) were from patients referred by the Emergency Department (ED), and 37 recordings were done on patients transported to HSC from other medical centers because HSC is the designated flagship neurosciences hospital for the province of Manitoba. These patients were transferred to HSC for EEG, while remaining technically admitted as an inpatient at another hospital within the province. Out of 196 recordings from patients receiving intensive care within our sample, 51 (26%) were from the coronary care unit (CCU), 4 (2%) were from the intermediate intensive care unit (IICU), 72 (36.7%) were from the medical intensive care unit (MICU), 4 (2%) were from the post-anesthesia care unit (PACU), and 65 (33.2%) were from the surgical intensive care unit (SICU).

One hundred and thirteen recordings were requested to query nonconvulsive status epilepticus, 218 were requested to rule out seizure, 24 were requested to diagnose an unexplained loss of consciousness, 93 were requested to follow up on a previous diagnosis of status epilepticus, 6 were requested to evaluate psychogenic nonepileptic seizures against epileptic seizures, and 54 EEGs were requested for a variety of other reasons. EEGs could have been requested for more than one reason. The median recording length was 1 hour and 6 seconds. The interquartile range

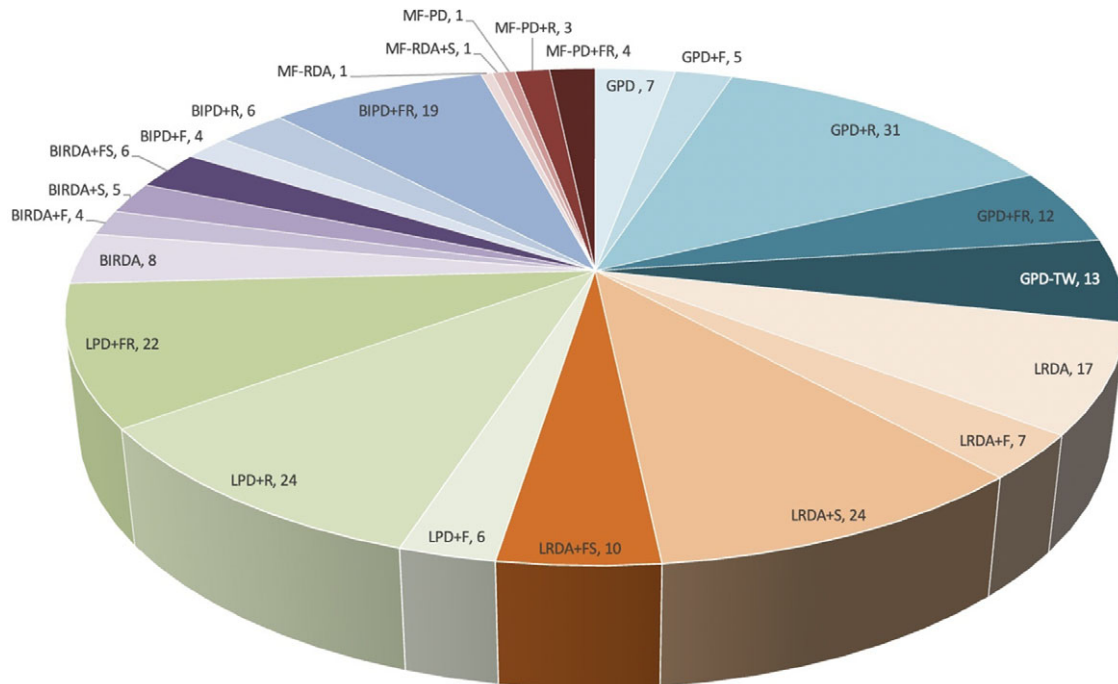


Figure 3: Breakdown of IIC pattern frequency in our EEG sample.

(IQR) was from 30 minutes and 40 seconds, to 2 hours, 21 minutes, and 10 seconds. The longest recording duration was 4 hours, 12 minutes, and 7 seconds. The shortest recording duration was 4 minutes and 24 seconds. Two hundred and thirty-one (46.3%) EEGs were under 1 hour, 99 (19.8%) EEGs were 1–1.5 hr in duration, 14 (2.8%) EEGs were 1.5–2 hours in duration, 42 (8.4%) EEGs were 2–3 hours in duration, 107 (21.4%) EEGs were 3–4 hours in duration, and 6 (1.2%) EEGs were over 4 hours in duration (Fig. 1B).

