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RESEARCH ARTICLE

Increased mortality in patients with standard EEG findings of 'diffuse slowing'

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BACKGROUND: We aimed to confirm the association between slow brain wave activity typically described as "diffuse slowing" on standard electroencephalogram (EEG) and patient outcomes, including mortality.

METHODS: This retrospective study was conducted with patient chart data from March 2015 to March 2017 at a tertiary care academic hospital in the midwestern United States. In total, 1,069 participants age ≥55 years on an inpatient floor or ICU received a standard 24-hour EEG. The primary outcome was all-cause mortality at 30, 90, 180, and 365 days. Secondary outcomes were time to discharge, and discharge to home.

RESULTS: Having diffuse slowing on standard EEG was significantly associated with 30-, 90-, 180-, and 365-day mortality compared with patients who had normal EEG findings, after controlling for age, sex, and Charlson Comorbidity Index score. When controlling for these factors, patients with diffuse slowing had a significant longer time to discharge and were significantly less likely to discharge to home. Our findings showed that a standard EEG finding of diffuse slowing for inpatients age ≥55 years is associated with poor outcomes, including greater mortality.

CONCLUSIONS: This study suggested that the finding of diffuse slowing on EEG may be an important clinical marker for predicting mortality in geriatric inpatients.

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INTRODUCTION

Delirium is defined as an acute decline in attention and either disorganized thinking or altered level of consciousness with a fluctuating course. Delirium can be considered acute brain failure[1] and is thought to be caused by many factors, including medications (especially those with high anticholinergic activity), substance abuse/withdrawal, major neurocognitive disorder (dementia), post-anesthesia, infections, CNS insults,[2] sleep disturbance,[3] metabolic disturbances,[4] and pain.[5] Advanced age and comorbidities predispose patients to developing delirium following any of these conditions.[6,7] Delirium is very common in older patients, complicating approximately one-third of hospital stays, and often persists after discharge.[8,9] Moreover, it is associated with higher mortality and worse functional outcomes.[10] Thus, identification of delirious patients to initiate treatment for potentially reversible causes is vital to improve patient outcomes.

Delirium is typically identified by clinical assessment using the Confusion Assessment Method (CAM)[11] or similar questionnaire-style instruments meant particularly for settings such as the ICU (CAM-ICU).[12] However, delirium is frequently underdiagnosed in the hospital because of its often subtle and varied presentations; agitated, hyperactive delirium represents the minority of cases, while mixed and hypoactive delirium are more common.[8] Reliable biomarkers of delirium are therefore desirable and needed for better patient care. Electrophysiological brain signals are a well-known biomarker, with a specificity of 91% in 1 study of patients with major cognitive disorder.[1] In that study, electroencephalogram (EEG) had a low sensitivity, but another study with a more general population found that 96% (50/52) of those with encephalopathy have "background slowing," indicating that EEG signals read by neurology experts as "diffuse slowing" are a sensitive marker for encephalopathy.[13]

A finding of diffuse slowing on standard EEG is a characteristic feature of delirium and helpful in identifying delirious patients, including those with an underlying cognitive impairment, such as major cognitive disorder.[1,14] Thus, the use of EEG could facilitate early identification of delirium. However, standard EEG is a burdensome procedure with many technical requirements.[15] Recently our group developed a screening tool for detecting slow brain wave activity using bispectral EEG (BSEEG), a handheld, point-of-care EEG device that reads signals obtained from just the forehead with limited channels. Our data showed that high BSEEG scores (indicating slower waves) were significantly associated with delirium.[16,17] Further, our additional study using BSEEG identified an association between a high BSEEG score and mortality among geriatric inpatients.[18] To confirm the association between slow brain wave activity detected by BSEEG and high mortality, this study aimed to test the association by investigating patient outcomes for those with diffuse slowing on standard EEG.

METHODS

Study oversight

This was a retrospective cohort study to determine the association between EEG findings of "diffuse slowing" and patient outcomes such as mortality. It was approved by the University of Iowa Institutional Review Board.

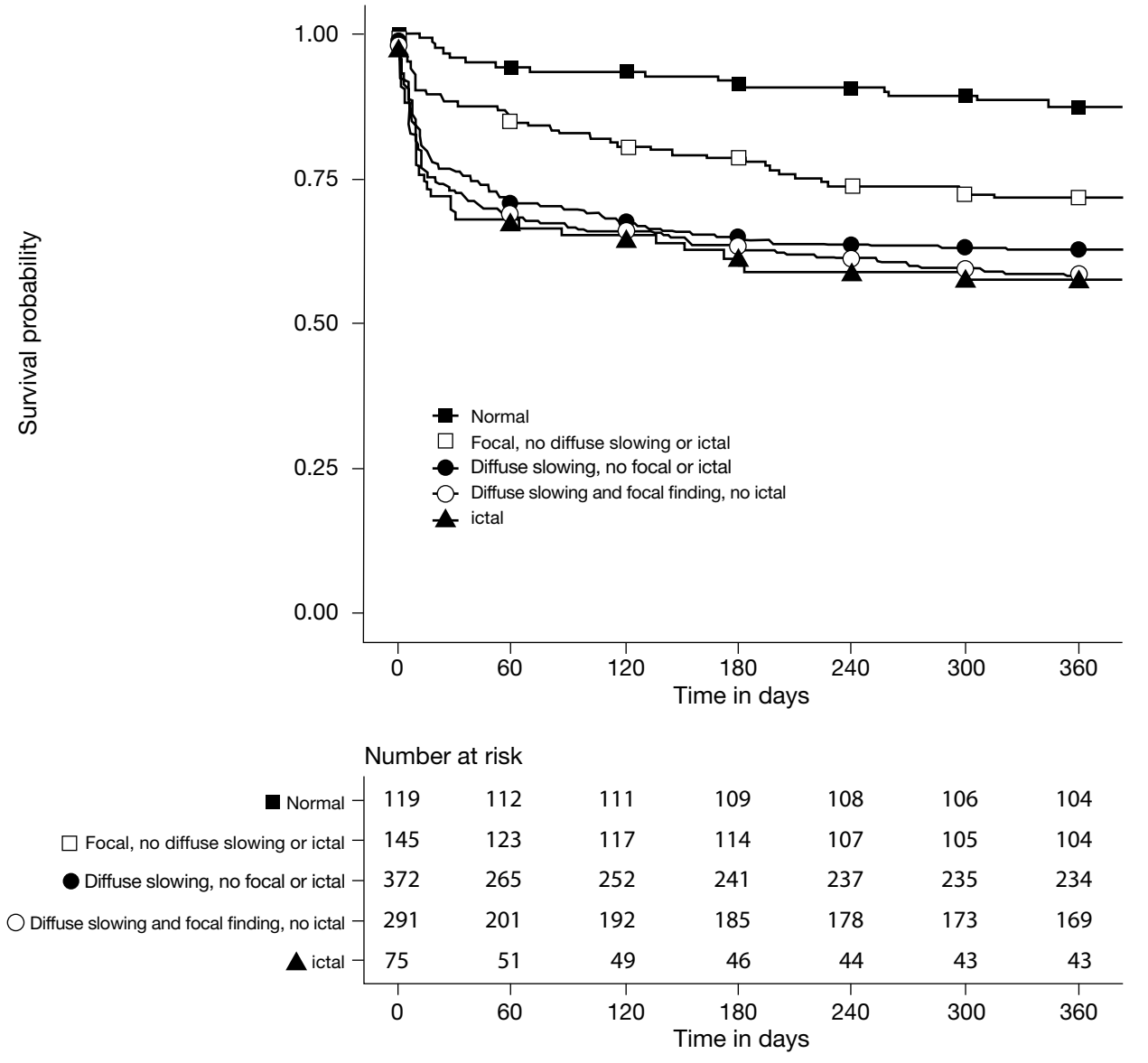
Patient population

We reviewed records of all patients who received a standard 24-hour EEG as an inpatient at the University of Iowa Hospitals and Clinics (UIHC) from March 2015 to March 2017. The study team selected potential participants based on age, including those ≥55 years, in an effort to focus on an older adult population, knowing that this population is more susceptible to delirium and mortality. To be inclusive, we did not exclude any patients from our analysis as long as they received EEG recordings during the study period.