Of 72 recordings with a seizure(s), 14/72 (19.4%) recordings from 10 patients still displayed seizure at EEG termination. 6/14 (42.9%) recordings from 5 patients demonstrated constant seizure for the entire runtime of the EEG. In eight recordings, a seizure(s) was detected after inpatient transport to the EEG laboratory where treatment cannot readily occur because the laboratory is designated as an outpatient space. In two recordings, seizures persisted despite treatment and outlasted EEG recording time due to limitations in after-hours EEG technologist and/or EEGer availability. In one recording each, seizures persisted due to a delay in treatment that outlasted EEG recording time, a declaration of medical futility by the treating intensivist, failure to recognize electrographic seizure, and discordance of bedside clinical improvement with ongoing electrographic seizure on recording.

Of all 499 recordings, 7 (1.4%) showed BIRDS. Of 68 (13.6%) generalized IIC patterns, there were 7 (1.4%) GPD, 31 (6.2%) GPD + R (6 were converted from GSW), 5 (1%) GPD + F (plus fast activity), 12 (2.4%) GPD + FR (plus fast and rhythmic activities), and 13 (2.6%) GPD-TW. Of 110 (22%) lateralized IIC patterns, there were 17 (3.4%) LRDA, 24 (4.8%) LPD + R, 6 (1.2%) LPD + F, 22 (4.4%) LPD + FR, 24 (4.8%) LRDA + S (plus sharp activity), 7 (1.4%) LRDA + F, and 10 (2%) LRDA + FS (plus fast and sharp activities). Of 52 (10.4%) bilateral independent IIC patterns, there were 8 (1.6%) BIRDA, 6 (1.2%) BIPD + R, 4 (0.8%) BIPD + F, 19 (3.8%) BIPD + FR, 5 (1%) BIRDA + S, 4 (0.8%) BIRDA + F, and 6 (1.2%) BIRDA + FS. Of 10 (2%) multifocal IIC

patterns, there were 1 (0.2%) MF-PD, 3 (0.6%) MF-PD + R, 1 (0.2%) MF-RDA, 4 (0.8%) MF-PD + FR, and 1 (0.2%) MF-RDA + S. One hundred and thirty-one (26.3%) EEGs had a pathologic pattern greater than 2 Hz in frequency. Eight (1.6%) recordings demonstrated TIRDA (Fig. 3).

Based on calculated 2HELPS2B scores (Fig. 1C), 125 recordings (25.1%) were stratified as low risk, 123 recordings (24.7%) as moderate risk, and 251 (50.3%) as high risk. Of high-risk EEGs, 2HELPS2B scores were 2 in 85/251 (33.8%), 3 in 52/251 (20.7%), 4 in 72/251 (28.7%), 5 in 36/251 (14.3%), 6 in 2/251 (0.8%), and 7 in 4/251 (1.6%). The median duration of low-risk recordings was 30 minutes and 47 seconds, with an IQR of 30 minutes and 9 seconds to 40 minutes and 4 seconds. The median duration of moderate-risk recordings was 39 minutes and 12 seconds, with an IQR of 30 minutes and 24 seconds to 1 hour, 30 minutes and 22 seconds. The median duration of high-risk recordings was 1 hour, 15 minutes and 35 seconds, with an IQR of 36 minutes and 52 seconds to 3 hours and 34 seconds. Across all eight analyses (Fig. 4), Shapiro-Wilk testing confirmed data nonnormality ($p < 0.00001$). For all recordings, median residual seizure risk was 16.6% (IQR 5.8%–21.1%) in analysis #1A and 20.13% (IQR 6.7%–24.4%) in analysis #1B. In the "seizure-free recordings" subset, median residual seizure risk was 10.59% (IQR 4%–20.6%) in analysis #2A and 13.51% (IQR 4.5%–23.2%) in analysis #2B. In the "seizure-only recordings" subset, median seizure residual risk was 20.13% (IQR 19.6%–23.2%) in analysis #3A and 20.83% (IQR 20.6%–26.6%) in analysis #3B. In the "ordinal" subset, median residual seizure risk was 10.59% (IQR 4%–20.6%) in analysis #4A and 13.51% (IQR 4.5%–23.7%) in analysis #4B. All analyses were determined to be significantly higher than the 5% benchmark ($p < 0.0001$).