EEG data collection

A total of 1,069 bedside 24-hour standard EEGs completed on inpatients age ≥55 years at UIHC between March 1, 2015, and March 1, 2017 were identified. The first day of EEG recording was used in our analysis, and EEGs from subsequent days were not included. Participants included patients from both the ICU and medical floors. Each participant's age, sex, date of admission, date of EEG, date of discharge, mortality status, and date of death were recorded, with a follow-up period of 1 year. In addition, participants' International Classification of Diseases-10 (ICD-10) diagnoses were recorded using data from the index admission and all previous admissions. To adjust for the effect of patients' comorbidities on mortality, Charlson Comorbidity Index (CCI) scores

FIGURE 1
Survival curve: All patients



were calculated using the participants' ICD-10 codes.[19,20] For each EEG performed, a corresponding report documented by neurologists who specialize in electrophysiology was extracted. EEG reports included data on indication for study; clinical state; EEG recording, including background, ictal, and interictal discharges; EEG reactivity; clinical (video) events; description of findings; and neurologist impression. Based on the neurologists' descriptions and impressions, reports were manually coded by the research team as having (a) a finding of diffuse slowing, diffuse delta and theta waves, background slowing, or similar terms, (b) a focal finding or lateralization, and (c) ictal or seizure findings in fitting with standard terminology.[21]

At the time of EEG recording, the 1,069 participants were on average age 69.5 years (median: 68 years; standard deviation: 9.7 years). Slightly more than one-half (53.5%) of participants were male. The average CCI score

TABLE 1
***P* values for group comparisons at 1 year[a]**

	DS + focal	DS + nonfocal	Ictal	Focal
DS + focal				
DS nonfocal	.147			
Ictal	.706	.138		
Focal	.00990[c]	.148	.0250[b]	
Normal	1.08e-05[d]	.000295[d]	5.55e-05[d]	.0293[b]

[a]*P* values are for multivariate linear regression controlling for age, sex, and Charlson Comorbidity Index score.
[b]*P* < .05.
[c]*P* < .01.
[d]*P* < .001.

DS: diffuse slowing.

was 3.6 (median: 3; range: 0 to 18). Reasons for the EEG requests included evaluation for seizure in 803 (75.1%) participants, and some form of altered mental status for 285 (26.7%) patients.

Outcome measures

The primary outcome was 30-, 90-, 180-, and 365-day mortality and was identified using chart review and obituary record. Secondary outcomes included time to discharge following EEG, and discharge disposition either to home or not to home.

Statistical analysis

Multivariate regression models were used to determine the association between findings and outcomes, controlling for age, sex, and CCI score. In an additional analysis, those with diffuse slowing were stratified by clinical status into 2 groups: those whose clinical status indicated "awake," and those whose clinical status did not indicate "awake." Two-sided *P* values ≤.05 were considered to indicate statistical significance. Statistical analysis was performed using RStudio software, version 1.2.1335.

RESULTS

Group comparisons

Overall, 707 participants (66.1%) had diffuse slowing, 75 (7.0%) had ictal findings (ie, seizures), 502 (47.0%) had some focal finding or lateralization of findings, and 119 (11.1%) had a normal EEG. There were 372 patients (34.8%) with diffuse slowing and no focal or seizure findings, 291 (27.2%) with diffuse slowing and some focal finding or lateralization but no seizure, and 145 (13.6%) with a focal finding but no diffuse slowing or seizure.

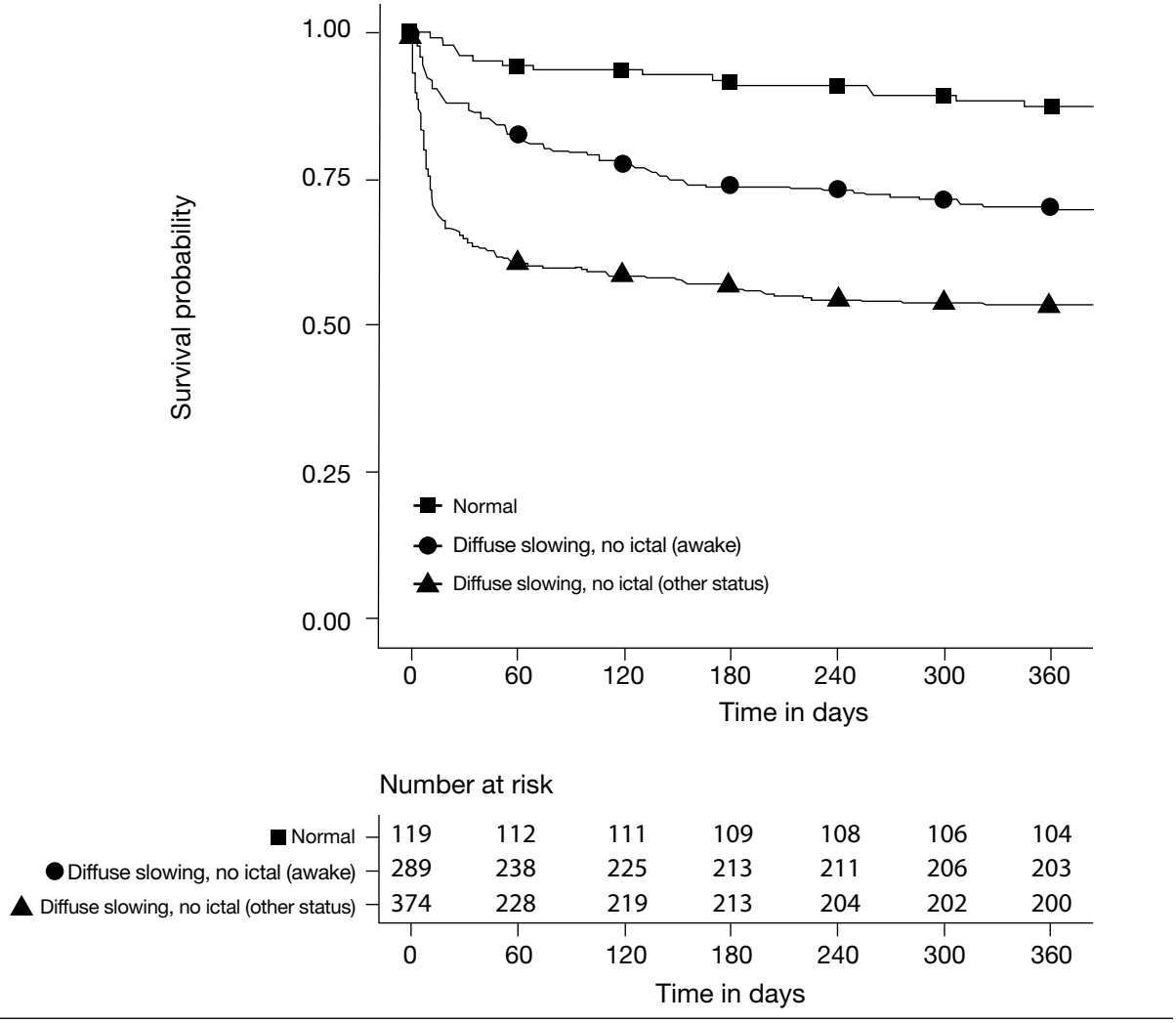
At 1 year, 15/119 (12.6%) with a normal EEG, 41/145 (28.2%) of those with focal findings without diffuse slowing or ictal findings, 138/372 (37.1%) of those with diffuse slowing without focal or ictal findings, 122/291 (42.0%) of those with diffuse slowing, a focal finding or lateralization, and no ictal finding, and 32/75 (42.7%) of those with ictal findings had died. Mortality at earlier time intervals is visualized with a survival curve (**FIGURE 1**), which also displays the number at risk at intervals of 60 days.