Discussion

By applying a cautiously modified 2HELPS2B criteria to a 4-month inpatient QI sample of non-cEEG recordings, we found an overall

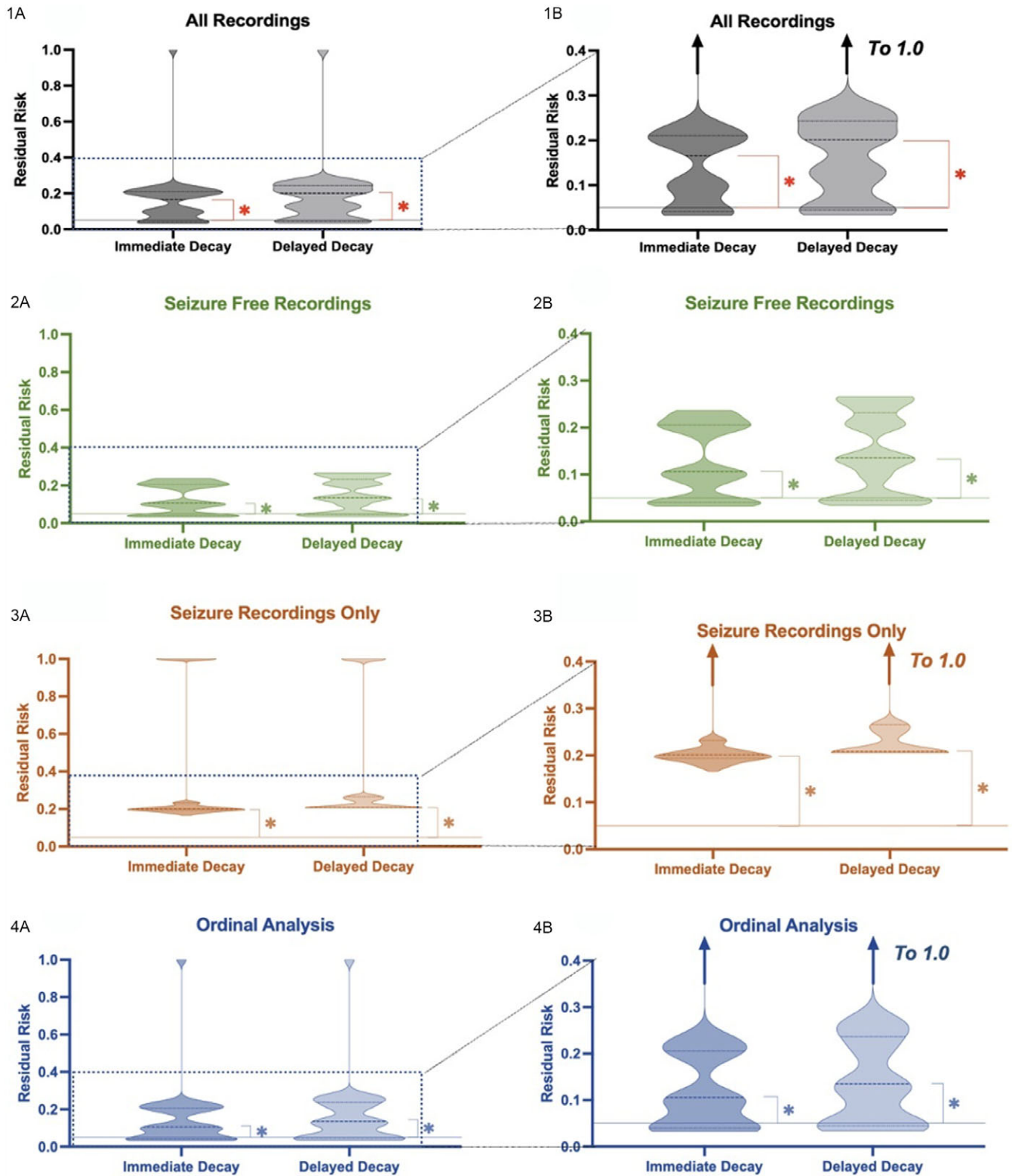


Figure 4: Violin plots displaying residual risk distribution for all recordings, seizure-free recordings, seizure recordings, and ordinal analysis. For each analysis, a plot was made with and without screening requirements. Additionally, Y axes were truncated to 0.4 for each analysis for better data visualization. Finally, lines were added to highlight 25 and 75 IQR, median, 5% acceptable benchmark for residual seizure risk, and a comparison interval. *Significantly above 5% ($p < 0.0001$).