At 1 year, all groups with abnormal findings appeared to do worse than those with normal findings, with ictal and diffuse slowing apparently similar to one another, and worse than those with only focal findings. These differences were significant after controlling for age, sex, and CCI score, except that the difference between the diffuse slowing nonfocal group were not significantly worse than the focal-only group ($P = .148$), as shown in **TABLE 1**.

Diffuse slowing analysis

Because the 2 diffuse slowing groups were similar, we combined the 2 for further analysis of mortality and secondary outcomes. We stratified the combined diffuse slowing group by clinical status into 2 groups: those whose status included "awake" during EEG recording, and those whose status did not. The survival curve shown in **FIGURE 2** shows the difference from normal is retained in the awake group and shows a worse outcome among those with diffuse slowing who were not awake. Multivariate regressions controlling for age, sex, and CCI score confirmed that the difference between the awake group and normal controls was significant at 90 days and beyond. **TABLE 2** shows the results of statistical analysis

FIGURE 2
Survival curve: Awake patients vs other status



for mortality outcomes as well as secondary outcomes, which were also significant. The other group was significantly different from both the normal and the awake groups (the *P* values listed in **TABLE 2** are those for difference from the awake group).

DISCUSSION

Based on a 2013 study,[22] continuous EEG (cEEG) monitoring is used for approximately 1 of every 100 mechanically ventilated patients, but likely is more common; another study found a 10-fold increase from 2004 to 2013.[23] Continuous EEG offers much better detection of seizure than routine EEG,[24,25] which is important because mortality is much higher in patients with nonconvulsive seizures (32% to 51%) than in those without the condition (13%).[26] While one study did not find better discharge Glasgow Coma Scale (GCS) scores in those who received cEEG compared with those who did not, it did note a difference in GCS at admission, which is consistent with an improvement related to EEG use, although such a retrospective study does not allow for inference of causation.[27] Other studies have found differences in in-hospital

TABLE 2
Primary and secondary outcomes for diffuse slowing groups[a]

	Normal (n = 119)	DS: Awake (n = 289)	DS: Other status (n = 374)
30-day mortality	5 (4.2%)	35 (12.1%) (NS)	130 (34.8%)[d]
90-day mortality	8 (6.7%)	59 (20.4%)[b]	150 (40.1%)[d]
180-day mortality	10 (8.4%)	76 (26.3%)[b]	161 (44.7%)[d]
1-year mortality	15 (12.6%)	86 (29.8%)[b]	174 (46.5%)[d]
Time to discharge (days)	Average: 4.6 Median: 2	Average: 7.2 Median: 5[c]	Average: 11.5 Median: 8[d]
Discharge to home	92 (77.3%)	100 (34.6%)[d]	63 (16.8%)[d]

[a]The diffuse slowing groups are a combination of the focal and nonfocal groups and do not have ictal findings. Results are of multivariate regression controlling for age, sex, and Charlson Comorbidity Index score comparing the awake group to normals and the other group to the awake group.
[b]$P < .05$
[c]$P < .01$
[d]$P < .001$.

DS: diffuse slowing; NS: not significant.

mortality with the use of cEEG,[22,26] and a randomized control study investigating differences in 6-month mortality between the use of routine and continuous EEG is underway.[28]

While investigation for seizure is often the stated indication for cEEG,[29] diffuse slowing is a common finding and may be given less attention than needed. In our retrospective study of standard, 24-hour EEG reports in 1,069 inpatients, we found that diffuse slowing on cEEG was significantly associated with mortality, after adjusting for age, sex, and CCI score, which confirms previous associations between diffuse slowing on EEG and mortality.[30,31] In addition, we demonstrated that the association persists even when limited to awake patients only. Our results also indicated that mortality among the group with diffuse slowing was as bad as that among those with seizures, and was worse than among those with only focal findings. That the association becomes significant at 90 days and continues to 1 year in awake patients suggests that diffuse slowing is not necessarily an acute process that resolves, but may be a marker of a more continual effect beyond its occurrence during hospitalization. Diffuse slowing may be important to screen for beyond its usual identification as an incidental finding in those evaluated for seizures. A recent study by Kimchi et al[32] clearly showed the association of "clinical EEG slowing" and heightened mortality. Their data and our data are consistent even though the studies were conducted at different institutions; 1 in Boston and the other in Iowa. Our study and their study therefore confirm the importance of the previously mentioned potential association between a high BSEEG score and increased mortality.[18]