“seizure miss rate,” residual seizure risk rate, or false-negative seizure detection rate at our institution that was significantly higher than the suggested 5% benchmark. To account for variations from the original 2HELPS2B criteria derived from cEEG, we conducted multiple analyses that accounted for seizures on serial intermittent EEG, repeated serial intermittent EEG recordings on the same patient, and lack of screening EEG. No matter the adjustment (i.e. excluding seizures, considering only the first unique EEG per patient, simulating a screening EEG), the median missed seizure percentage at our institution still remained significantly higher than 5% – ranging from 10.59% to 20.83% – which is over two to four times the quoted benchmark. These results suggest that in general, the results of a negative non-cEEG cannot be extrapolated to provide reassurance of continued seizure freedom beyond the duration of non-cEEG recording (if one accepts the suggested benchmark false-negative rate of 5%). Using pregnancy tests as reference, wherein a negative test ideally represents a 0% chance of pregnancy, a recent retrospective study at a large urban American academic medical center found a false-negative rate of just 1.6%, which was a reported cause for concern.¹⁴ Although our results agree with consensus in the literature reporting increased cEEG seizure detection rates compared to non-cEEG, we did not take the typical route of describing increased cEEG detections; rather, we adopted a unique approach of estimating the number of seizures left behind when cEEG is not used, allowing for more direct risk assessments of not using cEEG. To assist QI initiatives elsewhere, other centers may calculate their own “seizure miss rates” using our custom-coded MATLAB residual risk estimator to assess their own institutional risk tolerance based on existing 2HELPS2B criteria and to justify potential deviations below or above the suggested 5% benchmark.

For example, one may justify targeting a “seizure miss rate” lower than 5% based on evidence that while subclinical seizures are clinically silent at the bedside, they are nonetheless clinically relevant. Electrographic seizures have been linked to metabolic crises – with hypermetabolism directly visualized in positron emission tomography of patients along the IIC.¹⁵ As regional electrical activity increases during seizures, cerebral oxygenation requirements increase along with failure of local cerebral autoregulation.¹⁶ The subsequent inability of cerebral perfusion to accommodate these higher requirements can lead to real-time decreases in partial brain tissue oxygenation and regional cerebral blood flow,¹⁷ rises in intracranial pressure and lactate:pyruvate ratio,¹⁶ and longer-term measurable structural changes in a variety of conditions (e.g. traumatic brain injury, subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), ischemic stroke), such as hippocampal atrophy, greater midline shift, or herniation.^{18,19} These convergent lines of evidence demonstrate that electrographic seizures are independent factors contributing to patient morbidity and mortality,²⁰ as opposed to simple byproducts or epiphenomena of existing disease.^{21,22} These findings also provide mechanistic explanations for noted associations of higher subclinical seizure burden with greater morbidity and mortality.^{23,24,25} Clinically, a retrospective American cross-sectional study of just under 6,000 critically ill patients from 2005 to 2009 found higher inpatient survival with cEEG despite cEEG being used on clinically sicker patients.²⁶ Based in part on these findings, both the ACNS and European Society of Intensive Care Medicine recommend cEEG.^{27,17}

On the other hand, one may consider a “seizure miss rate” above 5% in certain cases, as the degree to which subclinical seizures contribute to morbidity and mortality varies between

patients depending on severity of underlying injury and premorbid status.²⁸ For example, a recent open-label cEEG study did not find a morbidity or mortality difference between cardiac arrest patients randomized to therapy suppressing electrographic seizures (and IIC patterns) against those who were not.²⁹ While this supports accepting false-negative rates above 5% in this population, not all cardiac arrest patients are alike, with some demonstrating favorable EEG characteristics^{30,31} and good outcomes,³² who may still merit a “seizure miss rate” of 5% or below. Excluding cardiac arrest patients, a recent American retrospective cross-sectional study of over 7 million critically ill patients from 2004 to 2013 found lower in-hospital mortality in over 22,000 patients with cEEG despite cEEG being used on clinically sicker patients.³³ Dividing cEEG patients by ICD-9 (International Classification of Diseases, Ninth Edition) diagnoses; however, mortality benefit remained significant for ICH, SAH, and “altered consciousness” – but not for “seizure/status epilepticus,” likely due to substantial subgroup heterogeneity.³³ In contrast, a recent Swiss multicenter trial that included cardiac arrest patients with “altered consciousness” while excluding “seizure/status epilepticus” found no mortality difference at 6 months after randomization to cEEG or non-cEEG.³⁴ However, various concerns have been raised, such as choice of endpoint, ability to convert to cEEG upon seizure/status epilepticus detection, delayed time to EEG start, and active cEEG monitoring during business hours only, which may explain a lower rate of cEEG intervention.^{35,36,37} While evidence emerges about what and in whom constitutes an acceptable “seizure miss rate,” our findings suggest that non-cEEG models of practice can face median false-negative rates as high as missing one in five seizures. Although the 2HELPS2B criteria imply that low-risk EEGs can safely stop running at 1 hour, approximately 3/4 of our recordings were medium or high risk, but median duration of all recordings was only just over 1 hour.