Indications for EEG and frequency of outcomes were comparable to those observed in a large, 3-center study by Alvarez et al.[33] In our study, 75.1% of EEG orders were for underlying seizures, while in Alvarez et al[33] 72.5% to 70% of indications were for nonconvulsive seizures. There were also similar rates of seizures, with our study finding seizures at a rate of 7.0% using the first 24 hours of continuous EEG, while Alvarez et al[33] found seizures at a rate of 12.9% over multiple-day recordings, with 87.2% of seizures found in the first day, for a 24-hour rate of 11.2%. The difference may be due to varying physician ordering patterns.

Limitations

There were several limitations to our study. The first is a feature of the finding of diffuse slowing itself. Anesthetic agents are commonly used and can cause diffuse slowing on EEG. However, we did not collect data on the use of anesthetic agents such as propofol or benzodiazepines, and thus we did not exclude patients receiving anesthetic agents, because doing so would likely eliminate many who had diffuse slowing for some other reason, or whose slowing was multiply determined. Our analysis of awake patients mitigates that problem to some extent, because awake patients are less likely to have received sedatives, and we can be more confident that participants in that group had a finding of diffuse slowing for other reasons.

Other limitations relate to the generalizability of the study and to treatment applications. The study was

performed at a single center in the midwestern United States, and the majority of patients were white. EEGs used in this study were not ordered at a standardized time or for a standardized indication, and results may have been affected by variations in the treating physicians' ordering patterns. This study did not include outpatients, and the finding of diffuse slowing may not be associated with mortality in that population. This study did not determine the meaning of diffuse slowing in biologic, biochemical, or anatomical terms. It did not compare other potential factors that could influence EEG findings, such as specific medical/neurologic conditions, medications, or interventions patients received prior to and after EEG findings, although including CCI scores was meant to help control for comorbidities. However, the CCI is limited because it does not distinguish between conditions occurring before admission or during admission, so it is unclear if or how such conditions affected the use of EEG. We did not compare our study participants with patients who did not receive EEGs and/or those who received only routine EEGs. This study does not demonstrate that identifying diffuse slowing or other abnormal findings leads to changes in management or outcomes. Nonetheless, the data presented here are supported by a large sample size and provide important information indicating that older patients who show slowing in EEG signals are at significant risk for high mortality.

CONCLUSIONS

Our findings show that an EEG finding of diffuse slowing in the inpatient setting for patients age ≥55 years is associated with greater mortality, similar to mortality found in those with seizures. Our study suggests that the finding of diffuse slowing on EEG, which is a characteristic EEG feature of delirium, is an important clinical marker for predicting mortality, and therefore our novel BSEEG methods, which can detect slow wave more easily at the bedside, may become a useful screening tool for geriatric patients if prompt identification of slowing can lead to better outcomes.