Limitations

Our study was limited by having to customize 2HELPS2B criteria to findings from our QI dataset; however, deviations were minor because we did not seek to refine or add to existing validated 2HELPS2B criteria – we simply applied them as best as possible for QI. Specifically, there was addition of just 1.6% TIRDA, 2% multifocal, and under 5% BIRDA patterns not originally described, and conversion of just 1.2% GSW into GPD + R. Though triphasic waves were reclassified as GPD-TW, this did not affect scoring. Although EEGs in our dataset were originally interpreted by four neurologists, only one neurologist participated in QI and performed the bulk of 2HELPS2B scoring; however, this was also the only neurologist at our center fluent in ACNS terminology, which has high inter-rater reliability.³⁸ While the 2HELPS2B criteria were developed using cEEG over 6 or 12 hours and our longest recording was just over 4.2 hours, there is no contraindication against applying 2HELPS2B to recordings under 6 or 12 hours; indeed, 2HELPS2B criteria are currently designed for initial application to screening EEGs of shorter duration. However, the need for screening in our serial intermittent dataset was obviated due to inability to convert to cEEG. As a result, we used total EEG duration for scoring instead of strictly adhering to a 1-hour screen, which was coincidentally similar to our median recording duration of 1 hour and 6 seconds. Furthermore, recommended screening EEG duration can vary; for example, up to 1.5 hours for patients with coma. If anything, our “seizure miss rates” are underestimates because we simulated 60 instead of 90-minute screening in

adjusted analyses B, which allowed residual seizure risks for all EEGs to decay by 30 extra minutes each. Another limitation relates to study timing, occurring on the eve of the COVID-19 pandemic. EEG capabilities have since declined,³⁹ likely resulting in even higher “missed seizure rates,” further supporting the notion that our reported false-negative rates are underestimates.

Our findings may also have been limited by institutional QI idiosyncrasies that could hinder generalizability. While EEG technology challenges are not unique to our institution,⁴⁰ technical failure was not responsible for EEGs that terminated in the middle of ongoing seizures despite our antiquated EEG technology. Rather, most such terminations occurred due to logistical impediments against treating seizures detected on inpatients recorded in the outpatient EEG laboratory where treatment could only start by calling a Code Blue. However, habitually calling Codes strains both the Code Team and overall EEG laboratory functioning. Alternatively, recording at the bedside where treatment more easily occurs was prevented by lack of recording EEG infrastructure built into patient rooms, lack of connections within the hospital for portable EEG machines to stream data, impracticalities of forcing EEGers to physically relocate beside a single portable machine to interpret only one of many simultaneously recording EEGs for prolonged periods, and general unfamiliarity of hospital staff with EEG equipment. If damaged, equipment repair may be impossible due to similar unfamiliarity of clinical engineering and information technology with EEG equipment. If irreparable, equipment may not be replaced due to extreme resource limitation. As a result, patients were usually transported from the wards, ED, and sometimes even lower acuity critical care for recording in the outpatient laboratory despite high likelihood of treatment unavailability. Nevertheless, EEGs with ongoing 100% residual seizure risk (i.e. terminated with ongoing seizure) accounted for only a fraction (2.8%) of our EEG cohort.

Conclusion

Altogether, our QI project provides an estimate of “seizure miss rates,” which are equivalent to “residual seizure risk rates,” or “false-negative seizure detection rates” for an institution with a non-cEEG model of practice. Based on existing 2HELPS2B criteria, our QI-driven MATLAB-coded residual risk estimator may help inform risk assessment decision-making around optimal EEG practice at other centers, health authorities, provinces, and territories. While scientific evidence continues to emerge about what and in whom constitutes an acceptable seizure miss rate, our findings suggest that resource-limited centers without cEEG may also be accepting, by default, median residual seizure risk rates of at least 10%–20%. Relative to the suggested benchmark false-negative rate of 5% (equivalent to missing 1 in 20 seizures), such rates are at least two to four times higher; in other words, having to accept the possibility of missing at least 1 in every 5–10 seizures after a non-cEEG is turned off within a 72-hour period. Future research is necessary to further refine the assessment of the direct clinical impact of these missed seizures on patient care.

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