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REFERENCES

1. Thomas C, Hestermann U, Walther S, et al. Prolonged activation EEG differentiates dementia with and without delirium in frail elderly patients. J Neurol Neurosurg Psychiatry. 2008;79:119-125.
2. Cirbus J, MacLullich AMJ, Noel C, et al. Delirium etiology subtypes and their effect on six-month function and cognition in older emergency department patients. Int Psychogeriatr. 2019;31:267-276.
3. Fadayomi AB, Ibala R, Bilotta F, et al. A systematic review and meta-analysis examining the impact of sleep disturbance on postoperative delirium. Crit Care Med. 2018;46:e1204-e1212.
4. Faigle R, Sutter R, Kaplan PW. Electroencephalography of encephalopathy in patients with endocrine and metabolic disorders. J Clin Neurophysiol. 2013;30:505-516.
5. Feast AR, White N, Lord K, et al. Pain and delirium in people with dementia in the acute general hospital setting. Age Ageing. 2018;47:841-846.
6. Inouye SK. Delirium in older persons. N Engl J Med. 2006;354:1157-1165.
7. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383:911-922.
8. Krewulak KD, Stelfox HT, Leigh JP, et al. Incidence and prevalence of delirium subtypes in an adult ICU: a systematic review and meta-analysis. Crit Care Med. 2018;46:2029-2035.
9. Cole MG, Ciampi A, Belzile E, et al. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. Age Ageing. 2009;38:19-26.
10. Witlox J, Eurelings LS, de Jonghe JF, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. 2010;304:443-451.
11. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941-948.
12. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29:1370-1379.
13. Wabulya A, Lesser RP, Llinas R, et al. Electroencephalography and brain MRI patterns in encephalopathy. Clin EEG Neurosci. 2016;47:150-156.
14. Morandi A, McCurley J, Vasilevskis EE, et al. Tools to detect delirium superimposed on dementia: a systematic review. J Am Geriatr Soc. 2012;60:2005-2013.
15. Herman ST, Abend NS, Bleck TP, et al; Critical Care Continuous EEG Task Force of the American Clinical Neurophysiology Society. Consensus statement on continuous EEG in critically ill adults and children, part II: personnel, technical specifications, and clinical practice. J Clin Neurophysiol. 2015;32:96-108.
16. Shinozaki G, Chan AC, Sparr NA, et al. Delirium detection by a novel bispectral electroencephalography device in general hospital. Psychiatry Clin Neurosci. 2018;72:856-863.
17. Lee S, Yuki K, Chan A, et al. The point-of-care EEG for delirium detection in the emergency department. Am J Emerg Med. 2019;37:995-996.
18. Shinozaki G, Bormann NL, Chan AC, et al. Identification of patients with high mortality risk and prediction of outcomes in delirium by bispectral EEG. J Clin Psychiatry. 2019;80:19m12749. doi: 10.4088/JCP.19m12749
19. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-383.
20. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol. 2004;57:1288-1294.
21. Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. J Clin Neurophysiol. 2013;30:1-27.
22. Ney JP, van der Goes DN, Nuwer MR, et al. Continuous and routine EEG in intensive care: utilization

and outcomes, United States 2005-2009. Neurology. 2013;81:2002-2008.
23. Scozzafava J, Hussain MS, Brindley PG, et al. The role of the standard 20 minute EEG recording in the comatose patient. J Clin Neurosci. 2010;17:64-68.
24. DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. Epilepsia. 1998; 39:833-840.
25. Pandian JD, Cascino GD, So EL, et al. Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit: clinical features and outcome. Arch Neurol. 2004;61:1090-1094.
26. Hill CE, Blank LJ, Thibault D, et al. Continuous EEG is associated with favorable hospitalization outcomes for critically ill patients. Neurology. 2019;92: e9-e18.
27. Khawaja AM, Wang G, Cutter GR, et al. Continuous electroencephalography (cEEG) monitoring and outcomes of critically ill patients. Med Sci Monit. 2017; 23:649-658.
28. Rossetti AO, Schindler K, Alvarez V, et al. Does continuous video-EEG in patients with altered consciousness improve patient outcome? Current evidence and randomized controlled trial design. J Clin Neurophysiol. 2018;35:359-364.
29. Hirsch LJ. Continuous EEG monitoring in the intensive care unit: an overview. J Clin Neurophysiol. 2004;21:332-340.
30. Azabou E, Magalhaes E, Braconnier A, et al T; Groupe d'Explorations Neurologiques en Réanimation. Early standard electroencephalogram abnormalities predict mortality in septic intensive care unit patients. PLoS One. 2015;10:e0139969.
31. Stecker MM. The EEG as an independent indicator of mortality and healthcare utilization. Clin Neurophysiol. 2009;120:1777-1781.
32. Kimchi EY, Neelagiri A, Whitt W, et al. Clinical EEG slowing correlates with delirium severity and predicts poor clinical outcomes. Neurology. 2019;93:e1260-e1271.
33. Alvarez V, Rodriguez Ruiz AA, LaRoche S, et al; Critical Care EEG Monitoring Research Consortium. The use and yield of continuous EEG in critically ill patients: a comparative study of three centers. Clin Neurophysiol. 2017;128:570-578.

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